Health Ministry of Ukraine

Zaporizhzhya State Medical University

Department of internal medicine 2

EXECUTABLE TASK FORCE

RHEUMATOLOGY DISEASES.

DIAGNOSIS AND MANAGEMENT APPROACHES

Zaporizhzhya, 2017

Guidelines were written by:

Vizir V.A. - Head of the Department, d.med.s.professor

Berezin A.E. - d.med.s., associate professor

Pysanko O.V. - laboratory assistant-in-chief

Executable task force is addressed to students of 5th and 6th courses of medical university for helping to study of internal medicine according rheumatology diseases. Zaporizhzhya, 2017. – 244 p.

Guidelines ratified on meeting of the Central methodical committee of Zaporizhzhya state medical university (protocol numbers5 “25” may 2017) and it is recommended for the use in educational process for foreign students.

CONTENTS

Index of acronyms.

aCL	anticardiolipin antibody
ACR	American College of Rheumatology
ADM	adenosine monophosphate
ADM	amyopathic dermatomyositis
ANA	autoantibodies to nuclear antigens
ANAs	antinuclear antibodies
ANC	absolute neutrophil count
Anti–Jo-1	antihistidyl transfer RNA [t-RNA] synthetase
anti–Scl-70	antibodies versus topoisomerase
aPL	antiphospholipid antibodies
APS	antiphospholipid syndrome
aPTT	activated partial thromboplastin time
AS	ankylosing spondylitis
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BD	Behçet disease
BMI	body mass index
CASPAR	classification criteria for psoriatic arthritis
CBC	complete blood cell
CFS	cerebral spinal fluid
CHCC	Chapel Hill Consensus Conference
CHF	congestive heart failure
CK	creatine kinase
COX	cyclooxygenase
CRP	C-reactive protein
CSS	Churg-Strauss syndrome
CT	computed tomography
CTDs	connective-tissue diseases

ACRONYMS

CVA cerebrovascular accident
CY cyclophosphamide
DEXA dual-energy X-ray absorptiometry
DILS diffuse infiltrative lymphocytic syndrome
DIP distal interphalangeal
DM dermatomyositis
DMARD disease-modifying anti-rheumatic drug
DRVVT dilute Russell viper venom test
DVT deep venous thrombosis
EMG electromyelogram
ESR erythrocyte sedimentation rate
ESR erythrocyte sedimentation rate
FDA Food and Drug Administration
GCs glucocorticoids
G-CSF granulocyte colony-stimulating factor
GERD gastroesophageal reflux disease
GFR glomerular filtration rate
GI gastrointestinal
HBV hepatis B virus
HCV hepatitis C virus
HIV human immunodeficiency virus
HLA human leucocytes antigen
HSPs heat shock proteins
IBD inflammatory bowel disease
ICU intensive care unit
IFN interferon
Ig immunoglobulin
IIM idiopathic inflammatory myopathy
IL interleukin
iv intravenously
IVIG intravenous immunoglobulin
JIA juvenile inflammatory arthritis
LCV leukocytoclastic vasculitis
LDH lactic dehydrogenase
LMWH low–molecular-weight heparin
MCP metacarpophalangeal
MCTD mixed connective-tissue disease
MI myocardial infarction
MPA microscopic polyangiitis
MRA magnetic resonance angiography
MSAs myositis-specific antibodies
MTP metatarsophalangeal
MTX methotrexate
NO nitric oxide
NO nitric oxide
NSAIDs non-steroid anti-imflammatory drugs
NSAIDsnonsteroidal anti-inflammatory drugs
OA osteoarthritis
PAN polyarteritis nodosa
p-ANCA perinuclear antineutrophil cytoplasmic antibody
PE pulmonary embolism
PIP proximal interphalangeal
PM polymyositis
PMN polymorphonuclear leukocyte
PMR polymyalgia rheumatic
PsA psoriatic arthritis
RA rheumatoid arthritis
ReA reactive arthritis
RFs rheumatoid factors
RS Reiter syndrome
RTA renal tubular acidosis.
sc subcutaneous
SEA syndrome seronegativity, enthesopathy, and arthropathy
SLE systemic lupus erythematosus
SpAs spondyloarthropathies
SPECT single-photon emission computed tomography
SS Sjögren syndrome
SSZ sulfasalazine
TAB temporal artery biopsy
TIA transient ischemic attack
TIMP tissue inhibitors of metalloproteinases
TLR Toll-like receptor
TNF tumor necrosis factor
UCTD undifferentiated connective-tissue disease
USpA undifferentiated spondyloarthropathy
WBC white blood cell
WG Wegener granulomatosis

Part 1.

ANKYLOSING SPONDYLITIS

Definition.

The spondyloarthropathies (SpAs) are a family of related disorders that includes ankylosing spondylitis (AS), Reiter syndrome (RS), reactive arthritis (ReA), psoriatic arthritis (PsA), spondyloarthropathy associated with inflammatory bowel disease (IBD), undifferentiated spondyloarthropathy (USpA), and, possibly, Whipple disease and Behçet disease.

Ankylosing spondylitis is the prototypical SpA and its name means "inflamed spine growing together." It has been designated by various names, including rheumatoid spondylitis in the American literature, *spondyloarthrite rhizomegalique* in the French literature, and the eponyms Marie-Strümpell disease and von Bechterew disease.The SpAs are linked by common genetics (human leukocyte antigen [HLA] class-I gene, *HLA-B27*) and a common pathology (enthesitis). Ankylosing spondylitis was the first disease to be linked with an HLA gene (1973). The first documented ankylosing spondylitis case was reported in 1691, although it may have been present in ancient Egyptians.

Pathophysiology

The SpAs are chronic inflammatory diseases involving the sacroiliac joints, axial skeleton, and to a lesser degree, peripheral joints and certain extra-articular organs, including the eyes, skin, and cardiovascular system. The etiology is unknown but involves the interaction of genetic and environmental factors.

The SpAs are associated strongly with *HLA-B27,* an HLA class-I gene. Several genotypic subtypes of *HLA-B27* are associated with the SpAs, with HLA-B*2705 having the strongest association. HLA-B*2702, *2703, *2704, and *2707 also are associated with ankylosing spondylitis. HLA-B27–restricted $CD8^+$ (cytotoxic) T cells may play an important role in bacterial-related SpAs such as ReA and RS.

Table 1.

Association of SpAs With *HLA-B27*

Population or Disease Entity	HLA-B27–Positive (%)
Healthy whites	8
Healthy African Americans	4
Ankylosing spondylitis (whites)	92
Ankylosing spondylitis (African Americans)	50
ReA/RS	60-80
Psoriasis associated with spondylitis	60
IBD associated with spondylitis	60
Isolated acute anterior uveitis	50
USpA	20-25

The shared amino acid sequence between the antigen-binding region of HLA-B27 and nitrogenase from *Klebsiella pneumoniae* supports molecular mimicry as a possible mechanism for the induction of SpAs in genetically susceptible hosts by an environmental stimulus, including bacteria in the gastrointestinal tract. In the presence of bacteria, *HLA-B27* transgenic rats develop an illness similar to the SpAs, with sacroiliitis, enthesitis, arthritis, skin and nail lesions, ocular involvement, and gastrointestinal tract involvement. Other genetic factors associated with ankylosing spondylitis include *HLA-B60* in both HLA-B27–positive and HLA-B27–negative individuals and *HLA-B39* in HLA-B27 negative individuals. The primary pathology of the SpAs is enthesitis with chronic inflammation, including $CD4^+$ and $CD8^+$ T lymphocytes and macrophages. Cytokines, in particular tumor necrosis factor-alpha (TNF-α) and transforming growth factor-beta (TGF-b), also are important in the inflammatory process by leading to fibrosis and ossification at sites of enthesitis.

Frequency

Ankylosing spondylitis is the most prevalent of the classic SpAs. Prevalence varies with the prevalence of the *HLA-B27* gene, which increases with distance from the equator. Ankylosing spondylitis is more common in whites than in nonwhites. Prevalence is *0.1-1%* of the general population, with the highest prevalence in northern European countries and the lowest in sub-Saharan Africa. Approximately *1-2%* of all people who are positive for *HLA-B27* develop ankylosing spondylitis. This increases to *15-20%* if they have a first-degree relative with ankylosing spondylitis. Prevalence data for undifferentiated spondylitis are scarce, although this disorder appears to be at least as com-

mon as ankylosing spondylitis, if not more so. Its actual prevalence may be as high as *1-2%* of the general population. The prevalence of ankylosing spondylitis in US is *0.1-0.2%* overall but is higher in certain Native American populations and lower in African Americans.

Mortality and Morbidity

The outcome in patients with SpAs, including ankylosing spondylitis, is generally good when compared to a disease such as rheumatoid arthritis. Many patients have few, if any, symptoms. A small minority of patients with chronic progressive disease develops disability due to spinal fusion, often with thoracic kyphosis or erosive disease involving peripheral joints, especially the hips and shoulders. Patients with spinal fusion are prone to spinal fractures that may result in neurologic deficits. Most functional loss in ankylosing spondylitis occurs during the first 10 years of illness. Patients with severe long-standing ankylosing spondylitis rarely may develop significant extra-articular manifestations such as cardiovascular disease, including cardiac conduction defects and aortic regurgitation; pulmonary fibrosis; neurologic sequelae (eg, cauda equina syndrome); or amyloidosis. Patients with severe long-standing ankylosing spondylitis have increased mortality compared to the general population. USpA appears to have a good-to-excellent prognosis, although some patients have chronic symptoms associated with functional disability. Erosive arthritis is very uncommon. Uveitis occasionally occurs and may be recurrent or chronic. Patients who develop sacroiliitis and spondylitis, by definition, have ankylosing spondylitis.

Race

Prevalence of ankylosing spondylitis parallels the prevalence of *HLA-B27* in the general population. Prevalence of *HLA-B27* and ankylosing spondylitis is higher in whites and certain Native Americans when compared to African Americans, Asians, and other nonwhite ethnic groups. USpA is not associated as strongly with *HLA-B27*, although it is more prevalent in whites than in nonwhite ethnic groups.

Sex and age particularities

Ankylosing spondylitis, in general, is diagnosed more frequently in males. Females, however, may have milder or subclinical disease. The male-to-female ratio of ankylosing spondylitis is 3:1. The male-to-female ratio of USpA is 1:3. The age of onset

of ankylosing spondylitis usually is from the late teens to age 40 years. Approximately 10-20% of all patients have onset of symptoms before age 16 years. Onset in persons older than 50 years is unusual, although diagnosis of mild or asymptomatic disease may be made at a later age. Age of onset of disease symptoms is 25 years in HLA-B27 positive and 28 years in HLA-B27 negative patients with a delay in diagnosis of 8.5 years in HLA-B27 positive and 11.4 years in HLA-B27 negative patients. USpA generally is found in young to middle-aged adults but can develop from late childhood into the fifth decade of life.

History of USpA

General symptoms

Symptoms include those related to inflammatory back pain, peripheral enthesitis, arthropathy, and constitutional and organ-specific extra-articular manifestations. Because ankylosing spondylitis is a systemic inflammatory disease, systemic features are common. Morning stiffness is characteristic, and fatigue is common. Fever and weight loss may occur during periods of active disease.

Inflammatory back pain

This is the most common symptom and the first manifestation in approximately 75% of patients. Symptoms associated with an inflammatory process include insidious onset occurring over months or years, generally with at least 3 months of symptoms before presentation. Symptoms include morning stiffness lasting at least 30 minutes, improvement of symptoms with moderate physical activity, and diffuse nonspecific radiation of pain into both buttocks. Patients often experience stiffness and pain that awakens them in the early morning hours, a distinctive symptom not generally found in patients with mechanical back pain. New criteria to define inflammatory back pain have been proposed; when all features are present, they have a sensitivity of 70.3% and specificity of 81.2%. These criteria include the following:

- Morning stiffness that lasts more than 30 minutes
- Improvement of back pain with exercise but not rest
- Nocturnal back pain during second half of the night only
- Alternating buttock pain

Acute onset of pain, exacerbation of symptoms with activity, and radicular radiation of pain suggest a mechanical or degenerative process such as disc disease. The

spinal disease starts in the sacroiliac joints (bilateral lumbosacral region). Most patients have mild chronic disease or intermittent flares with periods of remission. The spinal disease rarely is active persistently. Progression occurs from the lumbosacral region proximally, with ossification of the annulus fibrosus that results in fusion of the spine (bamboo spine).

Peripheral enthesitis and arthropathy

Peripheral musculoskeletal involvement occurs in 30-50% of all patients. Peripheral enthesitis is the basic pathologic process, involving inflammation at the site of insertion of ligaments and tendons on to bone. This often progresses from erosion and osteitis to ossification, resulting in telltale radiological signs of periosteal new bone formation. Sites commonly involved are the Achilles tendon insertion, the insertion of the plantar fascia on the calcaneus or the metatarsal heads, the base of the fifth metatarsal head, the tibial tuberosity, the superior and inferior poles of the patella, and the iliac crest. Other sites of involvement are the greater trochanter, ischial tuberosity, costochondral junctions, distal scapula, lateral epicondyle, and distal ulna. Enthesopathic lesions tend to be quite painful (eg, the plantar fascia when getting out of bed), especially in the morning. Some of the peripheral arthritis occurs at sites in which the major component is local enthesitis as suggested by MRI. Joint involvement tends to occur most commonly in the hips, shoulders, and joints of the chest wall, including the acromioclavicular and sternoclavicular joints, and often occurs in the first 10 years of disease. Involvement of the hips and shoulders may result in joint damage with radiographic changes. Other peripheral joints are involved less frequently and to a milder degree, usually as an asymmetric oligoarthritis predominantly involving the lower extremities. Temporomandibular joints occasionally may be involved.

Physical examination

Articular manifestations

Spine

Stiffness of the spine and kyphosis resulting in a stooped posture are characteristic of ankylosing spondylitis at advanced stages. Earlier in the course of the disease, indirect evidence of sacroiliitis and spondylitis may be observed, including tenderness of the sacroiliac joints (elicited by either direct pressure or indirect compression) or a li-

mited range of spine motion. Some patients may have a deformity of the spine, most commonly with a loss of lumbar lordosis and accentuated thoracic kyphosis. The range of motion of the lumbar spine can be assessed using various methods, of which the Schober test is the most popular. This test is not specific for ankylosing spondylitis. Perform the Schober test by marking a 10-cm length of the lumbar spine (with patient in the erect position), starting at the fifth lumbar spinous process. Instruct the patient to maximally flex his or her spine. Remeasure the distance between the marks. Normal flexion increases the distance by at least 5 cm. Loss of chest expansion (<3-cm difference between minimum and maximum chest diameter) usually is found only in patients with late-stage disease and, generally, is not helpful in making a diagnosis.

Peripheral entheses and joints

Peripheral enthesitis occurs in approximately 33% of patients. These lesions are painful and tender upon examination and may be associated with swelling of the tendon or ligament insertion. The most common and characteristic peripheral sites of enthesitis are the insertion of the Achilles tendon on the calcaneus and the insertion of the plantar fascia on the calcaneus. Certain anatomic areas may be more prone to enthesitis due to biomechanical stress. Carefully examine patients for tenderness upon palpation. Enthesitis and synovitis account for some of the peripheral joint involvement. Peripheral joint disease occurs in 33% of patients, most commonly in the hips. Hip involvement usually occurs in the first 10 years of the disease course and typically is bilateral. Other joints may be involved, including the shoulder girdle (glenohumeral, acromioclavicular, sternoclavicular joints), costovertebral joints, costosternal junctions, manubriosternal joints, symphysis pubis, and temporal mandibular joints. Other peripheral joints uncommonly are involved and, if so, in an asymmetric oligoarticular pattern. Dactylitis (sausage digit) is very uncommon in patients with ankylosing spondylitis. Isolated small-joint involvement of the hands, feet, or dactylitis strongly suggests Reiter syndrome (RS), reactive arthritis (ReA), psoriatic arthritis (PsA), or undifferentiated spondyloarthropathy (USpA). Destructive arthropathy may affect the hips or shoulder girdle, which may result in limited range of motion and flexion deformities.

Extraarticular manifestations

Uveitis (also called iritis or iridocyclitis)

Uveitis is the most common extra-articular manifestation, occurring in 20-30% of patients with ankylosing spondylitis. Of all patients with acute anterior uveitis, 30-50% have or will develop ankylosing spondylitis. The incidence is much higher in individuals who are HLA-B27–positive (84-90%). Patients with uveitis may also have or develop other spondyloarthropathies (SpAs), although less commonly, including RS (5-10%), USpA (2-5%), and PsA (<1%). Isolated inflammatory bowel disease (IBD) is also associated with uveitis. The uveitis associated with ankylosing spondylitis is usually acute in presentation and unilateral, with symptoms that include a painful red eye with photophobia, increased lacrimation, and blurred vision. The involvement is usually anterior, rarely involving posterior elements. Attacks usually resolve over 2-3 months with treatment and without residual visual impairment unless treatment is inadequate or delayed. Recurrences are common. Uveitis that develops in RS is similar to the uveitis that develops in ankylosing spondylitis, while uveitis that develops in PsA and SpA associated with IBD tends to be more chronic and bilateral and often involves posterior elements.

Cardiovascular involvement

Cardiovascular involvement of clinical significance occurs in fewer than 10% of patients, typically those with severe long-standing disease. However, subclinical disease can be detected in many patients and may occur as an isolated clinical entity in association with *HLA-B27*. Aortitis of the ascending aorta may lead to distortion of the aortic ring, resulting in aortic valve insufficiency. Mitral valve insufficiency rarely occurs. Fibrosis of the conduction system may result in various degrees of atrioventricular block, including complete heart block.

Pulmonary involvement

Restrictive lung disease may occur in patients with late-stage ankylosing spondylitis, with costovertebral and costosternal involvement causing limited chest expansion. Bilateral apical pulmonary fibrosis rarely occurs in the setting of severe disease. These lesions may cavitate and become colonized by bacteria or fungi (eg, *Aspergillus*), resulting in cough, dyspnea, and hemoptysis.

Renal involvement

Amyloidosis is a very rare complication of ankylosing spondylitis in patients with severe, active, and long-standing disease. These patients generally have active spondylitis, active peripheral joint involvement, and an elevated erythrocyte sedimentation rate (ESR) and C-reactive protein level. This may result in renal dysfunction with proteinuria and renal insufficiency or failure. Immunoglobulin A (IgA) nephropathy has been reported in association with ankylosing spondylitis.

Neurologic involvement

Neurologic complications may occur secondarily to fractures of a fused spine, which may be very difficult to detect with standard radiographs. Patients also are prone to atlantoaxial subluxation, which may result in cervical myelopathy. Cauda equina syndrome also may occur in patients with severe long-standing disease.

Gastrointestinal involvement

Asymptomatic inflammation of the proximal colon and terminal ileum has been observed in as many as 60% of patients with ankylosing spondylitis and USpA. Patients with established ankylosing spondylitis develop Crohn disease or ulcerative colitis only rarely.

Metabolic bone disease

Although ankylosing spondylitis is associated with new bone formation at sites of spinal and peripheral enthesitis, osteopenia and osteoporosis have been documented in patients with long-standing spondylitis, resulting in an increased risk of fracture. Reevaluate patients with ankylosing spondylitis who have severe spondylitis and who present with acute exacerbations of back or neck pain for possible fracture, especially in the setting of trauma. Standard radiographs may not be revealing; CT scan or MRI may be required to aid in diagnosis. Heterotopic bone formation may occur after total hip replacement.

Ankylosing spondylitis in women

Clinical ankylosing spondylitis is more common in men than in women, with a male-to-female ratio of approximately 3:1. Based on radiographic survey studies, prevalence rates of ankylosing spondylitis are approximately equal in men and women. Studies of clinical manifestations of ankylosing spondylitis in men and women show simi-

lar clinical manifestations, although men have more severe radiographic changes in the spine and hips than women.

Juvenile ankylosing spondylitis

Juvenile ankylosing spondylitis is clinically similar to adult ankylosing spondylitis. Approximately 10-20% of all cases have onset of symptoms before age 16 years. The male-to-female ratio of 3:1 is similar to that of adults. Enthesitis is prominent early in the course of the disease, while spinal symptoms and limitation of motion may not be present until several years later. Peripheral arthritis, especially in the lower extremities, and dactylitis are more common in children than in adults. Systemic manifestations (eg, fever, weight loss, anemia, leukocytosis) occur at the onset of disease in children more frequently than at the onset of disease in adults. Initial radiographs of the sacroiliac regions and spine often are normal or difficult to interpret in children. These factors make a definitive diagnosis of ankylosing spondylitis difficult in children. In such cases, the presence of *HLA-B27* would be supportive of the diagnosis of an SpA. Researchers describe a syndrome of seronegativity, enthesopathy, and arthropathy (SEA) in children that is clinically similar to USpA. These children often develop ankylosing spondylitis over time, with typical radiographic changes, usually by early adulthood. A variant, ankylosing tarsitis, is described in children who present with enthesitis in the tarsal region. This can lead to ossification, which results in a characteristic radiographic appearance. When tarsal inflammation is part of the clinical picture in a child or adult, strongly consider one of the SpAs.

Undifferentiated spondyloarthropathy

USpA is a syndrome with features consistent with the SpAs, but the patients do not fulfill criteria for any specific SpA (Table 2). USpA may represent an early phase or incomplete form of ankylosing spondylitis or another SpA. In fact, several studies of USpA included many patients who probably should have been diagnosed with ankylosing spondylitis, RS, ReA, or IBD-associated SpA, which made the clinical description very ambiguous. However, more recent data suggest that these patients may represent a distinct disease entity based on demographic and clinical criteria. Although no specific criteria are identified, using modified Amor criteria can be helpful in confirming a clinical diagnosis.

Table 2.

Diagnostic Criteria for USpA Using Modified Amor Criteria

Inclusion Criteria	Points	Exclusion Criteria
Inflammatory back pain	1	Diagnosis of specific SpA
Unilateral buttock pain	1	Sacroiliitis on radiograph, grade 2
Alternating buttock pain	2	Precipitating genitourinary/GI infection
Enthesitis	2	Psoriasis
Peripheral arthritis	2	Keratoderma blennorrhagicum
Dactylitis (sausage digit)	2	IBD (Crohn disease or ulcerative colitis)
Acute anterior uveitis	2	Positive rheumatoid factor
HLA-B27–positive or family history of SpA	2	Positive antinuclear antibody, titer >1:80
Good response to nonsteroidal anti-inflammatory drugs	2	
Diagnosis of SpA with 6 or more points		

Distinguishing features of USpA

The age of onset has a very wide range, with the peak onset at approximately age 50 years. The male-to-female ratio is 1:3. The onset usually is insidious and, even after years of active disease, sacroiliitis and spondylitis are either absent or appear very mild on routine radiographs. Clinical manifestations include inflammatory back pain (90%), buttock pain (80%), enthesitis (85%), peripheral arthritis (35%), dactylitis (17%), and fatigue (55%). Extraarticular manifestations are uncommon, occurring in fewer than 10% of patients, and include acute anterior uveitis (1-2%), oral ulcers, rash, nonspecific IBD, pleuritis, and pericarditis. Laboratory studies generally are unremarkable except for the presence of an elevated ESR or C-reactive protein (36%). HLA-B27 antigen is positive only in approximately 20-25% of patients.

These factors, especially the late age of onset, female predominance, and low *HLA-B27* positivity, suggest that USpA is distinct from ankylosing spondylitis and the other classic SpAs. In addition, when these patients are observed over long periods, they rarely develop clinical manifestations or radiographic changes that result in a change of diagnosis. Occasionally, radiographs show evidence of periosteal new bone formation at sites of enthesitis, especially at the insertion of the Achilles tendon or plantar fascia on the calcaneus, or early syndesmophytes on the lumbar spine without bridging.

Table 3.

Clinical and Laboratory Features of USpA

Clinical Feature of USpA	Frequency (%)
Inflammatory back pain	90
Unilateral buttock pain	80

Fatigue	55
Enthesitis	75
Peripheral arthritis	40
Dactylitis (sausage digit)	20
Acute anterior uveitis	1-2
HLA-B27–positive or family history of SpA	25
Elevated ESR	32

Although most patients with USpA have chronic, active disease and require long-term therapy, some patients with USpA have mild and intermittent symptoms that require intermittent symptomatic therapy. These episodes may last from 1-2 weeks to several months, with long asymptomatic periods that do not require therapy. Most patients (>75%) require long-term therapy for ongoing symptomatic disease. Most patients respond well to nonsteroidal anti-inflammatory drugs (NSAIDs). Most patients maintain good function without progressive disease or clinically significant radiographic changes. A small minority of patients does not respond well to or tolerate NSAIDs. In these patients, treatment progression is similar to patients with ankylosing spondylitis, including the use of sulfasalazine, methotrexate, and TNF-a, although no well-designed clinical trials have been conducted on the treatment of USpA.

The main causes of USpA

The cause of ankylosing spondylitis is unknown, but a combination of genetic and environmental factors work in concert to produce clinical disease.

Genetic predisposition

The strong association of ankylosing spondylitis with *HLA-B27* and a lesser association with *HLA-B60* and *HLA-B39* is direct evidence of the importance of genetic predisposition. The shared amino acid sequence between several *HLA-B27* genotypic subtypes and K. pneumoniae nitrogenase, especially HLA-B*2705, suggests a link between these enteric bacteria and the induction of ankylosing spondylitis that has yet to be proven. People who are homozygous for HLA-B27 are at an increased risk for ankylosing spondylitis compared with those who are heterozygous. The amino acid sequence of the *HLA-B27* molecule is located in the antigen-binding region. Thus, molecular mimicry may be the mechanism by which an environmental trigger (eg, Klebsiella) initiates immunologic and then pathologic changes in a genetically predisposed individual.

Immunologic mechanisms

Another possible mechanism in the induction of ankylosing spondylitis is presentation of an arthritogenic peptide from enteric bacteria by specific HLA molecules. Many patients with ankylosing spondylitis have subclinical gastrointestinal tract inflammation and elevated IgA antibodies directed against *Klebsiella*. The bacteria may invade the gastrointestinal tract of a genetically susceptible host, leading to chronic inflammation and increased permeability. Over time, bacterial antigens containing arthritogenic peptides enter the organism via the blood stream. Localization of pathology to certain types of connective tissues (eg, entheses) may be explained by affinity of bacterial antigens to these specific sites. Biomechanical stress, such as that which occurs at entheses in the spine and feet, may predispose to clinical enthesitis at these sites. The SpAs are the only known autoimmune diseases linked to a class-I and not a class-II HLA marker. The cytotoxic $CD8^+$ T-cell response appears to be important; it would respond to antigen presented by HLA class-I molecules on the surface of cells. The association of SpAs (eg, RS) with HIV infection in certain areas of the world supports the relative importance of the $CD8^+$ cytotoxic T-cell responses compared to the $CD4^+$ helper cells in these conditions.

Environmental factors

Ankylosing spondylitis does not develop in every person who is HLA-B27–positive, indicating that environmental factors are important. Even first-degree relatives who are HLA-B27–positive do not uniformly develop the disease. In fact, only 15-20% of such individuals develop the disease. HLA-B27–positive transgenic rats develop an illness similar to a SpA, with manifestations that include sacroiliitis, enthesitis, arthritis, skin and nail lesions, ocular inflammation, cardiac inflammation, and inflammation of the gastrointestinal and male genitourinary tracts. The severity of the clinical disease correlates with the number of copies of HLA-B27 expressed in the transgenic animal. If these HLA-B27–positive transgenic rats are raised in a germ-free environment, they do not develop clinical disease. Once introduced into a regular environment (ie, non–germ-free) and exposed to bacteria, the rats develop clinical manifestations of SpA.

Lab Studies

No laboratory tests are specific for ankylosing spondylitis. The diagnosis is made by combining clinical criteria of inflammatory back pain and enthesitis or arthritis with

radiological findings. Two sets of criteria, which are sensitive and specific, are available for diagnosis of spondyloarthropathies (SpAs) in general: the European Spondyloarthropathy Study Group (ESSG) criteria (Table 4) and the Amor criteria (Table 2). New York and Rome criteria (Table 5) are used widely for the diagnosis of ankylosing spondylitis. Approximately 15% of patients may present with a normochromic normocytic anemia of chronic disease. The ESR or C-reactive protein level is elevated in 75% of patients and may correlate with disease activity in some, but not all, patients.

Table 4

SpA Criteria

ESSG Criteria	Amor Criteria	Points
Inflammatory spinal pain or synovitis and one of the following:	Inflammatory back pain	1
Alternating buttock pain	Unilateral buttock pain	1
Enthesitis	Alternating buttock pain	2
Sacroiliitis	Enthesitis	2
IBD	Peripheral arthritis	2
Positive family history of SpA	Dactylitis (sausage digit)	2
	Acute anterior uveitis	2
	HLA-B27–positive or family history of SpA	2
	Good response to NSAIDs	2

Note: IBD - Inflammatory bowel disease

Alkaline phosphatase is elevated in 50% of patients, which indicates active ossification but does not correlate with disease activity. Creatine kinase (CK) occasionally is elevated but is not associated with muscle weakness. The serum IgA level may be elevated, correlating with elevated acute phase reactants.

HLA-B27

HLA-B27 positivity is present in 92% of white patients with ankylosing spondylitis and is present less commonly in patients of other ethnicities. Determining *HLA-B27* status is not a necessary part of the clinical evaluation. In patients suspected of having a SpA, determining *HLA-B27* status may help support the diagnosis, especially in populations with a low prevalence of HLA-B27.

Table 5.

Criteria for Diagnosis of Ankylosing Spondylitis

New York Criteria (1984)	Rome Criteria (1961)
Low back pain with inflammatory characteristics	Low back pain and stiffness for >3 months that is not relieved by rest
Limitation of lumbar spine motion in sagittal and frontal planes	Pain and stiffness in the thoracic region
Decreased chest expansion	Limited motion in the lumbar spine

Bilateral sacroiliitis grade 2 or higher	Limited chest expansion
Unilateral sacroiliitis grade 3 or higher	History of uveitis
Definite ankylosing spondylitis when the fourth or fifth criterion mentioned presents with any clinical criteria	Diagnosis of ankylosing spondylitis when any clinical criteria present with bilateral sacroiliitis grade 2 or higher

Imaging Studies

Standard radiographs

Radiographic studies are most helpful in establishing a diagnosis. In ankylosing spondylitis, sacroiliitis is usually bilateral, symmetric, and gradually progressive over years. The lesions progress from blurring of the subchondral bone plate to irregular erosions of the margins of the sacroiliac joints (pseudowidening) to sclerosis, narrowing, and finally, fusion. Erosions of the subchondral bone of the sacroiliac joint generally are seen earlier in the lower portion of the joint (because this portion is lined by synovium) and on the iliac side (due to the thinner cartilage covering this side of the joint). The spondylitis of ankylosing spondylitis starts in the lumbar or thoracolumbar spine and progresses proximally in a continuous fashion. The radiographic signs of ankylosing spondylitis are due to enthesitis, particularly of the annulus fibrosus. Early radiographic signs include squaring of the vertebral bodies caused by erosions of the superior and inferior margins of these bodies, resulting in loss of the normal concave contour of the anterior surface of the vertebral bodies. The inflammatory lesions at vertebral entheses may result in sclerosis of the superior and inferior margins of the vertebral bodies, called shiny corners (Romanus lesion). Ossification of the annulus fibrosus leads to the radiographic appearance of syndesmophytes, which, in ankylosing spondylitis, typically are marginal. Over time, development of continuous (bridging) syndesmophytes may result in a bamboo spine, which, essentially, is fused (Fig.1).

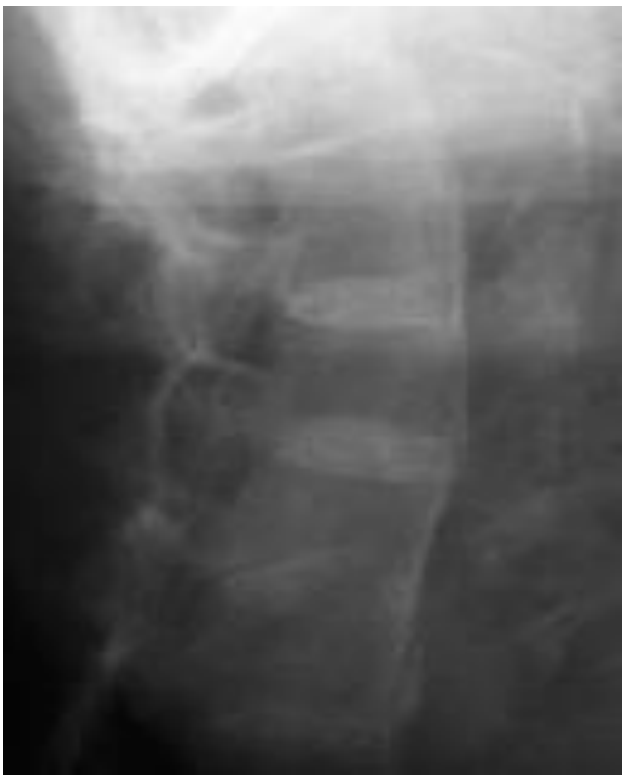
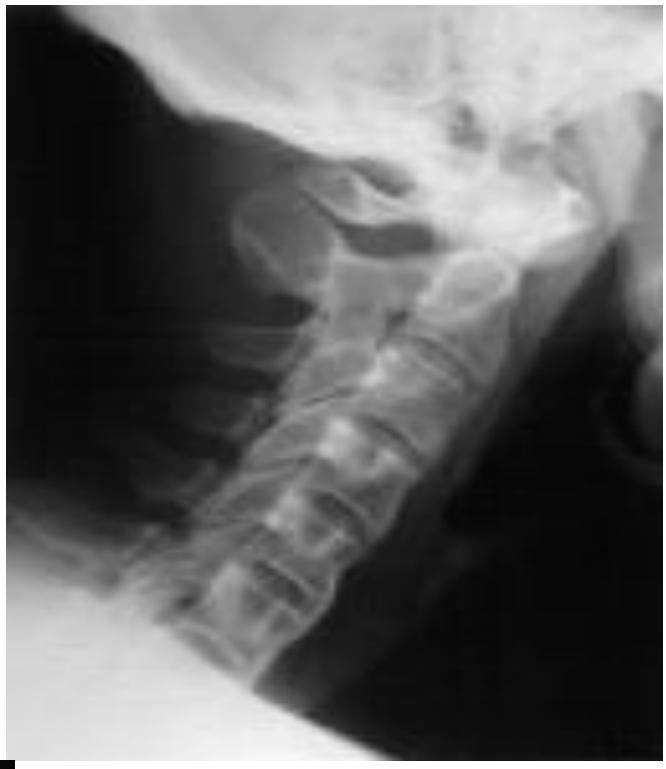


Figura 1

Radiograph of the lumbar spine of a patient with end-stage ankylosing spondylitis, associated with syndesmophytes, resulting in bamboo spine

Spinal disease associated with IBD is similar to ankylosing spondylitis with bilateral symmetric sacroiliitis and gradually ascending spondylitis and marginal syndesmophytes (Fig. 2). On the other hand, RS and PsA typically exhibit asymmetric sacroiliitis and discontinuous spondylitis with nonmarginal syndesmophytes.

Figura 2.



Radiograph of the cervical spine of a patient with ankylosing spondylitis. Fusion of vertebral bodies due to bridging syndesmophytes.

Radiographs of other areas may show evidence of enthesitis with osteitis or arthropathy. Radiographs of the pelvis may show ossification of various entheses, such as the iliac crest, ischial tuberosity, and femoral trochanter, which is termed whiskering (Fig.3).

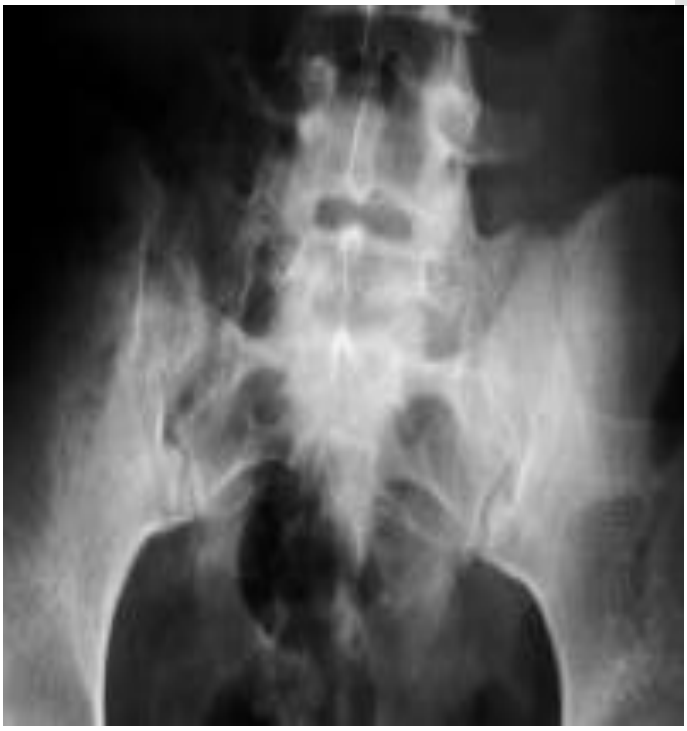


Figura 3.

Radiographs of the pelvis. Ossification of various entheses, such as the iliac crest, ischial tuberosity, and femoral trochanter

Occasionally, the symphysis pubis develops erosive changes (osteitis pubis). Peripheral entheses may develop radiographic changes, including erosion, periosteal new bone formation, and finally, ossification, especially in the feet at the insertion of the Achilles tendon and the plantar fascia on the calcaneus. Peripheral joint involvement is most common in the hips and shoulders and may result in uniform joint-space narrowing, cystic or erosive changes, and subchondral sclerosis without osteopenia. Heterotopic bone formation may occur after total joint replacement, especially in the hip. Ultimately, peripheral joints may undergo ankylosis.

Magnetic resonance imaging and computed tomography scan

Due to the insensitivity of standard radiographs in the clinical setting of acute back pain in advanced ankylosing spondylitis, an MRI and a CT scan may be useful in making the diagnosis of a spinal fracture in patients with late-stage spinal disease. MRI or CT scan of the sacroiliac and peripheral joints may reveal evidence of early sacroiliitis, erosions, and enthesitis that are not apparent on standard radiographs. MRI using fat-saturating techniques such as short tau inversion recovery (STIR) or MRI with gadolinium are sensitive for inflammatory lesions of enthesitis. However, they are not part of the routine evaluation of patients due to the expense of these studies.

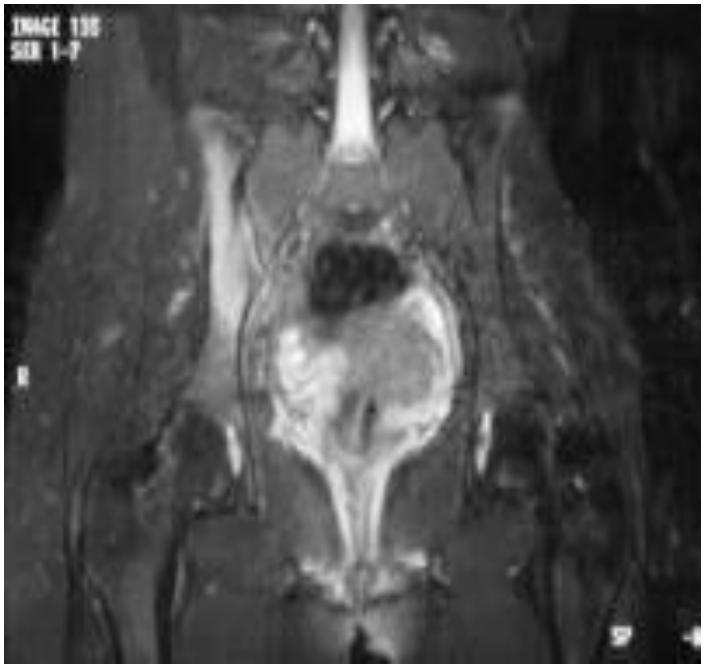


Figura 4.

Magnetic resonance imaging shows increased sinal intensity in the right sacroiliac joint, revealing sacroiliitis.

Histologic Findings

Histopathologic evaluation generally is not part of the diagnostic workup of patients with ankylosing spondylitis. The basic pathologic lesion is inflammation at the

enthesis (enthesitis), which occurs at the site of insertion of ligaments and tendons into bone. The histologic picture is that of chronic inflammation with $CD4^+$ and $CD8^+$ T lymphocytes and macrophages. Over time, fibrosis and ossification occur, which can be seen radiographically as periostitis and ossification at sites of enthesitis, particularly the sacroiliac joints, spine, and heels.

Quality of life assessment

Ankylosing spondylitis is a complex systemic rheumatological disease which often causes severe disability and impaired quality of life (QoL). Disease activity is one of the most powerful predictors of QoL, however latest advances in pharmacological treatment (namely, anti-TNF-α) along with physical exercise can minimize the effects of SpA on QoL. Psychological distress symptoms contribute to impaired QoL both directly and indirectly by influencing disease activity. The impact of other psychosocial variables, however, is less studied and more prospective investigations are necessary, which could eventually lead to the development of psychosocial interventions that are personalized to this patient population.

There are some scores with high validity of the quality of life assessement, i.e. Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and patient global visual analogue scale (VAS) scores.

Medical Care

Treatment of ankylosing spondylitis is divided into medical care, physical therapy, and surgical care. The goal of pharmacotherapy is to reduce morbidity and prevent complications.Patient education is important in the management of any chronic disease so that the patient is familiar with the symptoms, course, and treatment of the disease. No drugs have been proven to modify the course of the disease, although TNF-alpha antagonists have potential as disease-modifying agents (see additional materials).

Nonsteroidal anti-inflammatory drugs

NSAIDs improve the symptoms of the disease. Indomethacin may be more effective than other NSAIDs, although this has not been proven. Salicylates seldom give adequate relief. Cyclooxygenase-2 (COX-2) inhibitors appear to be as effective as nonselective NSAIDs. Give NSAIDs in full anti-inflammatory doses. Continuous treatment

with NSAIDs appears to reduce radiographic progression in ankylosing spondylitis. Common toxicities involve the gastrointestinal (nausea, dyspepsia, ulceration, bleeding), renal, and central nervous systems.

Sulfasalazine

Sulfasalazine is often used in the treatment of ankylosing spondylitis and other spondyloarthropathies (SpAs), especially for peripheral joint involvement, for which it has demonstrated efficacy. Sulfasalazine has been shown to be effective in ankylosing spondylitis, particularly in reducing spinal stiffness, peripheral arthritis, and reducing the ESR, but no evidence shows that spinal mobility, enthesitis, or physical function is benefited. Toxicities include rash, nausea, diarrhea, and agranulocytosis (rarely).

Other medications

Anecdotal reports suggest that other medications are helpful in the treatment of ankylosing spondylitis, including methotrexate, azathioprine, cyclophosphamide, and cyclosporine. Methotrexate may have some benefit in ankylosing spondylitis, although various studies have shown conflicting results.

The TNF-alpha antagonists have been shown to be effective in the treatment of ankylosing spondylitis, and etanercept, infliximab, and adalimumab are approved therapies. The TNF- alpha antagonists are biologic agents and include etanercept (fusion protein of the extracellular portion of the p75 TNF- alpha receptor and Fc portion of IgG), infliximab (chimeric anti–TNF-alpha monoclonal antibody [mab]), and adalimumab (humanized TNF- alpha mab). These agents inhibit TNF- alpha and have been shown to improve symptoms and function in patients with ankylosing spondylitis in clinical trials. All have been approved for the treatment of ankylosing spondylitis. These agents are also all approved for the treatment of rheumatoid arthritis (RA) and PsA (see additional materials). These agents are very effective with fairly rapid onset of action (2 weeks) and have been shown to reduce inflammatory activity of spinal disease as assessed with MRI.

Bisphosphonates may modestly affect clinical disease activity in ankylosing spondylitis.

Anakinra, a recombinant human interleukin 1 (IL-1) receptor antagonist, may be effective in treatment-resistant ankylosing spondylitis.

Corticosteroids

Oral corticosteroids occasionally are helpful in controlling symptoms; however, use them only for short-term management. No evidence exists that corticosteroids alter the outcome of the disease, and they increase the tendency towards spinal osteoporosis. Local corticosteroid injections are useful for symptomatic sacroiliitis, peripheral enthesitis, and arthritis, although the response typically is not as rapid as in patients with rheumatoid arthritis.

Treatment of extra-articular manifestations

Treat extra-articular manifestations as dictated by the clinical setting. Acute anterior uveitis presents as a painful, red eye that is associated with photophobia and often recurs. Untreated uveitis may lead to vision loss. Evaluation and treatment of uveitis should be delivered under the guidance of an ophthalmologist. Generally, patients respond well to topical corticosteroids, mydriatics, and artificial tears, with resolution of the attack over 2-3 months. Treatment may occasionally require topical NSAIDs, retrobulbar corticosteroid injections, or immunosuppressive drugs. TNF-alpha antagonists may be helpful in selected cases.

Surgical Care

Surgery occasionally is useful to correct spinal deformities or repair damaged peripheral joints. Vertebral osteotomy may be performed to correct spinal deformities, but significant morbidity is related to neurologic complications of this procedure. This procedure should be performed only by surgeons specializing in spine surgery who have experience with this procedure, as the risk of major neurologic morbidity is significant. Patients may need total hip replacement and, occasionally, total shoulder replacement. These procedures may be very useful to reduce pain and improve function when the hip and shoulder joints become severely damaged. Heterotopic bone formation may occur after total joint replacement, especially around the hip. Heterotopic bone formation can be reduced by using postoperative NSAIDs (eg, diclophenac, ibupropfen). In general, outcomes of total joint replacement in patients have been satisfactory.

Consultations

- Rheumatologist
- Physical medicine and rehabilitation specialist

- Orthopedic surgeon
- Neurosurgeon

Diet and physical therapy

No special diet is required. Physical therapy, including an exercise program and postural training, is important to maintain function. Spinal extension and deep-breathing exercises help maintain spinal mobility, encourage erect posture, and promote chest expansion. Maintaining an erect posture during daily activities and sleeping on a firm mattress with a thin pillow also tend to reduce the tendency towards thoracic kyphosis. Water therapy and swimming are excellent activities to maintain mobility and fitness.

Complications

Complications may occur from spinal and articular disease or extra-articular manifestations. A small minority of patients develop spinal fusion, which may result in severe kyphosis and limited motion of the spine, including the cervical region. The fused spine is more susceptible to fracture, even with relatively minor trauma. Occasionally, the hip and shoulder joints develop severe arthropathy, requiring total joint replacement. Extraarticular manifestations (eg, recurrent uveitis, cardiovascular involvement, pulmonary involvement, amyloidosis) rarely result in significant morbidity or mortality.

Prognosis for ankylosing spondylitis

Prognosis generally is good for ankylosing spondylitis and undifferentiated spondyloarthropathy (USpA). Patients often require long-term anti-inflammatory therapy. Morbidity can occur related to spinal and peripheral joint involvement or, rarely, extra-articular manifestations. Poor prognostic indicators include peripheral joint involvement, young age of onset, elevated ESR, and poor response to NSAIDs. Mortality is increased in patients with ankylosing spondylitis who have severe long-standing disease and significant extra-articular manifestations.

Patient Education with ankylosing spondylitis

Teach patients about the long-term nature of the illness, the use and toxicities of medications, and the importance of a well-balanced exercise program. Because of the joint involvement in the chest wall and the potential for pulmonary complications, include smoking cessation in recommendations.

Part 2.

PSORIATIC ARTHRITIS

In 1964, the American Rheumatism Association listed psoriatic arthritis as a clinical entity. However, diagnostic criteria have not been agreed on, and several proposed definitions have stressed separate features of this multifaceted disease. The high frequency of distal joint involvement in psoriatic arthritis compared with rheumatoid arthritis (RA) and arthritis mutilans (as an unusual but characteristic manifestation) has received special attention. The great variety of clinical manifestations was framed in the definition suggested by Moll and Wright in 1973, ie, "An inflammatory arthritis associated with psoriasis, usually with a negative sheep cell agglutination (SCA) test, ie, rheumatoid factor." Other more detailed criteria have been suggested. Psoriatic arthritis, a term used by the American Rheumatism Association, is widely accepted.

Pathophysiology

Psoriatic arthritis is an autoimmune disease with known human leukocyte antigen (HLA)–associated risk factors. Psoriatic arthritis affects the ligaments, tendons, fascia, and joints and occasionally develops in the absence of detectable psoriasis. Psoriatic arthritis may occur at higher frequencies when skin involvement is more severe, especially when pustular psoriasis is present; however, recent studies suggest that this may not be valid.

Frequency

Estimated rates of the frequency of psoriatic arthritis in persons with all types of psoriasis vary widely according to the nature of the diagnostic criteria and ascertainment used, but most fall into the range of 5-8%. Considering the rate of psoriasis to be 1-3%, the rate of psoriatic arthritis in the general white population ranges from 0.05-0.24%, a value approaching half that for seropositive RA. Psoriasis affects 2.5% of the white population of North America but is less prevalent in the African American and Native American populations. Psoriatic arthritis affects 5-8% of patients with psoriasis. Recent survey results indicate approximately 1 million US adults have psoriatic arthritis. This figure is significantly higher than researchers had previously believed and suggests

many people with psoriasis, a related skin disease, may not be aware that they have psoriatic arthritis.

Mortality and Morbidity

The course of psoriatic arthritis is usually characterized by flares and remissions. Arthritis mutilans is recognized as a typical but unusual form of psoriatic arthritis. Earlier studies have reported that psoriatic arthritis results in joint destruction and severe disability in a large proportion of patients. Of patients observed in a large outpatient psoriatic arthritis clinic, 7% required musculoskeletal surgery.

Race, sex and age particularities

Psoriatic arthritis is more common in white persons than in persons of other races. Men and women are affected equally; however, if the subsets of psoriatic arthritis are considered, male predominance occurs in the spondylitic form, whereas female predominance occurs in the rheumatoid form. Psoriatic arthritis characteristically develops in persons aged 35-55 years, but it can occur in persons of almost any age.

History of Psoriatic arthritis

Psoriatic arthritis may be present with or without obvious skin lesions, with minimal skin involvement (eg, scalp, umbilicus, intergluteal cleft), or with only nail malformations. Psoriasis usually precedes arthritis (occasionally by as many as 20 y); however, in as many as 15-20% of patients, arthritis appears before the psoriasis. If the latter is the case, a family history of psoriasis may reveal a hereditary pattern. Initial symptoms may be acute. When localized to the foot or toe, symptoms may be mistaken for gout. Alternatively, patients may experience only stiffness and pain with few objective findings.

The following list details the 5 patterns of psoriatic arthritis involvement:

- Asymmetrical oligoarticular arthritis
    - Until recently, this was thought to be the most common type.
    - Usually, the digits of the hands and feet are affected first, with inflammation of the flexor tendon and synovium occurring simultaneously, leading to the typical "sausage" appearance (dactylitis).
    - Usually, fewer than 5 joints are affected at any one time.

- Symmetrical polyarthritis

- Recently, this rheumatoidlike pattern has been recognized as one of the most common types. The hands, wrists, ankles, and feet may be involved.
- It is differentiated from rheumatoid arthritis (RA) by the presence of distal interphalangeal (DIP) joint involvement, the relative asymmetry, the absence of subcutaneous nodules, and a negative test result for rheumatoid factor (RF). This condition generally is milder than RA, with less deformity.

- Distal interphalangeal arthropathy
    - Although DIP joint involvement is considered classic and unique to psoriatic arthritis, it occurs in only 5-10% of patients, primarily men.
    - Involvement of the nail with significant inflammation of the paronychia and swelling of the digital tuft may be prominent, occasionally making appreciation of the arthropathy more difficult.

- Arthritis mutilans
    - Resorption of bone (osteolysis) with dissolution of the joint, observed as the "pencil-in-cup" radiographic finding, leads to redundant overlying skin with a telescoping motion of the digit.
    - This "opera-glass hand" is more common in men than in women and is more frequent in early-onset disease.

- Spondylitis with or without sacroiliitis
    - This occurs in approximately 5% of patients with psoriatic arthritis and has a male predominance.
    - Clinical evidence of spondylitis, sacroiliitis, or both can occur in conjunction with other subgroups of psoriatic arthritis.
    - Spondylitis may occur without radiologic evidence of sacroiliitis, which frequently tends to be asymmetric, or it may appear radiologically without the classic symptoms of morning stiffness in the lower back. Thus, the correlation between symptoms and radiologic signs of sacroiliitis can be poor.
    - Vertebral involvement differs from that observed in ankylosing spondylitis. Vertebrae are affected asymmetrically, and the atlantoaxial joint may be involved with erosion of the odontoid and subluxation.
    - Unusual radiologic features may be present, such as nonmarginal asymmetric syndesmophytes (characteristic), paravertebral ossification, and, less commonly, vertebral fusion with disk calcification.

- Juvenile psoriatic arthritis
    - Juvenile psoriatic arthritis accounts for 8-20% of childhood arthritis and is monoarticular at onset.
    - The mean age of onset is 9-10 years, with a female predominance. The disease is usually mild, although occasionally it may be severe and destructive, progressing into adulthood.

- In 50% of children, the arthritis is monoarticular; DIP joint involvement occurs at a similar rate.
- Tenosynovitis is present in 30% of children, and nail involvement is present in 71%, with pitting being the most common but least specific finding.
- In 47% of children, disordered bone growth with resultant shortening may result from involvement of the unfused epiphyseal growth plate by the inflammatory process.
- Sacroiliitis occurs in 28% of children and is usually associated with HLA-B27 positivity.
- Although the presence of HLA-B8 may be a marker of more severe disease, HLA-B17 is usually associated with a mild form of psoriatic arthritis.
- Children have a higher frequency of simultaneous onset of psoriasis and arthritis than adults, with arthritis preceding psoriasis in 52% of children.

Physical

Recognition of the patterns of joint involvement is essential to the diagnosis of psoriatic arthritis.

- Recently, the possibility that less joint tenderness occurs with psoriatic arthritis than with RA has been emphasized.
- The condition termed enthesopathy or enthesitis, reflecting inflammation at tendon or ligament insertions into bone, may be seen in psoriatic arthritis as in other spondyloarthropathies. This is observed more often at the attachment of the Achilles tendon and the plantar fascia to the calcaneus with the development of insertional spurs.
- Dactylitis with sausage digits is seen in as many as 35% of patients.
- Skin involvement includes the following:
    - Arthritis generally is not considered to correlate strongly to any particular type of psoriasis or to the severity of the skin disease. However, in one study, arthritis was noted more frequently in patients with severe skin disease, whereas in another, pustular psoriasis was associated with more severe psoriatic arthritis.
    - In patients presenting with an undefined seronegative polyarthritis, looking for psoriasis in hidden sites such as the scalp (where psoriasis frequently is mistaken for dandruff), perineum, intergluteal cleft, and umbilicus is extremely important.
    - A diagnosis of psoriatic arthritis may be missed because of an inadequate physical examination.

- Nail involvement includes the following:
    - Onycholysis, transverse ridging, and uniform nail pitting are 3 features of nail involvement that should be noted. A direct correlation exists between the number of pits and the diagnostic significance. When skin and joint

disease begin simultaneously, nail involvement is frequently present at the onset.
    - Involvement of DIP joints correlates moderately well with psoriasis in adjacent nails, although this is not an invariable association.
    - Nails are involved in 80% of patients with psoriatic arthritis but in only 20% of patients with uncomplicated psoriasis.
    - Severe deforming arthritis of the hands and feet is frequently associated with extensive nail involvement.
    - Fungal infection of the nails is the main consideration in the differential diagnosis in a patient with a seronegative polyarthritis.

- Extra-articular features include the following:
    - Extra-articular features are observed less frequently in patients with psoriatic arthritis than in those with RA. Patients with psoriatic arthritis have a predilection for synovitis to affect flexor tendon sheaths with sparing of the extensor tendon sheath; both are commonly involved in persons with RA. Subcutaneous nodules are rare in patients with psoriatic arthritis. If nodules are present in a patient who has psoriasis and arthritis, particularly if the RF titer is positive, they suggest the coincidental occurrence of psoriasis and RA.
    - Ocular involvement may occur in 30% of patients with psoriatic arthritis, including conjunctivitis in 20% and acute anterior uveitis in 7%. In patients with uveitis, 43% have sacroiliitis and 40% are HLA-B27–positive. Scleritis and keratoconjunctivitis sicca are rare.
    - Inflammation of the aortic valve root, which may lead to insufficiency, has been described in 6 patients with psoriatic arthritis and is similar to that observed more frequently in persons with ankylosing spondylitis or Reiter syndrome. Occasionally, patients may develop secondary amyloidosis.

- A large international study group recently developed a simple and highly specific classification known as CASPAR (classification criteria for psoriatic arthritis). These criteria were more specific (98.7% vs 96%) but less sensitive (91.4% vs 97.2%) than those of Vasey and Espinoza classification. The CASPAR criteria consist of established inflammatory articular disease with at least 3 points from the following features:
    - Current psoriasis (assigned a score of 2)
    - A history of psoriasis (in the absence of current psoriasis; assigned a score of 1)
    - A family history of psoriasis (in the absence of current psoriasis and history of psoriasis; assigned a score of 1)
    - Dactylitis (assigned a score of 1)
    - Juxtaarticular new-bone formation (assigned a score of 1)
    - RF negativity (assigned a score of 1)
    - Nail dystrophy (assigned a score of 1)

Causes

The pathogenesis of psoriatic arthritis remains unknown, but much information has been gathered. In addition to the genetic influences, environmental and immunological factors are thought to be prominent in the development and perpetuation of the disease. The de novo development or exacerbation of psoriasis and psoriatic arthritis in patients with human immunodeficiency virus (HIV) infection and CD4 deficiency remains controversial.

Psoriasis may remit following allogeneic bone marrow transplantation and may exacerbate with interferon-alfa treatment for hepatitis C.

- Genetics
    - Approximately 40% of patients with psoriasis or psoriatic arthritis have a family history of these disorders in first-degree relatives. The exact mechanism of the association between HLA and psoriatic arthritis is not clear.
    - Twin studies indicate a concordance rate among monozygotic twins of 35-70%, compared with 12-20% for dizygotic twins.
    - HLA-B17, -Cw6, -DR4, and -DR7 are found to occur with increased frequency in persons with either psoriasis or psoriatic arthritis when compared with the general population. The HLA-Cw*0602 variant is particularly associated with an early age of onset of psoriasis.
    - Psoriatic arthritis is associated with an increased frequency of HLA-B7 and HLA-B27 and a lower frequency of HLA-DR7 and HLA-Cw7.
    - HLA-B27 in the presence of HLA-DR7, HLA-DQ3 in the absence of HLA-DR7, and HLA-B39 are predictors for disease progression, whereas HLA-B22 is protective.
    - Additional loci that demonstrate association with psoriatic arthritis include the *MICA* (class I MHC chain-related) gene and microsatellite polymorphisms in the tumor necrosis factor (TNF) promoter.
    - In psoriasis, linkages with loci on 17q, 4q, and 6p have been reported in whole genome scans, with the strongest evidence for linkage on 6p.

- Immunologic factors
    - Certain immunoglobulin genes have also been suggested to be associated with psoriatic arthritis. Serum levels of immunoglobulin A and immunoglobulin G are higher in psoriatic arthritis patients, whereas immunoglobulin M levels may be normal or diminished.
    - Autoantibodies against nuclear antigens, cytokeratins, epidermal keratins, and heat-shock proteins have been reported in persons with psoriatic arthritis, indicating a humoral immune component of the disease.
    - The pathologic process of skin and joint lesions in psoriatic arthritis is an inflammatory reaction, and evidence also indicates autoimmunity, perhaps

mediated by complement activation. The inflammatory nature of the skin and joint lesions in psoriatic arthritis is demonstrated by synovial-lining cell hyperplasia and mononuclear infiltration, resembling the histopathologic changes of RA. However, synovial-lining hyperplasia is less, macrophages are fewer, and vascularity is greater in psoriatic arthritis compared with RA synovium.

- The cytokine profile for psoriatic arthritis reflects a complex interplay between T cells and monocyte macrophages. Type 1 helper T–cell cytokines (eg, TNF-alpha, interleukin [IL]–1 beta, IL-10) are more prevalent in psoriatic arthritis than in RA, suggesting that these 2 disorders may result from a different underlying mechanism.
- Several studies have shown a significant reduction in the number and percentage of $CD4^+$ T cells in the peripheral blood, whereas they are found throughout the skin lesions and synovium.
- Dendritic cells have been found in the synovial fluid of patients with psoriatic arthritis and are reactive in the mixed leukocyte reaction; the inference is that the dendritic cells present an unknown antigen to $CD4^+$ cells within the joints and skin of patients with psoriatic arthritis, leading to T-cell activation.
- Fibroblasts from the skin and synovia of patients with psoriatic arthritis have an increased proliferative activity and the capability to secrete increased amounts of IL-1, IL-6, and platelet-derived growth factors. Several studies suggest that cytokines secreted from activated T cells and other mononuclear proinflammatory cells induce proliferation and activation of synovial and epidermal fibroblasts.
- Psoriatic plaques in skin have increased levels of leukotriene B4. Injections of leukotriene B4 cause intraepidermal microabscesses, suggesting a role for this compound in the development of psoriasis.

- Infections
    - The temporal relationship between certain viral or bacterial infections and the development or exacerbation of psoriasis or psoriatic arthritis suggests a possible pathogenetic role for these organisms.
    - Pustular psoriasis is a well-described sequela of streptococcal infections. However, the response to streptococcal antigens by cells from patients with psoriatic arthritis is not different from that of cells from patients with RA, making the role of Streptococcus species in psoriatic arthritis doubtful.
    - Psoriasis and psoriatic arthritis have been reported to be associated with HIV infection and to be prevalent in some HIV-endemic areas. Although the prevalence of psoriasis in patients infected with HIV is similar to that in the general population, patients with HIV infection usually have more extensive erythrodermic psoriasis and patients with psoriasis may present with exacerbation of their skin disease after being infected with HIV.
- Trauma: A few studies have reported the occurrence of arthritis and acroosteolysis after physical trauma in patients with psoriasis.

Lab Studies

No specific diagnostic tests are available for psoriatic arthritis. Diagnosis of the disease is made based on clinical and radiologic criteria in a patient with psoriasis. The most characteristic laboratory abnormalities in patients with psoriatic arthritis are elevations of the erythrocyte sedimentation rate (ESR) and C-reactive protein level. The results from these laboratory tests help track the activity of the disease by measuring inflammation. An elevated ESR is usually found in approximately 40% of patients with psoriatic arthritis. Patients with psoriatic arthritis are typically seronegative for RF, although RF is detected in 5-9% of patients. RF testing is usually associated with a high false-positive rate; thus, RF-positive and RF-negative patients should undergo the same treatment. Antinuclear antibody titers in persons with psoriatic arthritis do not differ from those of age- and sex-matched control populations. In 10-20% of patients with generalized skin disease, the serum uric acid concentration may be increased and, on occasion, may predispose to acute gouty arthritis. Low levels of circulating immune complexes have been detected in 56% of patients with psoriatic arthritis but do not appear to parallel disease activity. Serum immunoglobulin A levels are increased in two thirds of patients with psoriatic arthritis and in one third of patients with psoriasis. Synovial fluid is inflammatory, with cell counts ranging from 5000-15,000/μL and with more than 50% of cells being polymorphonuclear leukocytes. Within the synovium, the infiltrate consists predominantly of T lymphocytes. Synovial fluid complement levels are either within reference ranges or increased, and glucose levels are within reference ranges.

Imaging Studies

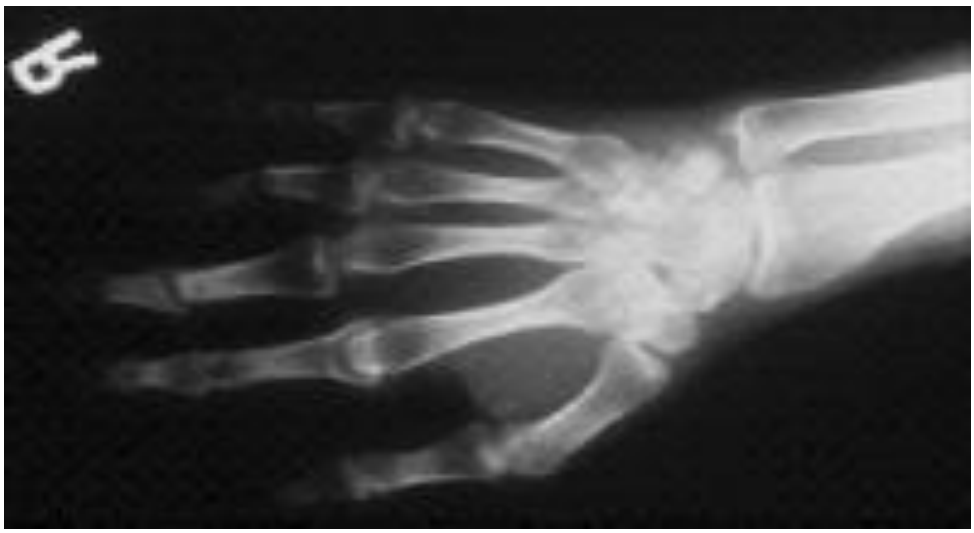
Radiological features have helped to distinguish psoriatic arthritis from other causes of polyarthritis. In general, the common subtypes of psoriatic arthritis, such as asymmetric oligoarthritis and symmetric polyarthritis, tend to result in only mild erosive disease. Early bony erosions occur at the cartilaginous edge, and, initially, cartilage is preserved, with maintenance of a normal joint space.

Juxta-articular osteopenia, which is a hallmark of rheumatoid arthritis (RA), is minimal in persons with psoriatic arthritis. Asymmetric erosive changes in the small joints of the hands and feet are typical of psoriatic arthritis and have a predilection (in

decreasing order) for DIP, proximal interphalangeal, metatarsophalangeal, and metacarpophalangeal joints (figura 5).

Figura 5

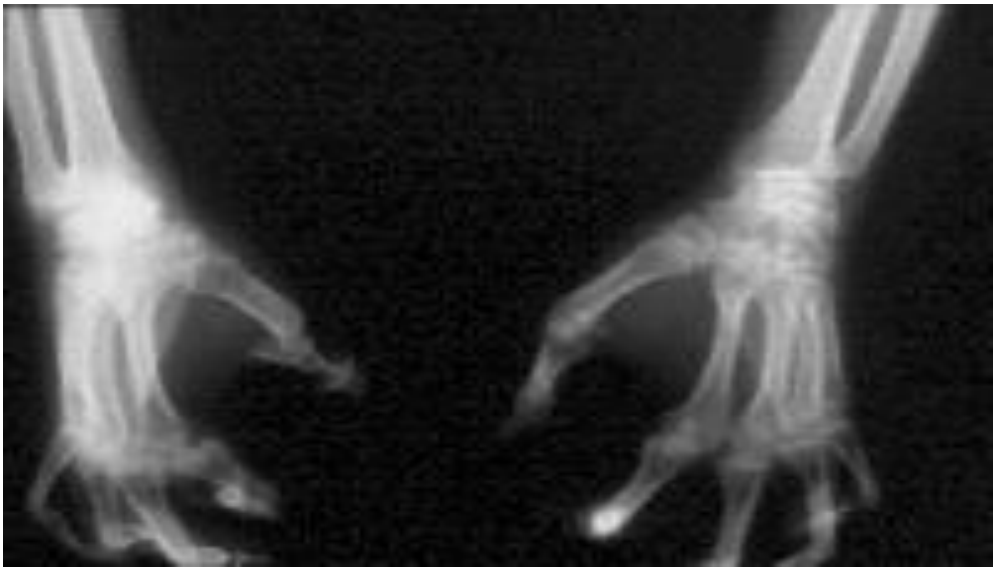
Psoriatic arthritis involving the distal phalangeal joint



Erosive disease frequently occurs in patients with either DIP involvement or progressive deforming arthritis and may lead to subluxation and, less commonly, bony ankylosis of the joint. Erosion of the tuft of the distal phalanx, and even the metacarpals or metatarsals, can progress to complete dissolution of the bone. Although this form of acroosteolysis is not diagnostic, it is highly suggestive of psoriatic arthritis. The pencil-in-cup deformity observed in the hands and feet of patients with severe joint disease usually affects the DIP joints but also may involve the proximal interphalangeal joints (figura 6).

Figura 6

Arthritis mutilans (ie, "pencil-in-cup" deformities).



CT scanning of the sacroiliac joint may be a sensitive method of visualizing involvement in patients with spondylitis or sacroiliitis. Recent studies have indicated that MRI may be a sensitive method for demonstrating the typical enthesopathic pathology of psoriatic arthritis, particularly in the hands and feet.

Other Tests

Traditional methods of monitoring patients with rheumatic conditions include clinical assessment for joint inflammation or damage and radiographic evaluations. The radiologic scoring methods for evaluating peripheral joints in persons with psoriatic arthritis were developed for patients with RA. A study validated the original Steinbrocker method, a modified Steinbrocker method, and the Larsen method for assessment of radiographs in patients with psoriatic arthritis. The latter 2 methods can now be used to assess disease progression in patients with psoriatic arthritis.

Histologic Findings

The histopathology of psoriatic synovitis is similar to that observed in other inflammatory arthritides, with a notable lack of intrasynovial immunoglobulin and RF production and a greater propensity for fibrous ankylosis, osseous resorption, and heterotopic bone formation.

Medical Care

The treatment of psoriatic arthritis is directed at controlling the inflammatory process. Although no clear correlation exists between the skin and joint inflammation in every patient, the skin and joint aspects of the disease often must be treated simultaneously.

Initial treatment includes nonsteroidal anti-inflammatory drugs (NSAIDs) for joint disease and topical therapies for the skin. In many patients, this approach is sufficient to control disease manifestations, although some patients have a worsening of psoriasis with NSAIDs. In these patients, a drug belonging to a different family of NSAIDs should be used.

Intra-articular injection of entheses or single inflamed joints with corticosteroids may be particularly effective in some patients. Use disease-modifying drugs in individuals whose arthritis is persistent. If the skin disease is well controlled with topical

medication, the joint disease can be treated with a variety of second-line or cytotoxic drugs. Intramuscular administration of gold has been used in the past but has been supplanted by newer disease-modifying antirheumatic drugs.

In patients with severe skin inflammation, medications such as methotrexate (MTX), retinoic-acid derivatives, and psoralen plus UV light should be considered. These medications have been shown to work for both skin and joint manifestations. Sulfasalazine and cyclosporine are two second-line agents that have received particular attention in the management of psoriatic arthritis. Although these drugs may control the acute inflammation in persons with psoriatic arthritis, they have not been helpful in arresting the progression of clinical and radiologic damage. Thus, the disease must be treated earlier or better drugs are necessary to prevent the damage that may ensue as a result of psoriatic arthritis.

Cyclosporine appears to be an effective agent for the treatment of psoriasis and psoriatic arthritis.

The major concern with cyclosporine is its toxicity, especially nephrotoxicity and hypertension. Combination therapy (eg, MTX/sulfasalazine, MTX/cyclosporine) may be more efficacious in some patients.

The use of biologic response modifiers that target TNF and other cytokines represents an advance in the treatment of several diseases involving autoimmune mechanisms. Several such agents have been developed, in the form of either soluble fusion proteins (eg, etanercept) or monoclonal antibodies (eg, infliximab, adalimumab), which have shown considerable efficacy in the treatment of rheumatoid arthritis (RA) and other autoimmune diseases.

Etanercept is approved by the US Food and Drug Administration for treating adult patients (age $\geq$18 y) with chronic, moderate-to-severe plaque psoriasis; reducing the symptoms and signs of moderate-to-severe polyarticular-course juvenile RA and ankylosing spondylitis; and reducing the signs and symptoms and inhibiting the progression of structural damage associated with psoriatic arthritis. Therefore, etanercept may be an effective and safe alternative monotherapy for the treatment of psoriatic arthritis.

Infliximab (Remicade) is another TNF-neutralizing agent that has been approved for the treatment of Crohn disease, ulcerative colitis, RA (in combination with MTX), ankylosing spondylitis, and psoriatic arthritis. It has shown successful results in reducing the signs and symptoms of psoriatic arthritis. However, the Food and Drug Administration issued safety warnings for infliximab concerning worsening heart failure in patients with moderate-to-severe congestive heart failure and opportunistic infections such as tuberculosis, histoplasmosis, listeriosis, and pneumocystosis. The effects of other anti-TNF medications on psoriasis and psoriatic arthritis are being studied. A recent randomized 6-month study by Scarpa et al (2007) showed the early use of MTX in patients with early psoriatic arthritis markedly improved tender and swollen joints and/or entheses; however, no significant difference was found after 3 months of treatment with NSAIDs or MTX. These results suggest that other therapeutic approaches capable of modifying the early course of the disease should be used.

Several other modalities have been tried in persons with psoriatic arthritis, including vitamin-D3, bromocriptine, peptide T, and fish oils, but their efficacy remains to be proven. Antimalarials, particularly hydroxychloroquine (Plaquenil), are usually avoided in patients with psoriasis for fear of precipitating exfoliative dermatitis or exacerbating psoriasis. Two studies showed that these reactions did not occur in patients treated with hydroxychloroquine; therefore, it is occasionally used to treat psoriatic arthritis. Systemic corticosteroids are usually avoided because of possible rebound of the skin disease upon withdrawal.

Surgical Care

Arthroscopic synovectomy has been effective in treating severe chronic monoarticular synovitis. Because of the enhanced tendency for fibrosis associated with this therapy, anti-inflammatory and physical therapy measures aimed at improving range of motion are important adjuncts to this intervention. Joint replacement and forms of reconstructive therapy are occasionally necessary.

Diet

For people who have morning stiffness, the optimal time for taking an NSAID might be after the evening meal and again upon awakening. Taking NSAIDs with food can reduce stomach discomfort. Any NSAID can damage the mucous layer and cause

ulcers and GI bleeding when taken for long periods. Cyclooxygenase (COX)–2 selective inhibitors are associated with a lower prevalence of gastric ulcer formation.

Activity

- Exercise
  - Exercise is an important part of the total treatment to limit the pain and swelling of arthritis, which can make joints stiff and hard to move.
  - A directed exercise program can improve movement, strengthen muscles to stabilize joints, improve sleep, strengthen the heart, increase stamina, reduce weight, and improve physical appearance.
- Rest
  - Generally, a normal amount of rest and sleep is sufficient to decrease fatigue and reduce joint inflammation.
  - In a very few people, psoriatic arthritis may cause extreme fatigue.

Further Outpatient Care

Heat and cold treatments can temporarily relieve pain and reduce joint swelling. Examples of treatments include soaking in a warm tub or placing a warm compress or cold pack on the painful joint.

Deterrence/Prevention

A number of medications cause an exacerbation of psoriasis; therefore, avoidance of these medications may help prevent or minimize flare-ups. Lithium and withdrawal from systemic corticosteroids are well known to cause flares of disease. Beta-blockers, antimalarials, and NSAIDs have also been implicated.

Complications

Until recently, psoriatic arthritis was generally believed to be a mild disease, with severe joint deformity and destruction (called arthritis mutilans) occurring in only approximately 5% of patients. This severe condition usually occurs in the small joints of the hands and feet. Some reports now suggest that arthritis mutilans may occur in as many as 16% of patients and that it may be as severe as rheumatoid arthritis (RA). Atlantoaxial subluxation with attendant neurological complications can occur. Rarely, patients with psoriatic arthritis may develop aortic insufficiency.

Prognosis

- Until recently, psoriatic arthritis generally had been considered a milder disease than RA. The following factors influence the degree of severity:
  - Clinical subset (eg, arthritis mutilans, symmetric polyarthritis)
  - Early age of onset

- Severity of skin involvement
- Female sex
- Family history of arthritis
- HLA marker: Patients with HLA-B39 and HLA-B27 in the presence of HLA-DR7 are more likely to experience disease progression, while those with HLA-B22 or HLA-DQw3 in the presence of HLA-DR7 may be protected from disease progression.
- ESR of greater than 15 mm/h, medication use before the first clinical visit, evidence of radiologic damage, and absence of nail lesions: These factors have been associated with increased mortality.

New evidence suggests that psoriatic arthritis may be as disabling and destructive as RA when the appropriate comparisons are made; thus, treatment should be aggressive in those individuals with progressive joint disease.

Part 3.

REACTIVE ARTHRITIS

In 1916, Hans Reiter described a triad of nongonococcal urethritis, conjunctivitis, and arthritis in a young German officer who had a bout of bloody dysentery. In 1916, Fiessinger and Leroy described 4 patients with what they called oculo-urethro-synovial syndrome and associated the syndrome with an outbreak of *Shigella* dysentery. Since then, many cases of what is now known as reactive arthritis (ReA) have been described. The older term Reiter's syndrome, used in the past to describe the same clinical presentations, is being used less frequently. This is because Reiter was a physician leader of the Nazi party in Germany during World War II and authorized medical experiments on concentration camp prisoners. The syndrome has been associated with gastrointestinal infections with *Shigella, Salmonella,* and *Campylobacter* species and other microorganisms, along with genitourinary infections (especially with *Chlamydia trachomatis*). Outbreaks of enteric Reiter syndrome have been reported aboard military vessels, cruise ships, and vessels transporting immigrants to the United States. In 1967, the term reactive arthritis was first used in cases associated with *Yersinia* gastroenteritis. A strong association with human leukocyte antigen (HLA)–B27 was found. This finding helped to confirm the concept of an incomplete Reiter syndrome, in which arthritis can occur in the absence of urethritis and conjunctivitis. Because of the association with HLA-B27 and its clinical overlap with ankylosing spondylitis and psoriatic arthritis, reactive arthritis is classified as a type of seronegative spondyloarthropathy. In this article, reactive arthritis encompasses the older concepts of complete and incomplete Reiter syndrome and a clinical syndrome of arthritis with or without extra-articular features following within 1 month of infectious diarrhea or genitourinary infection.

Pathophysiology

Reactive arthritis usually develops 2-4 weeks after a genitourinary or gastrointestinal infection. Recent evidence indicates that a preceding respiratory infection with *Chlamydia* may also trigger the disease. About 10% of patients do not have a preceding symptomatic infection. Inflammation of joints, entheses, axial skeleton, skin, mucous membranes, gastrointestinal tract, and eyes may occur. HLA-B27 is positive in 65-96% of patients (75% on average). Patients who are HLA-B27 positive have about a 50-fold

increased chance of developing reactive arthritis, but this syndrome can occur in patients who are HLA-B27 negative. Patients with HLA-B27, as well as those with a strong family clustering of the disease, tend to develop more severe and long-term disease. The frequency of reactive arthritis after enteric infection averages 1-4% but varies greatly, even among outbreaks of the same organism. The mechanism of the interaction of the inciting organism with the host (often HLA-B27 positive) leading to the development of reactive arthritis is not known. Synovial fluid cultures are negative for enteric organisms or *Chlamydia* species. However, a systemic and intrasynovial immune response to the organisms has been found with intra-articular antibody and bacterial reactive T cells. Furthermore, bacterial antigen has been found in the joints. Thus, the elements for an immune-mediated synovitis are present.

Molecular evidence of bacterial DNA (by polymerase chain reaction [PCR]) in synovial fluids has been found only in *Chlamydia*-related reactive arthritis, and one placebo-controlled trial of a tetracycline derivative (ie, lymecycline) showed a reduction in the duration of acute *Chlamydia*-related, but not enteric-related, reactive arthritis. This suggests that persistent infection may play a role, at least in some cases of chlamydial reactive arthritis. In a more recent trial, the combination of doxycycline and rifampin was superior to doxycycline alone in reducing morning stiffness and swollen and tender joints in patients with undifferentiated spondyloarthropathy.

The role of HLA-B27 in this scenario remains to be defined but, as discussed elsewhere (Ankylosing Spondylitis and Undifferentiated Spondyloarthropathies), molecular mimicry, presentation of pathogenic peptides, or an altered host response to the bacteria are all possible. Reactive arthritis, including classic Reiter syndrome, can occur in patients infected with HIV or who have AIDS. This is likely because both conditions can be sexually acquired rather than being triggered by HIV. The course of the illness tends to be severe, with a generalized rash that resembles psoriasis, profound arthritis, and frank AIDS. The frequency of HLA-B27 is the same of that associated with non–AIDS-related reactive arthritis in a similar demographic group. This association points out the likely importance of $CD8^+$ cytotoxic T cells compared to $CD4^+$ helper T cells in the pathogenesis of reactive arthritis.

Frequency

In Finland, the annual incidence is about 30-40 cases per 100,000 adults, but this varies greatly among different geographic locations.

Mortality and morbidity

Reactive arthritis typically follows a self-limited course, with resolution of symptoms by 3-12 months, even in patients who are acutely incapacitated. However, the condition has a high tendency to recur, particularly with ocular and urogenital inflammation. Individuals who are HLA-B27 positive have a higher frequency of recurrence. A new infection or other stress factor could cause a reactivation of the disease. About 15% of patients develop a long-term, sometimes destructive, arthritis or enthesitis or spondylitis. In a study by Amor et al (1994), seven factors were analyzed as predictors of long-term outcome in spondyloarthropathies. The number of patients with reactive arthritis in this study was low, and a valid subgroup analysis was impossible. The presence of hip joint involvement, an erythrocyte sedimentation rate (ESR) higher than 30, and unresponsiveness to nonsteroidal anti-inflammatory drugs (NSAIDs) probably are predictive of a severe outcome or chronicity in reactive arthritis.

Race, sex and age particularities

Prevalence of HLA-B27 and reactive arthritis is higher in white people than in black people, as in other spondyloarthropathies. Reactive arthritis following food-borne enteric infections affects males and females with the same frequency. Disease associated with venereally acquired infections occurs in a male-to-female ratio of 9:1. Most patients are aged 20-40 years.

History of Reactive arthritis

Reactive arthritis usually develops 2-4 weeks after a genitourinary or gastrointestinal infection. Recent evidence indicates that a preceding respiratory infection with *Chlamydia pneumoniae* may also trigger the disease. About 10% of patients do not have a preceding symptomatic infection. Nongonococcal urethritis, if present, can be one of the presenting symptoms for both postvenereal and postenteric forms. Mild dysuria, mucopurulent discharge, prostatitis and epididymitis in men, and vaginal discharge and/or cervicitis in women can be observed. The onset is most often acute, with malaise, fatigue, and fever. An asymmetrical predominately lower extremity oligoarthritis is the

major presenting symptom. Low back pain occurs in 50% of patients. Heel pain is common because of enthesopathies at the Achilles or plantar aponeurosis insertion on the calcaneus. The complete Reiter triad of urethritis, conjunctivitis, and arthritis may occur.

Physical examination fidings

Joints, axial skeleton, entheses

Peripheral joint involvement is typically asymmetric and most frequently affects the weight-bearing joints (ie, knees, ankles, hips), but the shoulders, wrists, and elbows are also affected. In more chronic and severe cases, the small joints of the hands and feet can also be involved. Dactylitis (ie, sausage digits) can be observed, as in other spondyloarthropathies. While low back pain may be present in 50% of patients, most patients with acute disease have minimal findings on physical examination except for decreased lumbar flexion. Patients with more chronic and severe axial disease may develop physical findings similar to ankylosing spondylitis. As with other spondyloarthropathies, the enthesopathy of reactive arthritis may be associated with findings of inflammation (ie, pain, tenderness, swelling) at the Achilles insertion. Other sites include the plantar fascial insertion on the calcaneus, ischial tuberosities, iliac crests, tibial tuberosities, and ribs.

Skin and nails

Keratoderma blennorrhagica observed in the palms and soles is indistinguishable from pustular psoriasis and is very suggestive of chronic reactive arthritis. Erythema nodosum can be observed but is uncommon. Nails can become thickened and crumble, resembling mycotic infection or psoriatic onychodystrophy, but nail pitting is not observed. Circinate balanitis can also be observed. Other mucosal signs and symptoms: Painless shiny patches in the palate, tongue, and mucosa of the cheeks and lips have been described.

Ocular findings

Conjunctivitis is part of the classic triad of Reiter syndrome, and it can occur before or at the onset of arthritis. Other ocular lesions include acute uveitis (20% of patients), episcleritis, keratitis, and corneal ulcerations. The lesions have a tendency to recur.

Enteric infections

Enteric infections can be the triggering event for reactive arthritis. Pathogens include *Salmonella, Shigella, Yersinia,* and *Campylobacter* species. The frequency of reactive arthritis after these enteric infections is about 1-4%. Some patients continue with intermittent bouts of diarrhea and abdominal pain. Lesions resembling ulcerative colitis or Crohn disease have been described when ileocolonoscopy is performed in patients with established reactive arthritis.

Other manifestations

Other manifestations of the disease include mild renal pathology with proteinuria and microhematuria. In severe chronic cases, amyloid deposits and immunoglobulin A (IgA) nephropathy have been reported. Cardiac conduction abnormalities can be observed, and aortitis with aortic regurgitation occurs in 1-2% of patients.

Causes

Reactive arthritis is usually triggered by a genitourinary or gastrointestinal infection.

Lab Studies

Acute phase reactants, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are usually elevated markedly but later return to the reference range with subsidence of the inflammation. Other laboratory findings include a normocytic normochromic anemia along with mild leukocytosis and thrombocytosis during the acute phase. IgA antibodies to specific bacterial antigens have been reported. Urinalysis can show aseptic pyuria.

Synovial fluid analysis reveals a high white blood cell count, most often with elevated polymorphonuclear leukocytes acutely. Gram stain and culture results are negative and are necessary to exclude septic arthritis. Microbial components and antigens have been identified in joint fluid using sophisticated laboratory techniques. Throat, stool, or urogenital tract cultures can be performed in an attempt to isolate the causative organism. Other serologic techniques for the detection of *Chlamydia* species, including PCR, could be considered. Test results for rheumatoid factor and antinuclear antibodies are negative.

Imaging Studies

Early in the disease, no abnormalities are found on radiograph. In more advanced or long-term disease, periosteal reaction and proliferation at sites of tendon insertion can

be observed. Exuberant plantar spurs are a common sign in long-term cases. In the hands and feet, marginal erosions with adjacent bone proliferation occur. Spinal radiographic findings include sacroiliitis and syndesmophytes. Sacroiliitis occurs in less than 10% of acute cases but may be observed in 50% of those patients with chronic severe disease. Syndesmophytes are usually asymmetrical and are found most commonly in the thoracolumbar region. Severe ankylosing spondylitis occurs in less than 5% of cases.

Other Tests

An ECG should be performed in patients having a prolonged course of the disease to evaluate for conduction disturbances. HLA-B27 testing yields positive results in 65-96% of cases. HLA-B27 testing is not necessary in classic Reiter syndrome but may be helpful to support the diagnosis of reactive arthritis in patients with joint-restricted symptoms.

Procedures

Needle aspiration of a joint may be necessary to rule out septic or crystalline arthritis.

Medical Care

The treatment of reactive arthritis is modified according to the severity of symptoms.

Nonsteroidal anti-inflammatory drugs

NSAIDs are the foundation of therapy. These agents should be used on a regular basis to achieve a good anti-inflammatory effect. The choice of a specific agent depends on the individual response to treatment, although the general impression is that indomethacin has greater potency. Physical therapy needs to be implemented to help reduce pain and to avoid muscle wasting in severe cases.

- Corticosteroids

These agents can be used as either intra-articular injection or systemic therapy. Joint injections can produce long-lasting symptomatic improvement and help avoid the use of other systemic therapy. Sacroiliac joints can be injected, usually under fluoroscopic guidance. Systemic corticosteroids can be used, particularly in patients with poor response to NSAIDs or in those who develop adverse effects related to their use. The starting dose is guided by a patient's symptoms and objective evidence of inflammation. Prednisone 0.5-1 mg/kg/d can be used initially and tapered according to response.

Antibiotics

The current concepts on the pathogenesis of reactive arthritis indicate that an infectious agent is the trigger of the disease, but antibiotic treatment does not change the course of the disease, even when a microorganism is isolated. In these cases, antibiotics are used to treat the underlying infection, but specific treatment for reactive arthritis is lacking. However, in chlamydial-induced reactive arthritis, studies have suggested that appropriate treatment of the acute urogenital infection can prevent reactive arthritis and that treatment of acute reactive arthritis with a 3-month course of tetracycline reduces the duration of illness. No evidence indicates that antibiotic therapy benefits enteric-related reactive arthritis or chronic reactive arthritis of any cause.

Quinolones have been studied because of their broad coverage, but no beneficial effect has been noted. Lymecycline was studied in a double-blind placebo-controlled study of patients with chronic reactive arthritis for a treatment period of 3 months. Those patients with *Chlamydia*-induced disease had a significant decrease in duration of illness, as opposed to those with disease triggered by enteric infections. More studies are needed before definite recommendations can be made as to the role of antibiotics in the management of reactive arthritis.

Disease-modifying antirheumatic drugs

In patients with chronic symptoms or in patients with persistent inflammation despite the use of the agents mentioned above, other second-line drugs may be used. Clinical experience with these so-called disease-modifying antirheumatic drugs (DMARDs) has been mostly in rheumatoid arthritis and in psoriatic arthritis. DMARDs have also been used in reactive arthritis, although their disease-modifying effects in the reactive arthritis setting are uncertain.

Sulfasalazine can be beneficial in some patients. The use of this drug in reactive arthritis is of interest because of the finding of clinical or subclinical inflammation of the bowel in many patients. Sulfasalazine is more widely used in ankylosing spondylitis.

In patients who present with rheumatoid-like disease, methotrexate can be used. Several reports have shown good response, but controlled studies are lacking. Reports also describe the use of azathioprine and bromocriptine in reactive arthritis, but, again, large studies have not been published. Patients with reactive arthritis and HIV/AIDS should not be placed on methotrexate or other immunosuppressive agents.

Although biologic agents such as TNF-blockers have been demonstrated to be beneficial and formally approved for the treatment of psoriatic arthritis and ankylosing spondylitis, double-blind, randomized trials have not been performed to prove clinical benefit in reactive arthritis or in undifferentiated spondyloarthropathy. A recent uncontrolled study in patients with either undifferentiated spondyloarthropathy or reactive arthritis showed potential efficacy in symptom relief.

Surgical Care

No surgical treatment of reactive arthritis is recommended.

Consultations

A rheumatologist should be consulted for confirmation of diagnosis and formulation of management plan. Consultation with a urologist may be necessary if particularly prominent genitourinary manifestations develop. An ophthalmologist may be consulted to confirm the diagnosis and to treat the ophthalmologic manifestations of the syndrome.

Activity

Physical therapy may be instituted to avoid muscle wasting and to reduce pain. Activities should otherwise be as tolerated by the patient.

Further Inpatient Care

Hospitalization of a patient with uncomplicated reactive arthritis is not indicated.

Deterrence and prevention

Even when a causal microorganism is isolated, antibiotic therapy does not change the course of the disease.

Part 4.
OSTEOARTHRITIS

Osteoarthritis (OA) is the most common articular disease worldwide, affecting over 20 million individuals in the United Europa. Its high prevalence entails significant costs to society. Direct costs include physician visits, medications, and surgical intervention. Indirect costs include such items as time lost from work. Costs can be particularly significant for the elderly, who face potential loss of independence and who may need help with daily living activities. As the populations of developed nations age over the next few decades, the need for better understanding of OA and for improved therapeutic alternatives will continue to grow.

Pathophysiology of osteoarthritis

Traditionally, OA has been considered a disease of articular cartilage. The current concept holds that OA involves the entire joint organ, including the subchondral bone and synovium. OA has always been classified as a noninflammatory arthritis; yet, there is increasing evidence for inflammation occurring with cytokine and metalloproteinase release into the joint. Therefore, the term degenerative joint disease is no longer appropriate when referring to OA. The joints predominantly involved are weight bearing and include the knees, hips, cervical and lumbosacral spine, and feet. Other commonly affected joints include the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints of the hands. Cartilage is grossly affected. Focal ulcerations eventually lead to cartilage loss and eburnation. Subchondral bone formation occurs as well, with development of bony osteophytes.

Frequency of osteoarthritis

OA is the most common articular disease. Estimates vary among different populations.

Mortality and morbidity of osteoarthritis

Disease progression characteristically is slow, occurring over several years or decades. Pain is usually the initial and principal source of morbidity in OA. The patient can become progressively more inactive leading to morbidities related to decreasing physical activity including potential weight gain.

Race, sex and age particularities

Different prevalences have been cited for different ethnic groups. African American women appear to have a greater prevalence of knee OA than other groups. Prevalence increases with age. Equivalent prevalence occurs in men and women aged 45-55 years. After age 55 prevalence becomes greater in women. DIP and PIP joint involvement resulting in Heberden's and Bouchard's nodes is more common in women. OA can be defined epidemiologically (ie, using radiographic criteria) or clinically (eg, radiographs plus clinical symptoms). Radiographic criteria indicate that OA occurs in 30% of affected individuals aged 45-65 years and in more than 80% by their eighth decade of life, although most are asymptomatic.

History of octeoarthritis

- Pain
    1. This is the main reason patients seek medical attention.
    2. Initially, symptomatic patients incur pain during activity, which can be relieved by rest and may respond to simple analgesics.
- Morning stiffness in the joint usually lasts for less than half an hour.
- Stiffness at times of rest (gelling) may develop.
- Joints may become unstable with disease progression; therefore, the pain can become more prominent (even at times of rest) and may not respond to medications.

Physical examination findings

Physical examination findings are mostly limited to the affected joints. Malalignment with a bony enlargement (depending on the disease severity) may occur. In most cases, erythema or warmth over the joint does not occur; however, an effusion may be present. Limitation of joint motion or muscle atrophy around a more severely affected joint may occur.

Sources of pain in OA

- Joint effusion and stretching of the joint capsule
- Increased vascular pressure in subchondral bone
- Torn menisci
- Inflammation of periarticular bursae
- Periarticular muscle spasm
- Psychological factors
- Crepitus (a rough or crunchy sensation) may be palpated during motion of an involved joint.

Causes

Risk factors

- Age
- Obesity
- Female sex
- Trauma
- Infection
- Repetitive occupational trauma
- Genetic factors
- History of inflammatory arthritis
- Neuromuscular disorder
- Metabolic disorder

The etiopathogenesis of OA has been divided into the following 3 stages:

Stage 1: Proteolytic breakdown of the cartilage matrix occurs. Chondrocyte metabolism is affected, leading to an increased production of enzymes, which includes metalloproteinases (eg, collagenase, stromelysin) that destroy the cartilage matrix. Chondrocytes also produce protease inhibitors, including tissue inhibitors of metalloproteinases (TIMP) 1 and 2 but in amounts insufficient to counteract the proteolytic effect.

Stage 2: This stage involves the fibrillation and erosion of the cartilage surface, with a subsequent release of proteoglycan and collagen fragments into the synovial fluid.

Stage 3: The breakdown products of cartilage induce a chronic inflammatory response in the synovium. Synovial macrophage production of cytokines, such as interleukin 1 (IL-1), tumor necrosis factor-alpha, and metalloproteinases, occurs. These can diffuse back into the cartilage and directly destroy tissue or stimulate chondrocytes to produce more metalloproteinases. Other pro-inflammatory molecules (eg, nitric oxide [NO], an inorganic free radical) also may be a factor. Eventually, these events alter the joint architecture, and compensatory bone overgrowth occurs in an attempt to stabilize the joint. As the joint architecture is changed and further mechanical and inflammatory stress occurs on the articular surfaces, the disease progresses unchecked.

Lab Studies

No specific laboratory abnormalities are associated with OA. The acute-phase reactants and erythrocyte sedimentation rate are not elevated. Synovial fluid analysis usually indicates a white cell count less than 2000 per mm3 with a mononuclear predominance.

Imaging Studies

Radiography

- Conduct imaging studies of the affected joint.
- The presence of osteophytes (ie, spurs at the joint margins) is the most characteristic findings.
- Other findings include asymmetric joint space narrowing, subchondral sclerosis, and subchondral cyst formation.

Roentgenographic findings are often poor predictors of the degree of symptomatology in a particular patient.

Procedures

Arthrocentesis of the affected joint can help exclude inflammatory arthritis, infection, or crystal arthropathy.

Histologic Findings

Histologically, the earliest changes occur in the cartilage. Proteoglycan staining is diminished, and, eventually, irregularity of the articular surface with clefts and erosions occurs.

Medical Care

Nonpharmacologic interventions are the cornerstones of OA therapy and include patient education, temperature modalities, weight loss, exercise, physical therapy, occupational therapy, and joint unloading in certain joints (eg, knee, hip).

Reduction of joint stress

Instruct the patient to avoid aggravating stress to the affected joint. Implement correction procedures if the patient illustrates poor posture. Encourage obese patients to lose weight, thus taking stress off the affected knees or hips. Occupational adjustments may be necessary.

Physical therapy

In OA of the knee, disuse atrophy of the quadriceps may occur. These muscles help protect the articular cartilage from further stress. Instruct the patient to perform aerobic

and muscle-strengthening exercises. Hydrotherapy may be beneficial. Some patients find relief with heat and capsaicin cream placed locally over the affected joint, and a minority of patients proclaim relief with ice.

Pharmacologic therapy

The goals of treatment are pain alleviation and improvement of functional status. Presently, no proven practical medication-based disease/structure-modifying intervention exists. Begin treatment with acetaminophen for mild or moderate pain without apparent inflammation. If clinical response to acetaminophen is not satisfactory or if clinical presentation is inflammatory, consider nonsteroidal anti-inflammatory drug (NSAIDs). Use the lowest effective dose or intermittent dosing if symptoms are present intermittently and then try full doses if the patient's response is insufficient. Options in patients at an elevated risk for GI toxicity due to NSAIDs include the addition of a proton-pump inhibitor or misoprostol to the treatment regimen or the use of a selective cyclooxygenase inhibitor instead of the nonselective NSAID. In patients with highly resistant pain, consider the analgesic tramadol. Muscle relaxants may benefit patients with evidence of muscle spasm. Contemplate intraarticular injections of glucocorticoids to improve symptoms. It is recommended that no more than 4 glucocorticoid injections be administered to a single joint per year because of the concerns with long-term damage to cartilage. Do not use systemic glucocorticoids; they have no role in the management of OA. Intraarticular injections of hyaluronic acid (HA) are approved as symptomatic therapy of OA in the knee. Prescribe as a series of 3 or 5 injections (depending on the product). Each injection is administered 1 week apart. Consider judicious use of narcotics (eg, acetaminophen with codeine) only in patients with severe OA.

Recommendations for the medical management of OA of the hip and knee

In 1995, the American College of Rheumatology (ACR) published recommendations for the medical management of OA of the hip and knee. Those guidelines outlined the use of nonpharmacologic modalities, including patient education and physical and occupational therapy-the foundation of treatment of individuals with OA, as well as the use of pharmacologic agents. Specific recommendations for surgical management of OA, however, were not included. Since that time, several systematic reviews of drug therapy for OA have been published, and many clinical trials have been conducted

which have resulted in the approval, or pending review, by the Food and Drug Administration (FDA) of new devices and drug treatments for OA. In 1998, the ACR established an ad hoc subcommittee, comprising several of the American authors of the 1995 recommendations, to review interim developments in the field and update the recommendations. As in the original review, the subcommittee followed the 1905 principles of evidence-based medicine as used in the process of making clinical decisions. As stated by Guyatt, "Physicians practicing [evidence-based medicine] will search for the highest evidence available, integrate this evidence with their clinical experience and judgment, and acknowledge the value judgments implicit in moving from evidence to action"

The goals of the contemporary management of the patient with OA continue to include control of pain and improvement in function and health-related quality of life, with avoidance, if possible, of toxic effects of therapy. The recommended approach to the medical management of hip or knee OA includes nonpharmacologic modalities and drug therapy. The Subcommittee on OA Guidelines emphasizes that these recommendations are not fixed, rigid mandates, and recognizes that the final decision concerning the therapeutic regimen for an individual patient rests with the treating physician.

Nonpharmacologic modalities

The components of nonpharmacologic therapy are outlined in Table 6. Patient education and, where appropriate, education of the patient's family, friends, or other caregivers are integral parts of the treatment plan for patients with OA. Patients should be encouraged to participate in self-management programs, such as the Arthritis Foundation Self-Management Program. Individuals who participate in these programs report decreases in joint pain and frequency of arthritis-related physician visits, increases in physical activity, and overall improvement in quality of life. Additional educational materials, including videos, pamphlets, and news letters, are available from the Arthritis Foundation and other national voluntary health organizations. Another cost-effective nonpharmacologic approach for patients with OA is provision of personalized social support, either directly or by periodic telephone contact. Studies of the results of monthly telephone calls by trained nonmedical personnel to discuss such issues as joint pain, medications and treatment compliance, drug toxicities, date of next scheduled visit, and barriers to keeping clinic appointments showed moderate-to-large degrees of im-

provement in pain and functional status without a significant increase in costs. These studies underscore the concept that improved communication and education are important factors in decreasing pain and improving function in patients with OA.

Table 6.

Nonpharmacologic therapy for patients with osteoarthritis

№	Nonpharmacologic therapy
1	Patient education
2	Self-management programs (e.g., Arthritis Foundation Self-Management Program)
3	Personalized social support through telephone contact
4	Weight loss (if overweight)
5	Aerobic exercise programs
6	Physical therapy Range-of-motion exercises
7	Muscle-strengthening exercises
8	Assistive devices for ambulation
9	Patellar taping
10	Appropriate footwear
11	Lateral-wedged insoles (for genu varum) Bracing
12	Occupational therapy
13	Joint protection and energy conservation
14	Assistive devices for activities of daily living

Individuals with OA of the lower extremity may have limitations that impair their ability to perform activities of daily living (ADLs), such as walking, bathing, dressing, use of the toilet, and performing household chores. Physical therapy and occupational therapy play central roles in the management of patients with functional limitations. The physical therapist assesses muscle strength, joint stability, and mobility; recommends the use of modalities such as heat (especially useful just prior to exercise); instructs patients in an exercise program to maintain or improve joint range of motion and periarticular muscle strength; and provides assistive devices, such as canes, crutches, or walkers, to improve ambulation. Similarly, the occupational therapist can be instrumental in directing the patient in proper joint protection and energy conservation, use of splints and other assistive devices, and improving joint function. In addition, the input of a vocational guidance counselor may be important to patients who are still actively employed.

Quadriceps weakness is common among patients with knee OA, in whom it had been believed to be a manifestation of disuse atrophy, which develops because of un-

loading of the painful extremity. Recent studies, however, have indicated that quadriceps weakness may be present in persons with radiographic changes of OA who have no history of knee pain, and in whom lower extremity muscle mass is increased, rather than decreased; and that quadriceps weakness may be a risk factor for the development of knee OA, presumably by decreasing stability of the knee joint and reducing the shock-attenuating capacity of the muscle.

The beneficial effects of both quadriceps strengthening and aerobic exercise for patients with knee OA, noted in the original recommendations, were confirmed in the Fitness Arthritis and Seniors Trial, in which patients with mild disability due to symptomatic knee OA were randomly assigned to aerobic exercise, resistive (muscle-strengthening) exercise, or an education/attention control group. Patients in both exercise groups had modest but significant improvement compared with the control group; this improvement was sustained over an 18-month followup period. In post hoc analyses, the authors found that the degree of adherence to the exercise regimen was significantly associated with the magnitude of improvement in pain and functional limitation. The ability of elderly subjects to maintain conditioning levels of exercise is noteworthy, since many patients with advanced hip or knee OA are sedentary, deconditioned, and at increased risk for cardiovascular disease.

Another recent study demonstrated the efficacy of an exercise program in improving muscle strength, mobility, and coordination in patients with OA of either the knee or hip. In this study, patients randomly assigned to the exercise group not only had improvement in pain and observed disability, but also reported taking less acetaminophen and had made fewer physician visits by 12 weeks after entry. The effectiveness of exercise was similar in patients with hip or knee OA. These exercise programs, however, require a commitment of time, and effort on the part of the patient. In addition to quadriceps weakness, sensory dysfunction, reflected by a decrease in proprioception, has been documented in patients with knee OA. The 1995 ACR guidelines also recommended that overweight patients with hip or knee OA lose weight. A randomized open trial of an appetite suppressant and low-calorie diet was completed in 40 overweight patients with knee OA; all patients received instruction in an exercise walking program. Patients randomly assigned to the appetite suppressant group lost a mean of 3.9 kg over the

course of 6 weeks, and also had significant improvement in their knee OA, as measured by the Lequesne algofunctional index. Although this study had limitations, it provided the only data from a randomized trial demonstrating a relationship between loss of body fat (rather than loss of body weight) and improvement in symptoms of knee OA. As noted in the 1995 ACR recommendations, proper use of a cane (in the hand contralateral to the affected knee) reduces loading forces on the joint and is associated with a decrease in pain and improvement of function. In addition, patients may benefit from wedged insoles to correct abnormal biomechanics due to varus deformity of the knee. Another useful maneuver for patients with OA of the knee who have symptomatic patellofemoral compartment involvement is medial taping of the patella.

Pharmacologic therapy

All of the pharmacologic agents discussed in this section should be considered additions to nonpharmacologic measures, such as those described above, which are the cornerstone of OA management and should be maintained throughout the treatment period. Drug therapy for pain management is most effective when combined with nonpharmacologic strategies.

For many patients with OA, the relief of mild-to-moderate joint pain afforded by the simple analgesic, acetaminophen, is comparable with that achievable with an NSAID. However, this finding was based on a post hoc analysis with limited statistical power that used a definition of inflammation which included joint-line and soft-tissue tenderness or soft-tissue swelling. Eccles and colleagues, in a metaanalysis of trials comparing simple analgesics with NSAIDs in patients with knee OA, did note that NSAID-treated patients had significantly greater improvement in both pain at rest and pain on motion.

The daily dose of acetaminophcn should not exceed 4 gm. Although it is one of the safest analgesics, acetaminophen can be associated with clinically important adverse events. Recent reports have highlighted long-recognized conditions in which increased awareness of potential toxicity is important. For example, because acetaminophen can prolong the half-life of warfarin sodium, careful monitoring of the prothrombin time is recommended in patients taking warfarin sodium who subsequently begin high-dose acetaminophen treatment. Hepatic toxicity with acetaminophen is rare with doses of <4

gm/day. Nonetheless, the drug should be used cautiously in patients with existing liver disease and avoided in patients with chronic alcohol abuse because of known increased risk in these settings. Even though acetaminophen was reported to be weakly associated with end-stage renal disease, the Scientific Advisory Committee of the National Kidney Foundation recommends it as the drug of choice for analgesia in patients with impaired renal function.

For those patients who fail to obtain adequate symptomatic relief with the above measures, alternative or additional pharmacologic agents should be considered. The choice should be made after evaluation of risk factors for serious upper gastrointestinal (GI) and renal toxicity. Data from epidemiologic studies show that among persons of age >=65 years, 20-30% of all hospitalizations and deaths due to peptic ulcer disease were attributable to therapy with NSAIDs. Furthermore, in the elderly, the risk of a catastrophic GI event in patients taking NSAIDs is dose dependent. Risk factors for upper GI bleeding in patients treated with NSAIDs include age ≥65 years, history of peptic ulcer disease or of upper GI bleeding, concomitant use of oral glucocorticoids or anticoagulants, presence of comorbid conditions, and, possibly, smoking and alcohol consumption (Table 7). Risk factors for reversible renal T2 failure in patients with intrinsic renal disease (usually defined as a serum creatinine concentration of ≥2.0 mg/dl) who are treated with NSAIDs include age ≥65 years, hypertension and/or congestive heart failure, and concomitant use of diuretics and angiotensin-converting enzyme inhibitors.

Table 7.

Risk factors for upper gastrointestinal adverse events in patients with OA

№	**Risk factors**
1	Age >=65 years
2	Comorbid medical conditions
3	Oral glucocorticoids
4	History of peptic ulcer disease
5	History of upper gastrointestinal bleeding
6	Anticoagulants

Additional considerations involved in a practitioner's decision to treat the individual OA patient include existing comorbidities and concomitant therapy, as well as the side effects and costs of specific treatments. In individuals with OA of the knee who have mild-to-moderate pain, do not respond to acetaminophen, and do not wish to take sys-

temic therapy, the use of topical analgesics (e.g., methylsalicylate or capsaicin cream) is appropriate as either adjunctive treatment or monotherapy. Capsaicin cream should be applied to the symptomatic joint 4 times daily; a local burning sensation is common, but rarely leads to discontinuation of therapy. A systematic review of topical NSAIDs also demonstrated efficacy in patients with OA; there are no published findings of trials comparing the same NSAID administered orally versus topically. Initiation of treatment in the patient at increased risk for an upper GI adverse event. Of further advantage with respect to upper GI bleeding, neither of the COX-2-specific inhibitors has a clinically significant effect on platelet aggregation or bleeding .time. This is a consideration, especially in preand perioperative management of patients with OA (in whom nonselective NSAIDs have traditionally been discontinued as long as 2 weeks prior to surgery), as well as for patients taking warfarin sodium. Accordingly, these agents appear preferable to currently available nonselective NSAIDs for use in patients at risk for upper GI complications.

Tramadol, a centrally acting oral analgesic, is a synthetic opioid agonist that also inhibits reuptake of norepinephrine and serotonin. It has been approved by the FDA for the treatment of moderate-to-severe pain and can be considered for use in patients who have contraindications to COX-2-specific inhibitors and nonselective NSAIDs, including impaired renal function, or in patients who have not responded to previous oral therapy. Although there are numerous studies of the use of tramadol in general pain, few controlled studies have examined its use in OA. The efficacy of tramadol has been found to be comparable with that of ibuprofen in patients with hip and knee OA, and it has been found to be useful as adjunctive therapy in patients with OA whose symptoms are inadequately controlled with NSAIDs. Mean effective daily doses of tramadol have generally been in the range of 200-300 mg, given in 4 divided doses. Side effects are common and include nausea, constipation, and drowsiness. Despite its opioid pharmacology, a comprehensive surveillance program has failed to demonstrate significant abuse, and tramadol remains an unscheduled agent.

Although the efficacy of therapy with combinations of the above pharmacologic agents has not been established in controlled clinical trials, in general, it is reasonable to use the recommended agents in combination in an individual patient. However, only a

single NSAID should be used at any given time, the sole exception being the concomitant use of a cardioprotective dose of aspirin (81-325 mg/day) with other NSAIDs. Even these low doses of aspirin, however, will increase the risk of upper GI bleeding in patients taking NSAIDs. In this regard, it should be noted that the incidence of endoscopically identified ulcers in patients taking a COX-2-specific inhibitor and a cardioprotective dose of aspirin was lower than that in comparator groups taking nonselective NSAIDs with or without concomitant lowdose aspirin.

Surgical Care

Closed-needle joint lavage may benefit a small subgroup of patients. Arthroscopy may help patients with OA of the knee that has specific structural damage on imaging (eg, repairing meniscal tears, removing fragments of torn menisci that are producing symptoms). Overall, arthroscopy is not recommended for nonspecific "cleaning of the knee" in OA.

Osteotomy

Consider this procedure for those patients with a malaligned hip or knee joint. The procedure usually is recommended in younger patients with OA. This surgery can lessen pain, although it can lead to more challenging surgery later if the patients requires arthroplasty.

Arthroplasty

Perform this procedure if all other modalities are ineffective and osteotomy is not viable or if a patient cannot perform his or her daily activities despite maximal therapy. This procedure alleviates pain and may improve function. Approximately 8-15 years of viability are expected from the joint replacement if there are no complications.

Consultations

A physiatrist may help in formulating a nonpharmacologic management plan. A referral to an orthopedic surgeon may be necessary if a patient fails to respond to a medical management plan. A nutritionist may help the patient achieve some weight loss.

Diet and activity

A diet to achieve some degree of weight loss may be beneficial.OA may severely hinder the patient's ability to work or even to perform daily living activities, depending on the joints involved and the degree of involvement.

Part 5.
RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown cause that primarily affects the peripheral joints in a symmetric pattern. Constitutional symptoms, including fatigue, malaise, and morning stiffness, are common. Extra-articular involvement of organs such as the skin, heart, lungs, and eyes can be significant. RA causes joint destruction and thus often leads to considerable morbidity and mortality. The treatment of RA is rapidly advancing with the recent addition of new and innovative therapies.

Pathophysiology

RA has an unknown cause. Although an infectious etiology has been speculated (eg, Mycoplasma organisms, Epstein-Barr virus, parvovirus, rubella), no organism has been proven responsible. RA is associated with a number of autoimmune responses, but whether autoimmunity is a secondary or primary event is still unknown. RA has a significant genetic component, and the so-called shared epitope of the HLA-DR4/DR1 cluster is present in up to 90% of patients with RA, although it is also present in more than 40% of controls. Synovial cell hyperplasia and endothelial cell activation are early events in the pathologic process that progresses to uncontrolled inflammation and consequent cartilage and bone destruction. Genetic factors and immune system abnormalities contribute to disease propagation.

Major cellular roles are played by CD4 T cells, mononuclear phagocytes, fibroblasts, osteoclasts, and neutrophils, while B lymphocytes produce autoantibodies (ie, rheumatoid factors [RFs]). Abnormal production of numerous cytokines, chemokines, and other inflammatory mediators (eg, tumor necrosis factor alpha [TNF-alpha, interleukin (IL)–1, IL-6, transforming growth factor beta, IL-8, fibroblast growth factor, platelet-derived growth factor) have been demonstrated in patients with RA. Ultimately, inflammation and exuberant proliferation of synovium (ie, pannus) leads to destruction of various tissues such as cartilage, bone, tendons, ligaments, and blood vessels. Although the articular structures are the primary sites, other tissues are also affected.

Frequency

The worldwide incidence of RA is approximately 3 cases per 10,000 population, and the prevalence rate is approximately 1%. RA affects all populations, although a few groups have much higher prevalence rates (eg, 5-6% in some Native American groups) and some have lower rates (eg, black persons from the Caribbean region). First-degree relatives of patients with RA have an increased frequency of disease (approximately 2-3%). Disease concordance in monozygotic twins is approximately 15-20%, suggesting that nongenetic factors play an important role. Because worldwide frequency is relatively constant, a ubiquitous infectious agent has been postulated to play an etiologic role.

Mortality and morbidity of rheumatoid arthritis

RA does not usually follow a benign course. It is associated with significant morbidity, disability, and mortality. Daily living activities are impaired in most patients. Spontaneous clinical remission is uncommon (approximately 5-10%). After 5 years of disease, approximately 33% of patients will not be working; after 10 years, approximately half will have substantial functional disability. Poor prognostic factors include persistent synovitis, early erosive disease, extra-articular findings (including subcutaneous rheumatoid nodules), positive serum RF findings, family history of RA, male sex, and advanced age.

Life expectancy for patients with RA is shortened by 5-10 years, although those who respond to therapy may have lower mortality rates. Increased mortality rates are associated with poor functional status, age, male sex, socioeconomic factors (eg, level of education), positive RF findings, extra-articular disease, elevated acute phase response (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]), and increased clinical severity (eg, more involved joints). Mortality is increased by causes such as infections, cardiovascular disease, renal disease, GI bleeding, and lymphoproliferative disorders; these events may be directly due to the disease and its complications (eg, vasculitis, amyloidosis) or to therapy-induced adverse effects.

Race, sex and age particulaties.

RA affects all populations, although a few groups have much higher prevalence rates (eg, 5-6% in some Native American groups) and some have lower rates (eg, black persons from the Caribbean region). Females are 2-3 times more likely to develop RA than males. The frequency of RA increases with age and peaks in persons aged 35-50

years. Nevertheless, the disease is observed in both elderly persons and children. Juvenile inflammatory arthritis (JIA) has been classified as polyarticular (multiple joints), pauciarticular (<5 joints), and systemic. Systemic JIA is often associated with fever, rash, and organ involvement; it is also called Still disease. Children with polyarticular RF-positive arthritis generally have a clinical course similar to those with adult RA.

History of RA

The American College of Rheumatology developed the following criteria for the classification of RA.

- Morning stiffness: This occurs in and around the joints and lasts at least 1 hour before maximal improvement.
- Arthritis of 3 or more joint areas: At least 3 joint areas simultaneously have soft tissue swelling or fluid (not bony overgrowth) observed by a physician. The 14 possible areas are right or left proximal interphalangeal (PIP), metacarpophalangeal (MCP), wrist, elbow, knee, ankle, and metatarsophalangeal (MTP) joints.
- Arthritis of hand joints of at least one area swollen in a wrist, MCP, or PIP joint
- Symmetric arthritis with simultaneous involvement of the same joint areas on both sides of the body: Bilateral involvement of PIPs, MCPs, and MTPs is acceptable without absolute symmetry.
- Rheumatoid nodules: Subcutaneous nodules are present over bony prominences or extensor surfaces or in juxta-articular regions.
- Serum RF: Abnormal amounts of serum RF are demonstrated by any method for which the result has been positive in fewer than 5% of healthy control subjects.
- Radiographic changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints: Osteoarthritic changes alone do not qualify.

A patient can be classified as having RA if 4 of 7 criteria are present. Criteria 1-4 must be present for at least 6 weeks, and a physician must observe criteria 2-5. These criteria are intended as a guideline for classification of patients, often for research purposes. They do not absolutely confirm or exclude a diagnosis of RA in a particular patient, especially in those with early arthritis.

Patients often present with constitutional complaints including malaise, fever, fatigue, weight loss, and myalgias. They may report difficulty performing activities of daily living (eg, dressing, standing, walking, personal hygiene, using their hands).

Most patients with the disease have an insidious onset. It may begin with systemic features, such as fever, malaise, arthralgias, and weakness, before the appearance of

overt joint inflammation and swelling. A small percentage of patients (approximately 10%) have an abrupt onset with the acute development of synovitis and extra-articular manifestations. Spontaneous remission is uncommon, especially after the first 3-6 months.

Physical examination findings

Joint involvement is the characteristic feature of patients with RA. In general, the small joints of the hands and feet are affected in a relatively symmetric distribution. Those most commonly affected joints, in decreasing frequency, are the MCP, wrist, PIP, knee, MTP, shoulder, ankle, cervical spine, hip, elbow, and temporomandibular. Joints show inflammation with swelling, tenderness, warmth, and decreased range of motion. Atrophy of the interosseous muscles of the hands is a typical early finding. Joint and tendon destruction may lead to deformities such as ulnar deviation, boutonnière and swan-neck deformities, hammer toes, and occasionally joint ankylosis.

Other commonly observed musculoskeletal manifestations are tenosynovitis and associated tendon rupture (due to tendon and ligament involvement, most commonly involving the fourth and fifth digital extensor tendons at the wrist), periarticular osteoporosis due to localized inflammation and generalized osteoporosis due to systemic chronic inflammation, immobilization-related changes or corticosteroid therapy, and carpal tunnel syndrome. Most patients have muscle atrophy from disuse, which is often secondary to joint inflammation.

Effect of RA on organs and organ systems

- **Skin**: Subcutaneous nodules (rheumatoid nodules) occur in many patients with RA whose RF value is abnormal. They are often present over pressure points (eg, olecranon). Vasculitic lesions of the skin may manifest as palpable purpura or skin ulceration.
- **Cardiac**: The incidence of cardiovascular morbidity and mortality is increased in patients with RA. Nontraditional risk factors appear to play an important role. Myocardial infarction, myocardial dysfunction, and asymptomatic pericardial effusions are common; symptomatic pericarditis and constrictive pericarditis are rare. Myocarditis, coronary vasculitis, valvular disease, and conduction defects are occasionally observed.

- **Pulmonary**: RA involvement of the lungs may take several forms, including pleural effusions, interstitial fibrosis, nodules (Caplan syndrome), and bronchiolitis obliterans-organizing pneumonia.
- **GI**: Intestinal involvement, as with kidney involvement, is often secondary to associated processes such as medication effects, inflammation, and other diseases. The liver is often affected in patients with Felty syndrome (ie, RA, splenomegaly, and neutropenia).
- **Renal**: The kidneys commonly are not affected directly by RA. Secondary involvement is common, including that due to medications (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], gold, cyclosporin), inflammation (eg, amyloidosis), and associated diseases (eg, Sjögren syndrome with renal tubular abnormalities).
- **Vascular**: Vasculitic lesions can occur in any organ but are most commonly found in the skin. Lesions may present as palpable purpura, skin ulcers, or digital infarcts.
- **Hematologic**: Most active patients have an anemia of chronic disease. Several hematologic parameters parallel disease activity, including normochromic-normocytic anemia, thrombocytosis, and eosinophilia, although the latter is uncommon. Leukopenia is a finding in patients with Felty syndrome.
- **Neurologic**: Entrapment of nerves is common, such as with the median nerve in carpal tunnel syndrome. Vasculitic lesions, mononeuritis multiplex, and cervical myelopathy may cause serious neurological consequences.
- **Ocular**: Keratoconjunctivitis sicca is common in RA and is often the initial manifestation of secondary Sjögren syndrome. The eye may also have episcleritis, uveitis, and nodular scleritis that may lead to scleromalacia.

The American College of Rheumatology developed criteria to aid in determining the progression, remission, and functional status of patients with RA. Progression of RA (clinical and radiological staging)

Stage 1 (early RA)

- No destructive changes observed upon roentgenographic examination
- Radiographic evidence of osteoporosis possible

Stage II (moderate progression)

- Radiographic evidence of periarticular osteoporosis with or without slight subchondral bone destruction
- Slight cartilage destruction possible
- Joint mobility possibly limited; no joint deformities observed
- Adjacent muscle atrophy
- Extra-articular soft tissue lesions (eg, nodules, tenosynovitis) possible

Stage III (severe progression)

- Radiographic evidence of cartilage and bone destruction in addition to periarticular osteoporosis
- Joint deformity (eg, subluxation, ulnar deviation, hyperextension) without fibrous or bony ankylosis
- Extensive muscle atrophy
- Extra-articular soft tissue lesions (eg, nodules, tenosynovitis) possible
- Stage IV (terminal progression)
- Fibrous or bony ankylosis

Criteria of stage III

- Remission of RA - Five or more of the following conditions present for at least 2 consecutive months
- Duration of morning stiffness not exceeding 15 minutes
- No fatigue
- No joint pain
- No joint tenderness or pain with motion
- No soft tissue swelling in joints or tendon sheaths
- ESR of less than 30 mm/h for a female or less than 20 mm/h for a male

Functional status of patients with RA

- Class I - Completely able to perform usual activities of daily living
- Class II - Able to perform usual self-care and vocational activities but limited in avocational activities
- Class III - Able to perform usual self-care activities but limited in vocational and avocational activities
- Class IV - Limited in ability to perform usual self-care, vocational, and avocational activities

Causes

The cause(s) of RA is unknown. Genetic, environmental, hormonal, immunologic, and infectious factors may play significant roles. Socioeconomic, psychological, and lifestyle factors may influence disease outcome.

Genetic

Approximately 60% of US patients with RA carry the so-called shared epitope of the HLA-DR4 cluster, which constitutes one of the peptide binding sites of certain HLA-DR molecules associated with RA (eg, HLA-DR beta *0401, 0404, or 0405); in addition, HLA-DR1 (HLA-DR beta *0101) also carries this shared epitope and confers risk, particularly in certain southern **European areas.**

Other HLA-DR4 molecules (eg, HLA-DR beta *0402) do not share the same epitope and do not confer risk. Genes other than those of the major histocompatibility complex are also involved, and results from sequencing genes of RA families suggest the presence of several susceptibility genes and several resistance genes.

Environmental factors

For many decades, numerous infectious agents have been suggested to induce RA. Among these are Mycoplasma organisms, Epstein-Barr and rubella viruses, and others. This supposition is further supported indirectly by the following:

- Occasional reports of flulike disorders preceding the start of arthritis
- The inducibility of arthritis in experimental animals with different bacteria or bacterial products (eg, streptococcal cell walls)
- The presence of bacterial products including bacterial RNA in patients' joints
- The activity of several agents that have antimicrobial effects as disease-modifying drugs (eg, gold salts, antimalarials, minocycline)

Hormonal factors

Sex hormones may play a role, as evidenced by the disproportionate number of females with RA, its amelioration during pregnancy, its recurrence in the early postpartum period, and its reduced incidence in women using oral contraceptives.

Hyperprolactinemia may be a risk factor for RA.

Immunologic factors

All of the major immunologic elements play fundamental roles in the initiation, propagation, and maintenance of the autoimmune process of RA. The exact orchestration of the cellular and cytokine events that lead to pathologic consequences, such as synovial proliferation and subsequent joint destruction, is complex. It involves T and B lymphocytes, antigen-presenting cells (eg, B cells, macrophages, dendritic cells), and

numerous cytokines. Aberrant production and regulation of both pro- and anti-inflammatory cytokines and cytokine pathways are found in RA.

T cells are assumed to play a pivotal role in the initiation of RA, and the key player in this respect is assumed to be the Th1 CD4 cells. (T helper 1 cells produce IL-2 and interferon gamma.)

These cells may subsequently activate macrophages and other cell populations, including synovial fibroblasts. The latter 2 populations are the main producers of the proinflammatory cytokines TNF-alpha and IL-1 that appear to be the major driving forces of inflammation.

B cells are important in the pathologic process because they may serve as antigen-presenting cells and activated T cells, produce numerous autoantibodies (eg, RF, to citrullinated proteins), and secrete cytokines. Elimination of populations of B cells with monoclonal antibodies (eg, rituximab) offers another effective therapeutic option.

Experimental models suggest that synovial macrophages and fibroblasts may become autonomous and thus lose responsiveness to T-cell activities in the course of the disease. The hyperactive and hyperplastic synovial membrane is ultimately transformed into pannus tissue and invades cartilage and bone, the latter being degraded by activated osteoclasts. The major difference between RA and other forms of inflammatory arthritis, such as psoriatic arthritis, does not lie in their cytokine patterns but rather in the highly destructive potential of the RA synovial membrane and in the local and systemic autoimmunity. Whether these 2 events are linked is unclear; however, the autoimmune response conceivably leads to the formation of immune complexes activating the inflammatory process to a much higher degree than is otherwise the case. This theory is supported by the much worse prognosis of RA among patients positive for RF. In patients with RA, autoantibodies are not only directed against immunoglobulin G (IgG), ie, RFs, but also against a variety of other antigens such as nuclear antigens (RA 33, EBNA), citrullinated proteins (anti-CCP antibodies), collagen, and glucose-6-phosphate isomerase.

Differencial diagnosis.

Other Problems to be Considered

- Infectious arthritis - Bacteria (eg, Lyme disease, fungi, mycobacteria), viruses (eg, hepatitis B, rubella, parvovirus, human T-cell leukemia virus 1)
- Autoimmune connective tissue diseases (eg, systemic lupus erythematosus, progressive systemic sclerosis, mixed connective tissue disease, Sjögren syndrome, vasculitis, cryoglobulinemias)
- Other rheumatic diseases (eg, polyarticular gout, seronegative spondyloarthropathy [eg, ankylosing spondylitis, reactive arthritis])
- Subacute bacterial endocarditis
- Hemoglobinopathies
- Angioimmunoblastic lymphadenopathy

Lab Studies

- No pathognomonic test is available to help confirm the diagnosis of RA; instead, the diagnosis is made using clinical, laboratory, and imaging features.
- Markers of inflammation, such as ESR and CRP, are associated with disease activity; additionally, the CRP value over time correlates with radiographic progression.
- Hematologic parameters include a CBC count and synovial fluid analysis.
- Complete blood cell count
- Anemia of chronic disease is common and correlates with disease activity; it improves with successful therapy.
- Hypochromic anemia suggests blood loss, commonly from the GI tract (associated with NSAIDs).
- Anemia may also be related to disease-modifying antirheumatic drug (DMARD) therapy.
- Thrombocytosis is common and is also associated with disease activity.
- Thrombocytopenia may be a rare adverse event of therapy and may occur in patients with Felty syndrome.
- Leukocytosis may occur but is usually mild.
- Leukopenia may be a consequence of therapy or a component of Felty syndrome, which may then respond to DMARD therapy.

Synovial fluid analysis

- An inflammatory synovial fluid (WBC count >2000/μL) is present with counts generally from 5,000-50,000/μL.
- Usually, neutrophil predominance (60-80%) is observed in the synovial fluid (in contrast with mononuclear cell predominance in the synovium).
- Note that because of a transport defect, the glucose levels of pleural, pericardial, and synovial fluids from patients with RA are often low compared to serum glucose levels.
- Immunologic parameters include RF, antinuclear antibodies, and, possibly, other newer antibodies (anti-RA33, anti-CCP).

Rheumatoid factor

- RF is present in approximately 60-80% of patients with RA over the course of their disease but is present in fewer than 40% of patients with early RA.
- RF values fluctuate somewhat with disease activity, although high-titered RF generally remains present even in patients with drug-induced remissions.
- Antinuclear antibodies: These are present in approximately 40% of patients with RA, but test results for antibodies to most nuclear antibody subsets are negative.
- Newer antibodies (eg, anti-RA33, anti-CCP): Recent studies of anti-CCP antibodies suggest a sensitivity and specificity equal to or better than those of RF, with an increased frequency of positive results in early RA. The presence of both anti-CCP antibodies and RF is highly specific for RA. Additionally, anti-CCP antibodies, as do RF, indicate a worse prognosis.

Imaging Studies

Radiographs: Note that erosions may be present in the feet, even in the absence of pain and in the absence of erosions in the hands.

Extremities - Hands, wrists, knees, feet, elbows, shoulders, hips, cervical spine.

Others when indicated

MRI: This modality is primarily used in patients with abnormalities of the cervical spine; early recognition of erosions based on MRI images has been sufficiently validated.

Sonography: This allows recognition of effusions in joints that are not easily accessible (eg, hip joints, shoulder joints in obese patients) and cysts (Baker cysts). High-resolution ultrasound images may allow visualization of tendon sheaths, changes and degree of vascularization of the synovial membrane, and even erosions; however, this needs further validation. Sonography may be used as an office-based procedure.

Bone scanning: Findings may help to distinguish inflammatory from noninflammatory changes in patients with minimal swelling.

Densitometry: Findings are useful for helping diagnose changes in bone mineral density indicative of osteoporosis.

Other Tests

HLA-DR4 (shared epitope) may constitute a helpful marker in early undifferentiated arthritis.

Procedures

Joint aspiration, diagnostic arthroscopy (histology), and biopsies (eg, skin, nerve, fat, rectum, kidney) may be considered if vasculitis or amyloidosis is suggested.

Histologic Findings

The lymphoplasmacytic infiltration of the synovium with neovascularization seen in RA is similar to that seen in other conditions characterized by inflammatory synovitis. Early rheumatoid nodules are characterized by small vessel vasculitis and later by granulomatous inflammation.

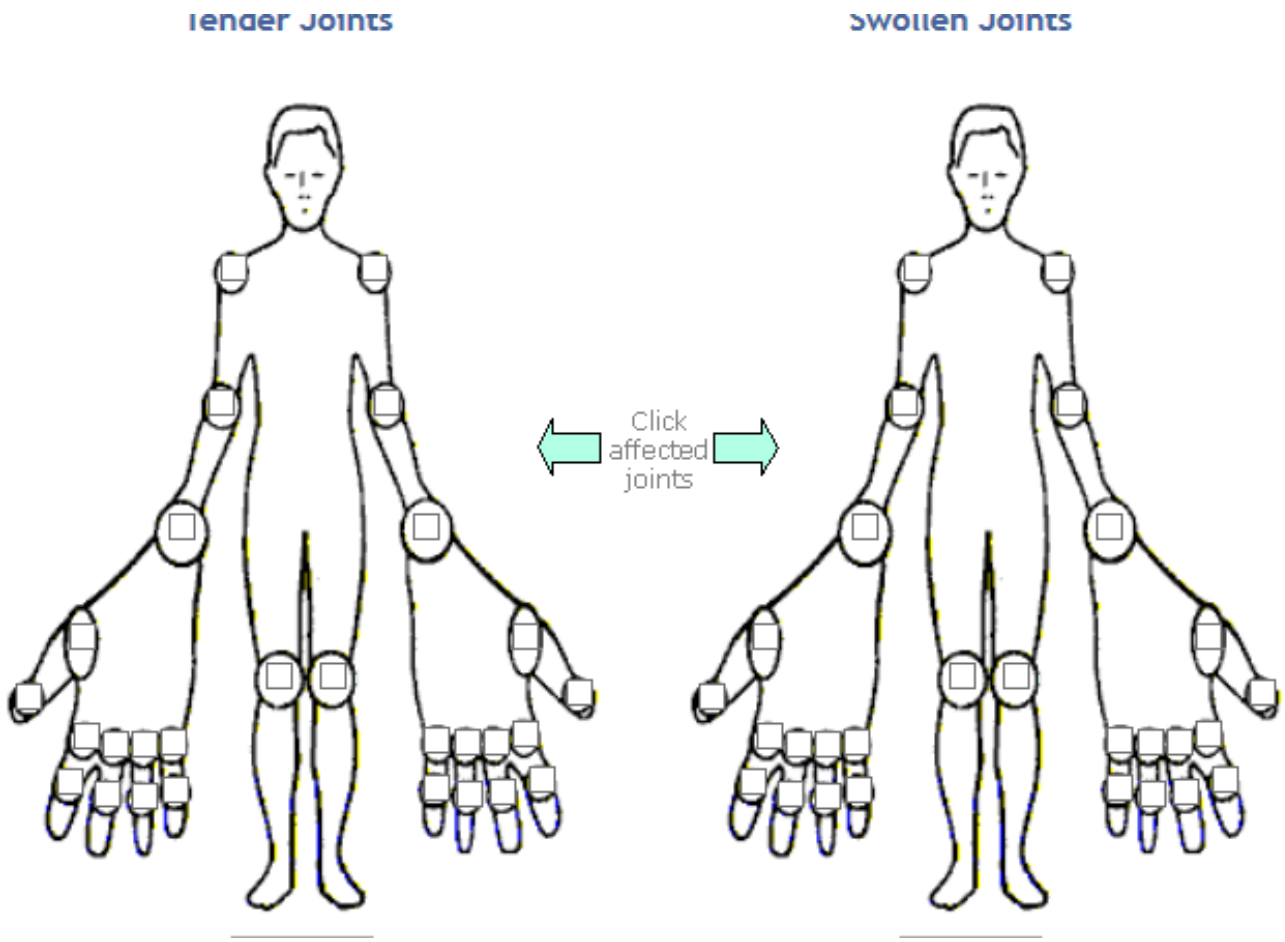
Measures of symptoms and disease status in rheumatoid arthritis

Activity RA is calculated using special calculator DAS-28 (Scheme 1) by formula:

*DAS28 = 0.56*sqrt(t28) + 0.28*sqrt(sw28) + 0.70*Ln(ESR) + 0.014*GH*

This calculation may be done using free on-line calculator http://www.das-score.nl

Scheme 1: DAS 28



The DAS28 is a measure of disease activity in rheumatoid arthritis (RA). DAS stands for 'disease activity score' and the number 28 refers to the 28 joints that are examined in this assessment.

There are a wide range of measures of disease activity in RA including:-

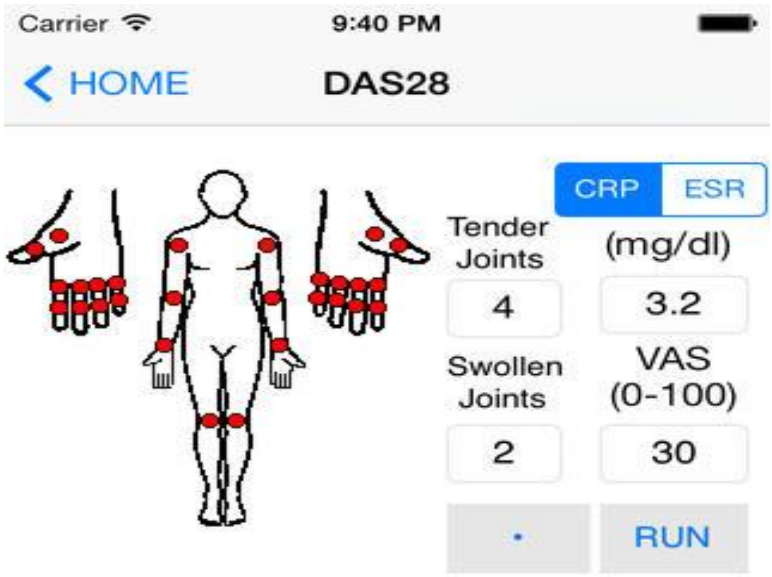
- examination of your joints for swelling and tenderness,
- global scores of pain and overall status,
- blood markers of inflammation (e.g. ESR and CRP)
- questionnaires (e.g. the HAQ which assesses function),
- X-rays, and newer imaging techniques such as ultrasound and MRI.

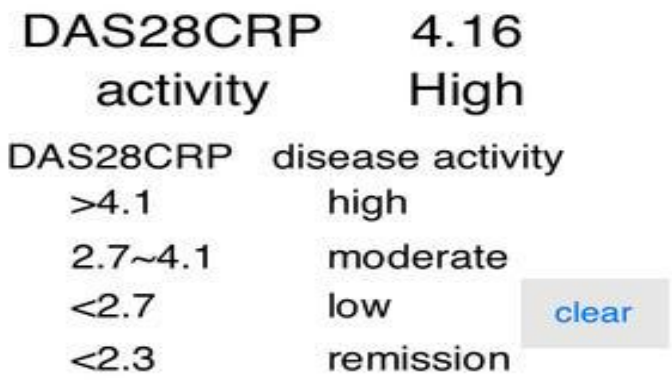
The DAS28 is a composite score derived from 4 of these measures. This '28' version is a simplification of the original DAS score, which requires 44 joints to be counted. Other versions of the DAS28 allow the CRP to be used instead of the ESR, or the omission of either. To calculate the DAS28 your rheumatologist or specialist nurse will:-

- count the number of swollen joints (out of the 28),
- count the number of tender joints (out of the 28),
- take blood to measure the erythrocyte sedimentation rate (ESR) or C reactive protein (CRP), ask you (the patient) to make a 'global assessment of health' (indicated by marking a 10 cm line between very good and very bad).

These results are then fed into a complex mathematical formula to produce the overall disease activity score. A DAS28 of greater than 5.1 implies active disease, less than 3.2 low disease activity, and less than 2.6 remission. A sample the received results using DAS-28 is reported on the Scheme 2.

Scheme 2: Principles of interpretation of DAS-28





The HAQ questionnaire assesses function

The DAS score was originally developed by Dutch rheumatologists for the purpose of standardizing and comparing results in clinical trials of new drugs for treating RA . With time the DAS28 has also been applied to routine clinical practice. In the UK a score equal or greater than 5.1 on two occasions is one of the mandatory criteria required to be eligible for NHS funded treatment with biologic (including anti-tumour necrosis factor) therapies.

The DAS-CRP score

The DAS-CRP is a modification of the DAS28 (Disease Activity Score 28). Originally the DAS28 includes the measured erythrocyte sedimentation rate (ESR) value, while the DAS-CRP uses the C-Reactive Protein (CRP) value instead. The DAS-CRP is often used in clinical trials for the development of RA. The DAS-CRP is also referred to as DAS28(CRP).

DAS-CRP values range from 2.0 to 10.0 while higher values mean a higher disease activity. A DAS-CRP below the value of 2.6 is interpreted as Remission. Studies that compared the DAS-CRP and the DAS28 (ESR) showed that DAS-CRP underestimates disease activity and overestimates the improvement in disease activity compared with DAS28-ESR.

As the original DAS28 the DAS-CRP uses 28 different joints for its calculation:

- proximal interphalangeal joints (10 joints)
- metacarpophalangeal joints (10)
- wrists (2)
- elbows (2)
- shoulders (2)
- knees (2)

When looking at these joints, both the number of joints with tenderness upon touching and swelling are counted. In addition, the erythrocyte sedimentation rate is measured. Also, the patient makes a subjective assessment of disease activity during the preceding 7 days on a scale between 0 and 100, where 0 is "no activity" and 100 is "highest activity possible".

With the above mentioned parameters, DAS-CRP is calculated as:

$DAS-CRP=0.56 \times \sqrt{TEN28} + 0.28 \times \sqrt{SW28} + 0.36 \times \ln(CRP+1) + 0.014 \times SA+0.96$

With:

- TEN28: number of joints with tenderness upon touching
- SW28: number of swollen joints
- CRP: C-reactive Protein
- SA: subjective assessment of disease activity by the patient during the preceding 7 days on a scale betweenn 0 and 100 ("0":no activity, "100": highest activity possible)

The DAS-CRP provides an absolute indication of RA disease activity on a scale of 0.49 to 9.07

- A DAS-CRP value >5.1 corresponds to a high disease activity
- A DAS-CRP value between 3.2 and 5.1 corresponds to a moderate disease activity
- A DAS-CRP value between 2.6 and 3.2 corresponds to a low disease activity
- A DAS-CRP value < 2.6 corresponds to remission

Medical Care

Optimal care of patients with RA requires an integrated approach of pharmacologic and nonpharmacologic therapies.

Nonpharmacologic

Education is important in helping patients to understand their disease and to learn how to cope with its consequences. Physiotherapy and physical therapy are initiated to help improve and sustain range of motion, increase muscle strength, and reduce pain. Occupational therapy is initiated to help patients to use joints and tendons efficiently without stressing these structures, to help patients decrease tension on the joints through the use of specially designed splints, and to help patients to cope with daily life through the use of adaptations to the patients' environment and the use of different aids. Orthopedic measures include reconstructive and replacement-type surgical measures.

Pharmacologic

The most important measure to successfully treat RA is the use of DMARDs. DMARDs can retard or prevent disease progression and, thus, joint destruction and subsequent loss of function. Successful DMARD therapy may eliminate the need for other anti-inflammatory or analgesic medications. Until the full action of DMARDs takes effect, anti-inflammatory or analgesic medications may be required as bridging therapy to reduce pain and swelling. DMARDs can be classified into xenobiotic and biologic agents.

Xenobiotic agents

The xenobiotic DMARDs, ie, gold salts (eg, aurothiomalate, auranofin, others), D-penicillamine, chloroquine and hydroxychloroquine, sulfasalazine (SSZ), methotrexate (MTX), azathioprine, and cyclosporin A, have been widely used to treat RA; some have been used for decades.

MTX and SSZ are the most active compounds in terms of frequency of remissions and time to onset of action and provide the best risk-benefit ratios. MTX alone or

in combination with other agents has become the standard of care for moderate-to-severe RA.

Interest in the use of minocycline has recently been increasing because of its capacity to act as a DMARD. Leflunomide is the most recent addition to the xenobiotics and has an activity similar to that of SSZ and MTX. SSZ is dosed up to 2-4 g/d, while MTX is administered up to 25 mg once a week (PO, IV, IM, or SC). Both SSZ and MTX are started at low dosages and are increased to full dosages within approximately 4-6 weeks. Monitoring of CBC counts and liver enzymes is important because of the drugs' hematologic and hepatic toxicities. Approximately 1% of patients develop agranulocytosis to SSZ or pneumonitis to MTX. Leflunomide is usually initiated with a loading dose of 100 mg/d for 3 days and is then continued at 20 mg/d. CBC counts and liver enzymes also must be monitored. Most of these drugs have been shown to improve signs and symptoms (as well as quality of life) and to significantly retard radiographic progression of RA.

Combination therapy appears to be helpful in patients whose RA insufficiently or completely fails to respond to monotherapy with a DMARD. Several compounds have been successfully combined without unexpected added risks; these usually include MTX as one of the drugs, ie, MTX plus cyclosporine A, MTX plus SSZ plus an antimalarial, MTX plus leflunomide, or MTX plus biologics. In general, the same precautions are needed as with the single compounds, although liver and bone marrow toxicity may be increased if compounds affecting these organs are combined.

The most important and most common adverse events relate to liver and bone marrow toxicity (MTX, SSZ, leflunomide, azathioprine, gold compounds, D-penicillamine), renal toxicity (cyclosporine A, parenteral gold salts, D-penicillamine), pneumonitis (MTX), allergic skin reactions (gold compounds, SSZ), autoimmunity (D-penicillamine, SSZ, minocycline) and infections (azathioprine, cyclosporine A). Antimalarials may cause ocular toxicity. Nevertheless, these drugs, when used with appropriate clinical and laboratory control monitoring, are usually tolerated well. Adverse events typically become more rare after the first 2-3 months. Most adverse events are reversible with cessation of the drugs or with reduction of the doses.

It has been shown that approximately 30-70% of patients using DMARDs, either alone or in combination therapy, achieve partial responses according to the American College of Rheumatology's disease activity score. Predicting which patients will not respond is impossible. In clinical practice, attempting to reduce disease activity as much as possible by increasing the dose of medication (eg, MTX), switching to other DMARDs in those who do not respond or in those with responses regarded as insufficient, or initiating combination therapy is important. Because patients may require 2-3 months to achieve a full response to DMARDs, decisions regarding changes in medication are often delayed until that time.

New anti-RA drug: Tofacitinib

Tofacitinib is an oral immunosuppressant approved for the treatment of rheumatoid arthritis (RA) and is currently undergoing investigation (Phase III trials) for treating chronic plaque psoriasis. Tofacitinib inhibits Janus kinases (JAKs), which are essential for the signaling of multiple inflammatory pathways and have been implicated in the pathogenesis of RA and psoriasis. Treatment with tofacitinib was generally well-tolerated, with the most frequently reported adverse events and does not increase the risk for malignancies.

Biologic agents

The recognition of TNF-alpha and IL-1 as central proinflammatory cytokines has led to the development of agents that block these cytokines or their effects. The TNF blockers include etanercept, infliximab, and adalimumab. Etanercept, a bivalent p75–TNF receptor linked to the Fc portion of human IgG, is administered at 25 mg SC twice weekly or 50 mg SC weekly, with or without concomitant MTX. Infliximab, a chimeric monoclonal antibody against TNF-alpha, is administered at doses of 3 mg/kg IV at weeks 0, 2, and 6 and then every 4-8 weeks, usually with MTX. Adalimumab, a recombinant human IgG1 monoclonal antibody specific for human TNF monoclonal antibody, is administered 40 mg SC every 2 weeks.

These agents are expensive. Consensus statements do not recommend their use until at least one xenobiotic DMARD, usually MTX, has been administered without sufficient success. In clinical trials, up to 70% of patients achieve significant responses, but remissions are not usually observed.

These agents bind TNF and thus prevent its interaction with its receptors; infliximab binds to cells that express membrane TNF, while etanercept binds lymphotoxin (formerly termed TNF-beta) in addition to soluble TNF-alpha. Failure to respond to one TNF blocker does not preclude response to another. As with xenobiotics, the decision to continue or stop biologic agents can often be made within 3 months after initiation of therapy.

Adverse effects associated with the biologic agents include the generation of antibodies against these compounds, emergence of antinuclear antibodies, occasional drug-induced lupus like syndromes, and infections (including tuberculosis). Rarely, demyelinating disorders and bone marrow suppression may occur. Acute and chronic infections, demyelinating disorders, and recent malignancies are contraindications for TNF blockers. Thoroughly searching for latent tuberculosis using chest x-ray films and/or purified protein derivative (PPD) testing is recommended before starting these agents.

Another biologic is anakinra (IL-1 receptor antagonist [IL-1ra]). IL-1ra occupies the IL-1 receptor without triggering it and prevents receptor binding of IL-1. It is given at a dose of 100 mg/d SC. In clinical trials, a significant response was observed in approximately 40% of patients with RA.

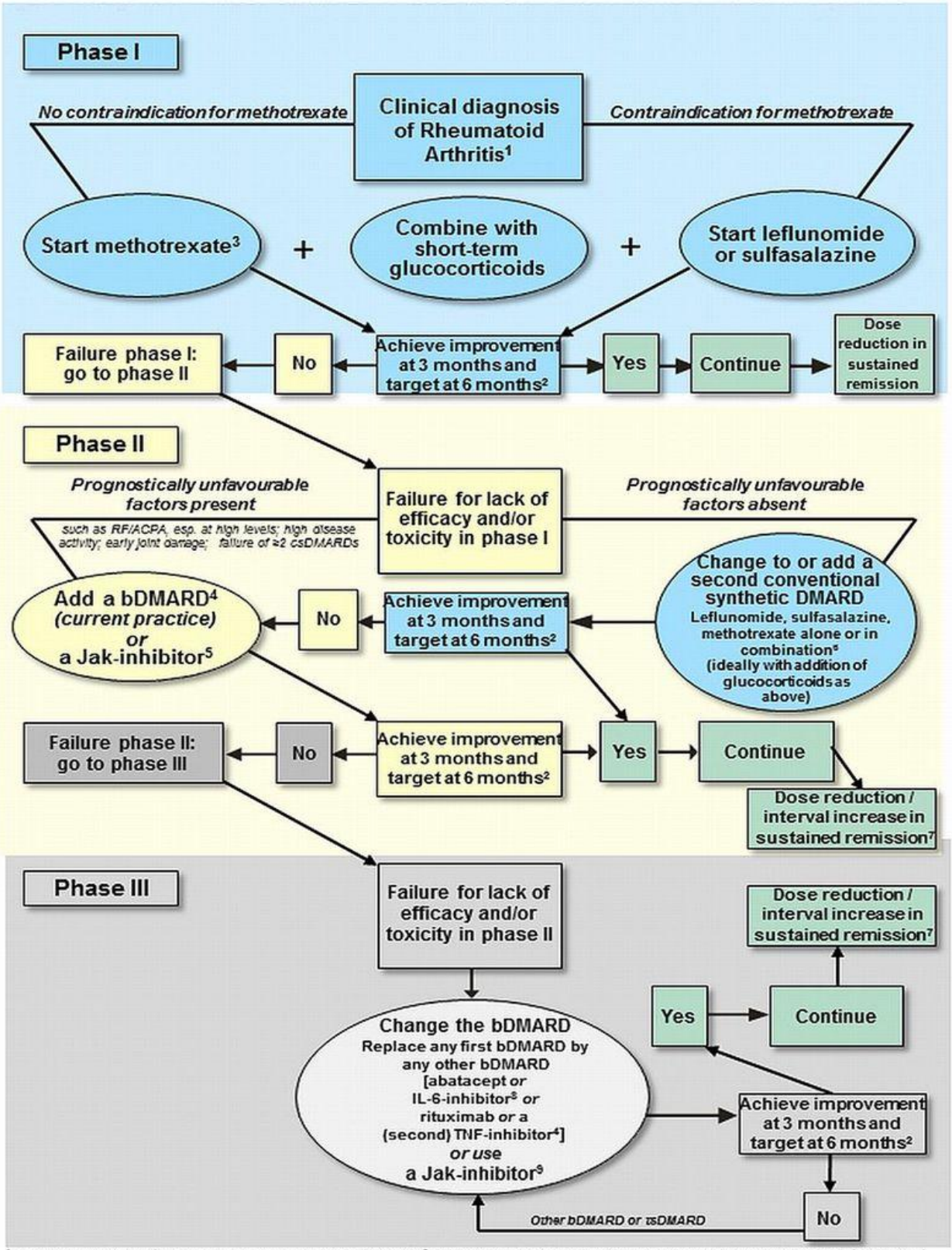
Abatacept is a selective costimulation modulator that inhibits T-cell activation by binding to CD80 and CED86, thereby blocking CD28 interaction. CD28 interaction provides a signal needed for full T-cell activation that is implicated in RA pathogenesis. It is dosed according to body weight (vida infra); after initial infusion, repeat on week 2 and week 4, then every 4 weeks following.

In addition to improving signs and symptoms and quality of life, all biologics significantly retard radiographic progression of joint erosions.

An algorithm based on the 2016 European League Against Rheumatism (EULAR) recommendations on RA management is reported on Scheme 3.

Glucocorticoids

Glucocorticoids are potent anti-inflammatory drugs and are commonly used in patients with RA to bridge the time until DMARDs are effective. Doses of up to 10 mg of prednisone per day are typically used, but some patients may require higher doses. Timely dose reductions and cessation are important because of the adverse effects associated with long-term steroid use.



[1]2010 ACR-EULAR classification criteria can support early diagnosis. [2]The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if no sufficient improvement is seen after 3 months. [3]"Methotrexate should be part of the first treatment strategy"; while combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs. [4]TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6-inhibitors, or rituximab; in patients who cannot use csDMARDs as comedication, IL6-inhibitors and tsDMARDs have some advantages. [5]Current practice would be to start with a bDMARD (in combination with MTX or another csDMARD) because of the long-term experience compared with tsDMARDs (Jak-inhibitors). [6]The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine. [7]Dose reduction or interval increase can be safely done with all bDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD. [8]Efficacy and safety of bDMARDs after Jak-inhibitor failure is unknown; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. [9]Efficacy and safety of a Jak-inhibitor after insufficient response to a previous Jak-inhibitor is unknown.

Scheme 3. Algorithm based on the 2016 European League Against Rheumatism (EULAR) recommendations on RA management.

Abbreviations: ACPA, anticitrullinated protein antibody; ACR, American College of Rheumatology; bDMARD, biological DMARD; bsDMARD, biosimilar DMARDs; csDMARDs, conventional synthetic DMARDs; DMARDs, disease-modifying antirheumatic drugs; EMA, European Medicines Agency; FDA, Food and Drug Administration; IL, interleukin; MTX, methotrexate; RF, rheumatoid factor; TNF, tumour necrosis factor; tsDMARDs, targeted synthetic DMARDs

The coxibs (COX-2 inhibitors), a new group of compounds, have recently been developed. These compounds have a significant preference for COX-2 over COX-1. COX-1 has a protective role, particularly in the stomach, while COX-2 is strongly upregulated during inflammation. Coxibs, with their selectivity for COX-2, have been shown to be clinically efficacious and are accompanied by significantly reduced GI toxicity, the major adverse event related to the use of nonselective COX inhibitors (ie, NSAIDs). Other adverse effects, such as water retention, hypertension, and abnormal transaminase levels, are observed with both nonselective and COX-2–selective drugs. Whether and to what degree nonaspirin NSAIDs, coxibs, or both have cardiovascular toxicity has not been definitively settled.

Analgesics

Acetaminophen/paracetamol, tramadol, codeine, opiates, and a variety of other analgesic medications can also be employed to reduce pain. These agents do not affect swelling or joint destruction.

Experimental therapies

Despite significant advances over the past decades, RA continues to be an incurable disease. The disease remains active in many patients whose conditions partially or completely fail to respond to DMARDs. Therefore, a vigorous search is underway for new therapeutic agents. Although not truly experimental because it has been approved for use in RA, an immunoadsorbent column (Prosorba) is used on occasion to treat patients with resistant disease. Weekly exchanges are given for 12 weeks. New TNF blockers are in clinical trials and include CDP 870, a Fab fragment of a humanized monoclonal antibody; and a pegylated version of the p55 TNF receptor. Biologics capable of block-

ing IL-6 or interfering with T-cell/non–T-cell interactions may also be promising. Xenobiotics directed at molecules involved in transduction of TNF or IL-1–mediated signals could prove helpful. Inhibition of matrix metalloproteinases, although initially unsuccessful, could prove to be efficacious, as could agents that inhibit activation of osteoclasts. Apheresis procedures are being investigated. High-dose immunosuppression combined with autologous stem cell transplantation has been used in study protocols for patients whose conditions are resistant to other therapies.

Early therapy

Many studies have revealed that early treatment of RA (ie, within 3-12 mo of onset) with DMARDs can not only more efficiently retard disease progression than later treatment, but also may induce more remissions. Thus, early therapy with DMARDs has become the standard of care. Importantly, note that patients with early forms of arthritis should be evaluated by, and if necessary, referred to physicians who are experienced in the diagnosis and treatment of this disease.

Surgical Care

Cervical spine involvement usually affects C1-C2 and may potentially cause serious neurological consequences. Patients who are to undergo intubation or procedures that may involve manipulation of the neck should have careful evaluation of the cervical spine. Patients with RA often need multiple operations over time (eg, synovectomy, tendon corrections, joint replacements).

Consultations

- Orthopedists
- Physical and rehabilitative medicine specialists

Deterrence and Prevention

RA is a progressive inflammatory disease historically treated according to a pyramid or sequential strategy, beginning with NSAID therapy. The current approach to management emphasizes aggressive control of inflammation to prevent long-term damage using early DMARD therapy, including the use of single or combination DMARDs. Early use of DMARDs had traditionally been avoided until patients show signs of joint damage; however, this strategy has proved ineffective over several years. Patients experience poor long-term outcomes, including severe functional declines, radiographic pro-

gression of disease, work disability, and premature mortality.Two issues appear to be sources of confusion regarding long-term outcomes of treatment. First, a small percentage of patients who meet diagnostic criteria for RA have a self-limited process with spontaneous remission.

Thus, in the absence of signs of progression, some patients are diagnosed with, and subsequently treated for, other conditions. Second, measures of inflammatory activity, such as joint swelling or ESRs, are often used to assess inflammatory activity. However, these indices are less useful end points for evaluation than severe long-term outcomes such as work disability or joint deformity and radiographic changes, in which the latter two are irreversible. During a period in which inflammatory markers may be stable or even improved, radiographic progression and functional decline can occur.The traditional DMARDs, injectable gold salts and penicillamine, rarely induce sustained remission and are usually discontinued within 2 years. Because better agents are available, they are rarely used. Newer DMARDs, such as MTX and SSZ, have greater long-term effectiveness but still rarely induce true remission. Optimal control may require combination therapy. Recent studies have shown that MTX combined with other DMARDs is more effective and has acceptable toxicity when compared with use of a single agent. In combination with cyclosporine, MTX results in greater clinical improvement than MTX alone. Triple therapy with MTX, SSZ, and hydroxychloroquine provides substantially greater clinical improvement than MTX alone or SSZ plus hydroxychloroquine.1 In combination with infliximab, MTX provides a superior response to monotherapy.2 In combination with etanercept, MTX provides a higher rate of meaningful clinical response. Toxicities of these drug combinations are rarely more significant than those occurring with any of the individual agents used alone. The goal of contemporary management of RA should be complete remission or no evidence of disease activity. Achieving this goal likely requires ongoing drug therapy, probably using a combination of MTX with some other DMARD, although some patients may still respond satisfactorily to monotherapy. More long-term studies are needed to evaluate potential important adverse effects associated with combination therapy before definite recommendations can be made.

Complications

RA is not fatal, but complications of the disease may shorten survival by a few years in some individuals. In general, RA is progressive and cannot be cured; in some, the disease gradually becomes less aggressive and symptoms may even improve. However, if bone and ligament destruction and any deformities have occurred, the effects are permanent.

Joint disability and pain with daily life are common. Affected joints can become deformed, and the performance of even ordinary tasks may be very difficult or impossible. According to one survey, 70% of patients with RA believe the disease prevents them from living a fully productive life. In 2000, a study in England found that approximately one third of individuals stop working within 5 years of the onset of disease. RA is a systemic disease that can affect other parts of the body in addition to joints. These effects include the following:

Peripheral neuropathy: This condition affects nerves, most often those in the hands and feet. It can result in tingling, numbness, or burning.

Anemia

Scleritis: This is an inflammation of the blood vessels in the eye that can result in corneal damage, scleromalacia, and, in severe cases of nodular scleritis, perforation.

Infections: Patients with RA have a higher risk for infections, particularly from some of the immunosuppressive drugs required for treatment.

GI problems: Although patients may experience stomach and intestinal distress, lower rates of stomach and colorectal cancers have been reported among patients with RA.

Osteoporosis: Osteoporosis is more common than average in postmenopausal women with RA. The hip is particularly affected. The risk for osteoporosis also appears to be higher than average in men with RA who are older than 60 years.

Lung disease: One small study found a very high prevalence of lung disease (pulmonary inflammation and fibrosis) in patients newly diagnosed with RA. However, the association between a history of smoking and a higher risk for RA may at least partially account for this finding. Cigarette smoking, in any case, may increase the severity of the disease.

Heart disease: RA can affect the blood vessels and increases the risk for coronary ischemic heart disease.

Sjögren syndrome: Keratoconjunctivitis sicca is a common complication of RA. Oral sicca and salivary gland enlargement are less common.

Felty syndrome: The combination of splenomegaly, leukopenia (neutropenia), and recurrent bacterial infections, this syndrome sometimes responds to DMARD therapy.

Lymphoma and other cancers: Alterations in the immune system associated with RA may play a role in the higher risk for lymphoma observed in patients with RA. Aggressive treatments for RA that suppress the immune system may help prevent this cancer, but more research is needed to evaluate this possibility. Other cancers that may occur with increased frequency in patients with RA include prostate and lung cancers.

Macrophage activation syndrome: This is a life-threatening complication of RA and requires immediate treatment with high-dose steroids and cyclosporin A. Patients should be aware of symptoms, which include persistent fever, weakness, drowsiness, and lethargy.

Prognosis

The clinical course is generally one of exacerbations and remissions. Approximately 40% of patients become disabled after 10 years, but outcomes are highly variable. Some patients experience a relatively self-limited disease, and others have a chronic progressive illness.

Improvements in the detection of early joint injury have provided a previously unappreciated view of the ubiquity and importance of early joint damage. Nonetheless, predicting the course of an individual case at the outset remains difficult, although the HLA-DRB1*04/04 genotype, a high serum titer of RF, extra-articular manifestations, a large number of involved joints, age younger than 30 years, female sex, and systemic symptoms all correlate with an unfavorable prognosis with joint damage and disability. Insidious onset is also an unfavorable sign.

Disease that remains persistently active for more than a year is likely to lead to joint deformities and disability. Cases in which periods of activity lasting only weeks or a few months are followed by spontaneous remission have a better prognosis.

The absence of RF does not necessarily portend a good prognosis. Outcome is compromised when diagnosis and treatment are delayed. Other laboratory markers of a poor prognosis include early radiologic evidence of bony injury, persistent anemia of

chronic disease, elevated levels of the C1q component of complement, and the presence of anti-CCP antibodies.

The overall mortality rate for patients with RA is reportedly 2.5 times that of the general population. In those with severe articular and extra-articular disease, the mortality rate approaches that of patients with 3-vessel coronary disease or stage IV Hodgkin disease. Much of the excess mortality derives from infection, vasculitis, and poor nutrition. Mortality from cancer is unchanged.

Most data on rates of disability derive from specialty units caring for referred patients with severe disease. Little information is available on patients cared for in primary care community settings. Estimates suggest that more than half of these patients remain fully employed, even after 10-15 years of disease, with a third having only intermittent low-grade disease and another third experiencing spontaneous remission.

Patient Education

Patient education and counseling are well worth the time invested because they help to reduce pain, disability, and frequency of physician visits. They represent the most cost-effective intervention.

Informing the patient of the diagnosis

With a potentially disabling disease such as RA, the act of informing the patient of the diagnosis takes on major importance. The goal is to satisfy the patient's informational needs regarding the diagnosis, prognosis, and treatment without going into an overwhelming and excessive amount of detail. Careful questioning and empathic listening are required to understand the patient's perspective, requests, and fears.

Telling patients more than they are intellectually or psychologically prepared to handle (a common practice) risks making the experience so intense as to trigger withdrawal. Conversely, failing to address issues of importance to the patient compromises the development of trust. The patient needs to know that the primary physician understands the situation and is available for support, advice, and therapy as the need arises. Encouraging the patient to ask questions helps to communicate interest and caring.

Discussing prognosis and treatment

Patients and families do best when they know what to expect and can view the illness realistically. Uncertainty greatly contributes to the disease of RA. Many patients fear crippling consequences and dependency.

The most common disease manifestations should be described. Without building false hopes, the physician can point out that spontaneous remissions can occur and that more than two thirds of patients live independently without major disability. In addition, emphasize that much can be done to minimize discomfort and to preserve function. A review of available therapies and their efficacy helps to overcome feelings of depression stemming from an erroneous expectation of inevitable disability. Even in patients with severe disease, guarded optimism is now appropriate, given the host of effective and well-tolerated disease-modifying treatments that are emerging.

Abandonment is a major fear. Patients are relieved to know that they will be closely observed by the primary physician and health care team, working in conjunction with a consulting rheumatologist and physical/occupational therapist, all of whom are committed to maximizing the patient's comfort and independence and to preserving joint function.

Dealing with misconceptions

Several common misconceptions deserve attention. A substantial proportion of patients and their families feel that they have done something to cause the illness. Explaining that no known controllable precipitants exist helps to eliminate much unnecessary guilt and self-recrimination.

Dealing in an informative, evidence-based fashion with a patient who expresses interest in alternative and complementary forms of therapy can help limit expenditures on ineffective treatments.

Another misconception is that a medication must be expensive to be helpful. Aspirin, generic NSAIDs, low-dose prednisone, and the first-line disease-modifying agents are quite inexpensive, yet remarkably effective, a point that bears emphasizing. The sense that one must be treated with the latest TNF inactivator can be addressed by a careful review of the overall treatment program and the proper role of such agents in the patient's plan of care.

The active participation of the patient and family in the design and implementation of the therapeutic program helps to boost morale and ensure compliance, as does explaining the rationale for the therapies used.

Preserving a sense of self-worth

A major goal is to preserve the patient's sense of worth and independence. However, when fatigue, morning stiffness, or specific joint disease interferes with a patient's capacity to carry out the usual responsibilities at work and at home, counseling will be necessary to recommend modification of work responsibilities and perhaps retraining. Recognition and treatment of concomitant depression is important. With the use of occupational therapy, the treatment effort is geared to helping the patient maintain a meaningful work role within the limitations of the illness. The family plays an important part in striking the proper balance between dependence and independence. Household members should avoid overprotecting the patient (eg, refraining from intercourse out of fear of hurting the patient) and should work to sustain the patient's pride and ability to contribute to the family. Allowing the patient with RA to struggle with a task is sometimes constructive.

Supporting the patient with debilitating disease

Persons with long-standing severe disease who have already sustained much irreversible joint destruction benefit from an emphasis on comfort measures, supportive counseling, and attention to minimizing further debility. Such patients need help in grieving for their disfigurement and loss of function.

An accepting, unhurried, empathic manner allows the patient to express feelings. The seemingly insignificant act of touching does much to restore a sense of self-acceptance. Attending to pain with increased social support, medication, and a refocusing of attention to function are useful. A trusting and strong patient-doctor relationship can do much to sustain a patient through times of discomfort and disability.

Part 6.

FELTY SYNDROME

First described in 1924, Felty syndrome (FS) is a potentially serious condition that is associated with seropositive (rheumatoid factor [RF] positive) rheumatoid arthritis (RA). Felty syndrome is characterized by the triad of RA, splenomegaly, and granulocytopenia. Although many patients are asymptomatic, some develop serious and life-threatening infections secondary to granulocytopenia.

Pathophysiology

Although the pathophysiology of Felty syndrome is not fully known, evidence points to splenic sequestration and subsequent granulocyte destruction. Studies performed almost 50 years ago demonstrated lower granulocyte counts in the splenic vein compared with those in the splenic artery. Researchers have shown immune complexes coating granulocytes, diminished granulocyte growth factor levels, and numerous circulating autoantibodies, including those against granulocyte surface antigens. A recent study in Germany examined 15 patients with neutropenia from Felty syndrome and matched them to a control group of 16 patients with normocytic RA. In addition, 16 patients with neutropenia and systemic lupus erythematosus (SLE) were matched to a control group of 16 patients with SLE. Antibodies against granulocyte colony-stimulating factor (G-CSF) were measured. Eleven patients with Felty syndrome demonstrated anti–G-CSF immunoglobulin G (IgG); none of the patients in the RA control group demonstrated anti–G-CSF IgG. Six patients with both neutropenia and SLE and 6 patients in the SLE control group also had anti–G-CSF antibodies. These antibodies appeared to have a neutralizing effect on G-CSF.

Frequency

Felty syndrome affects approximately 1-3% of all patients diagnosed with RA, and RA occurs in about 1% of the general population. The true prevalence of Felty syndrome is difficult to ascertain because many patients are asymptomatic. Felty syndrome rarely occurs in children. The prevalence of Felty syndrome may be decreasing with the advent of more potent antirheumatic agents. It seems to be quite rare in the African American population.

Mortality and Morbidity of Felty syndrome

Although many patients are asymptomatic, others progress and develop life-threatening infections. Pulmonary and skin infections are common. The level of debilitation from the underlying RA as well as the extent of immunosuppression used in treating both RA and Felty syndrome heavily influence mortality and morbidity. One study from the southwest of England observed 32 patients with Felty syndrome; 5 patients died from overwhelming bronchopneumonia during a mean follow-up period of 5.2 years. Curiously, in the past 20 years in the United States, the frequency of hospitalization for rheumatoid vasculitis and ultimate splenectomy in patients with Felty syndrome has dropped. This drop is theorized to be secondary to earlier and more aggressive treatment of RA, controlling the disease before the manifestations of Felty syndrome appear.

Race, sex and age particularities of Felty syndrome

Felty syndrome most often occurs in whites and infrequently occurs in blacks. The human leukocyte antigen DR4 (HLA-DR4) genotype, which is a marker for more aggressive RA and more frequent extra-articular manifestations in whites, is strongly associated with Felty syndrome. The incidence in women exceeds the incidence in men by a ratio of 3:1. Underreporting and asymptomatic cases cause difficulty in determining the true sex ratio. Patients most commonly develop Felty syndrome during the fifth through the seventh decades of life. The condition is usually associated with more than 10 years of preceding RA activity. Men are affected with Felty syndrome earlier in the course of RA than women are.

History of Felty syndrome

Many years of aggressive destructive RA precede the onset of Felty syndrome. On occasion, RA and Felty syndrome simultaneously develop. The extra-articular manifestations of RA (eg, rheumatoid nodules, pleuropericarditis, vasculitis, peripheral neuropathy, episcleritis, other forms of eye involvement, Sjögren syndrome, adenopathy, skin ulcers) are more common in patients who develop Felty syndrome. Patients with Felty syndrome often report current symptoms of mild inflammatory joint disease caused by synovitis. The patient's history, however, usually reveals a long preceding period of active and aggressive joint disease, which can be confirmed by physical examination and

plain radiography. Some patients present with quiescent or so-called "burned-out" joint disease. A lack of synovitis or active joint disease should not dissuade the clinician from considering the diagnosis of Felty syndrome. Patients commonly present with bacterial infections of the skin and respiratory tract. An aggressive level of immunosuppression directed at the underlying RA may contribute to the susceptibility to infection. Patients may present with left upper quadrant pain, initiated by splenic infarcts or capsular distension.

Physical examination findings

- Splenomegaly, although it may not be palpable
- Hepatomegaly, usually mild
- Lymphadenopathy
- Weight loss
- Rheumatoid nodules
- Sjögren syndrome
- Articular findings of long-standing RA
    - Joint deformities typical of RA
    - Synovitis (joint swelling and tenderness), may be mild at presentation
- Small-vessel inflammation (vasculitis)
    - Lower extremity ulcers
    - Palpable purpura and brownish pigmentary changes of the lower extremities
    - Periungual infarcts
- Signs of systemic vasculitis
    - Mononeuritis multiplex
    - Extremity ischemia
- Others findings, including pleuritis, peripheral neuropathy, episcleritis, and signs of portal hypertension

Causes of Felty syndrome

- Risk factors for Felty syndrome include the following:
    - RF positivity in high titers
    - Long-standing disease
    - Aggressive and erosive synovitis: Patients with Felty syndrome may present with mild RA, but Felty syndrome is clearly associated with severe disease and extra-articular manifestations.
    - HLA-DR4 positivity and DR4 homozygosity: This may be due to the presence of HLA-DR4 in patients who have severe disease.
    - Extra-articular RA manifestations

Lab Studies

CBC count with differential is as follows:

Obtain a white blood cell (WBC) count and differential, which are crucial when determining the degree of granulocytopenia. Studies show that the greatest risk for infection occurs when the patient's granulocyte count is less than 1000/µL. Bear in mind, however, that the level of neutropenia varies over time without medical intervention. Granulocyte dysfunction and an absolute decrease in number of granulocytes are factors that may predispose patients to infection. Anemia and thrombocytopenia may result from hypersplenism. Anemia of chronic disease may result from the underlying inflammatory disease.

Mild elevations of alkaline phosphatase and transaminase levels may occur.

High titers of RF are almost always present in patients with Felty syndrome (98%). This is because extra-articular manifestations of RA are strongly associated with RF.

Antinuclear antibodies (ANAs), found in 67% of cases; antihistone antibodies; and even antineutrophil cytoplasmic antibodies (perinuclear pattern; p-ANCA), found in 77% of cases, commonly occur in patients with Felty syndrome. The significance of autoantibodies in Felty syndrome is unknown, and their contribution, if any, to the disease itself is uncertain.

Erythrocyte sedimentation rate (ESR) and serum immunoglobulin levels invariably are elevated in patients with Felty syndrome.

Cryoglobulins may be present.

Imaging Studies

Radionuclide studies, ultrasonography, or computed tomography (CT) scanning may define the presence and extent of splenomegaly. The same modalities can also be used to assess patient response to therapy.

Procedures

Bone marrow aspiration and biopsy are especially important to rule out LGL syndrome. The bone marrow of patients with Felty syndrome shows adequate megakaryocytes and myeloid hyperplasia with arrested development at the level of immature cell forms.

Histologic Findings

An unusual type of liver involvement known as nodular regenerative hyperplasia is associated with Felty syndrome. It is characterized by mild portal fibrosis or lymphocyte and plasma cell infiltration but is not typical of cirrhosis. It may be complicated by portal venule occlusion and regenerative nodule formation.

Medical Care

The best treatment for Felty syndrome is to control the underlying RA. Immunosuppressive therapy for RA often improves granulocytopenia and splenomegaly; this finding reflects the fact that Felty syndrome is an immune-mediated disease. Most of the traditional medications used to treat RA have been used in the treatment of Felty syndrome. No well-conducted, randomized, controlled trials support the use of any single agent. Most reports on treatment regimens involve small numbers of patients.

Historically, most patients have been treated with gold salts, reflective of their long history of use in RA prior to the advent of methotrexate; however, the response of the condition is slow. Older studies report a response rate of 60-80%. Intramuscular aurothioglucose (Solganal) was the agent most commonly used. Methotrexate acts faster than gold and now is the preferred agent of rheumatologists for treating RA. As experience using methotrexate in Felty syndrome increases, this drug is likely to become the agent of choice for therapy. If urgent correction of neutropenia is not necessary, most practicing rheumatologists use this drug first when treating Felty syndrome. It is usually combined with folic acid to minimize adverse effects. Note that the beneficial effects of methotrexate may not be evident for 4-8 weeks. The potential for leukopenia limits the use of cyclophosphamide, although it may have a role in some cases. A recent report described 2 patients with refractory Felty syndrome who responded to high-dose cyclophosphamide; however, physicians have had far more experience using cyclophosphamide for rheumatoid vasculitis and other serious RA extra-articular manifestations than for Felty syndrome. For this reason, it is not an initial choice of therapy. Penicillamine is being used less frequently for RA because of its adverse effect profile. Penicillamine never is a first-choice therapy for patients with Felty syndrome.

Etanercept, adalimumab, and infliximab are all newer agents prescribed for RA. These agents act by blocking the effects of tumor necrosis factor-a (TNF-a). These

drugs are very effective in the treatment and control of RA the experience of using them for Felty syndrome is limited. Intravenous immunoglobulin (IVIG) does not show reproducibly demonstrable success. Recombinant granulopoietic growth factors, such as G-CSF and granulocyte-monocyte colony-stimulating factor (GM-CSF), effectively and quickly raise the granulocyte count, which is important for patients with life-threatening infections. Initial treatment of patients with Felty syndrome and life-threatening infections should include the administration of a growth factor. Long-term use of G-CSF appears to be well tolerated, although hypersensitivity vasculitis and flare-ups of the underlying RA in these patients have been reported. At high doses, corticosteroids can increase the granulocyte count, partly through demargination. This effect does not persist when tapering the patient to a typical low dose (<10 mg/d) used for RA articular disease. Empiric administration of high-dose intravenous methylprednisolone is often prescribed for Felty syndrome, but the effect is time limited. Long-term use of high-dose corticosteroids further increases the risk for infection. Corticosteroids should probably be viewed as a second-line treatment modality. Case reports in the past few years have noted a lack of efficacy with rituximab (Rituxan), a response to leflunomide (Arava), and a response to salazosulfapyridine (see additional materials). These were all single-patient reports.

Surgical Care

Splenectomy is only recommended for patients with severe intractable disease who exhibit no improvement with medical therapy and experience recurrent or serious infection. Less commonly, extrinsic hemolysis or recurrent cutaneous ulcers may indicate a need for splenectomy. Granulocytopenia recurs in approximately 25% of patients who have undergone splenectomy.

Consultations

- Rheumatologist
- Hematologist
- Infectious diseases specialist

Activity

Dictate patient activity according to infection risk and spleen size. Recommend that the patient avoid any activity that could result in blunt trauma to the left upper quadrant.

Complications

- Splenic rupture
- Life-threatening infection
- Toxicity from immunosuppressive regimens
- Portal hypertension and gastrointestinal bleeding from nodular regenerative hyperplasia of the liver

Prognosis

Granulocytopenia is defined as an absolute neutrophil count (ANC) of less than 2000/μL, and infection risk increases as the ANC drops. Infection incidence increases significantly when the polymorphonuclear leukocyte (PMN) count is less than 1000/μL. Lymphoproliferative malignancies were more prevalent in a retrospective study of male patients treated at the Department of Veterans Affairs. In particular, the patients had an increased prevalence of non-Hodgkin lymphoma

Part 7.

GOUT

Gout is a common disorder of uric acid metabolism that can lead to recurrent episodes of joint inflammation, tissue deposition of uric acid crystals, and joint destruction if left untreated. Unlike many other rheumatic diseases, gout is very treatable. A definitive diagnosis can be made using joint aspiration and synovial fluid analysis. Early diagnosis and treatment have made a significant impact in this disorder, as evidenced by the declining incidence of chronic tophaceous gout. However, tophaceous gout may occur due to misdiagnosis, poor management, and poor patient compliance.

Pathophysiology

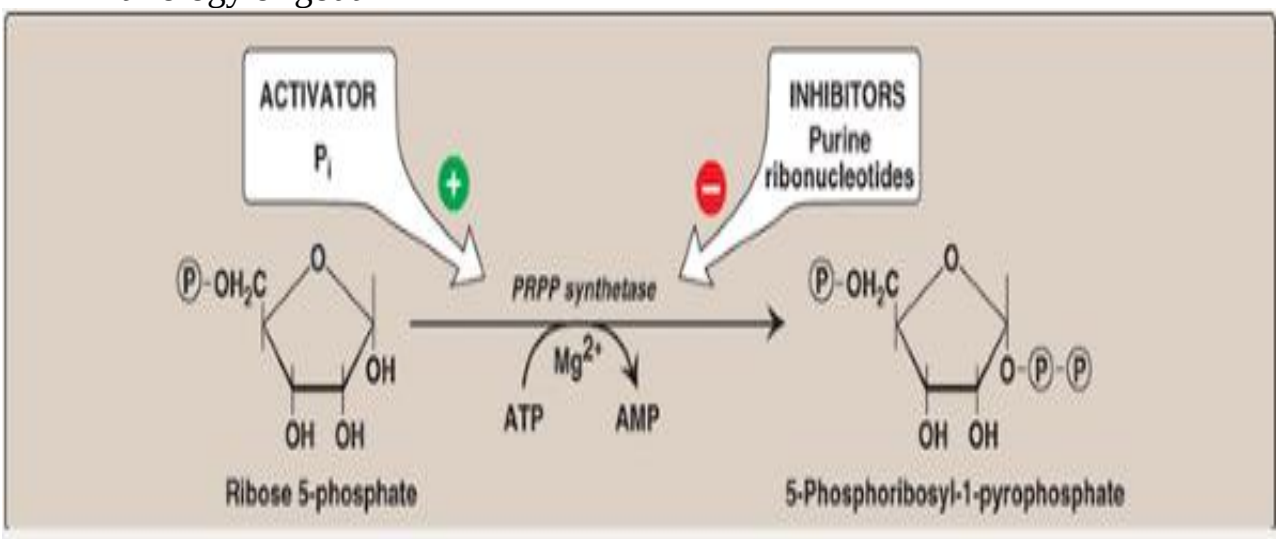
High levels of uric acid circulating in the blood, which can cause needle-shaped urate crystals to settle in the tissues of the joints as well as the kidneys. These crystals are sodium urate crystals which are the end products of purine matabolism. This inherited gene causes an abnormality in the enzyme of purine metabolism (primary gout). Several X-linked mutations have been identified in the PRPP synthetase gene which results in the enzyme having either:

- Increased V_{max} for the production of PRPP
- A lower K_m for ribose 5-phosphate
- Decreased sensitivity to its purine nucleotide inhibitors

The overall result is increased purine production resulting in high levels of plasma uric acid (figura 7).

Figura 7

Ethiology of gout



Gout is caused by excess stores of uric acid that accumulate in tissues, including the synovium. Lowering serum uric acid levels can prevent attacks of gouty arthritis. However, urate crystals also can be found in synovial fluid in the absence of joint inflammation. Thus, the mere presence of intrasynovial urate crystals is not sufficient to cause flares of gouty arthritis.

Because urate crystals can be coated with apolipoprotein (apo) E or apo B, a reasonable hypothesis is that this protein coating prevents the crystals from triggering an inflammatory response. Therefore, situations that lead to exposure of bare areas of the crystals may trigger an inflammatory response. Clinically, gout flares can be triggered by fluxes in uric acid levels or by microtrauma, each of which can lead to shedding of uncoated crystals. When bare areas of the urate crystals are exposed, they can bind immunoglobulin G (IgG). Such binding stimulates neutrophils to engulf and phagocytose the crystals. Once this occurs, there is a brisk influx of neutrophils associated with elevated levels of interleukin-1, interleukin-6, interleukin-8, tumor necrosis factor-alpha, prostaglandin E2, leukotriene B4, kinins, C5a, and other inflammatory mediators. It is also conceivable is that recoating of uric acid crystals by apo E or apo B could lead to the spontaneous resolution of attacks.

Mortality and Morbidity

Gout is associated with considerable morbidity. During acute episodes, patients often are incapacitated. Untreated chronic tophaceous gout can develop and lead to severe joint destruction. Hyperuricemia is associated with increased all-cause mortality. This is not due to gout, per se, but to diseases associated with gout, such as insulin resistance, type 2 diabetes mellitus, abdominal obesity, hypercholesterolemia, and hypertension.

Race, sex and age particularities

Blacks have a slightly higher prevalence compared to whites. The prevalence for men is 13.6 cases per 1000 men, and the prevalence for women is 6.4 cases per 1000 women. This difference is largely a manifestation of age of onset because estrogenic hormones have a mild uricosuric effect; therefore, gout is unusual in premenopausal women. As a general rule, uric acid levels are elevated for 20 years before the onset of gout. In men, uric acid levels rise at puberty, and peak age of onset of gout is in the fourth to sixth decades. In women, uric acid levels rise at menopause, and peak age of

onset is in the sixth to eighth decades. Gout is unlikely to present in premenopausal women or in men younger than 30 years unless renal insufficiency or a genetic abnormality of purine metabolism is present, such as hypoxanthine-guanine phosphoribosyltransferase deficiency or phosphoribosylpyrophosphate synthetase superactivity. The higher prevalence of gout in elderly persons may also reflect an increased prevalence of the metabolic syndrome, high rates of diuretic treatment for hypertension and congestive heart failure, and the use of low-dose acetylsalicylic acid. Typically, tophi may be clinically detected approximately 10 years after the first attack of gout. Cyclosporin A can cause an accelerated form of gout, even in premenopausal women, that can present after only a few years of hyperuricemia, particularly if the patient also is treated with diuretics.

History of gout

Acute monoarticular arthritis is the initial presentation of gout in 90% of patients. In early gout, usually only 1 or 2 joints are involved. Typically, they are the smaller, lower-extremity joints. Podagra (inflammation of the first metatarsophalangeal joint) is the initial joint manifestation involved in 50% of cases. Eventually, it is involved in 90% of cases. Podagra is not synonymous with gout. Podagra can be observed in patients with pseudogout, sarcoidosis, gonococcal arthritis, psoriatic arthritis, and reactive arthritis. The attacks begin abruptly and reach maximum intensity in 8-12 hours. The joints are red, hot, and exquisitely tender; even a bed sheet on the swollen joint is uncomfortable. Untreated, the first attacks resolve spontaneously in less than 2 weeks. Intermittent inflammatory arthritis, in which the joints return to normal between attacks, typically is caused by crystalline disorders and is true of gouty arthritis early in its course. Gout can initially present as a polyarticular arthritis in 10% of patients. Elderly women, particularly women with renal insufficiency and taking a thiazide diuretic, often develop polyarticular arthritis as their first manifestation of gout. These attacks may occur in coexisting Heberden and Bouchard nodes. Such patients also may develop tophi more quickly, occasionally without prior episodes of acute gouty arthritis. Untreated, the clinical characteristics of gout change over time. The attacks become more polyarticular. Although more joints may become involved, inflammation in a given joint may become

less intense. More proximal and upper-extremity joints become involved. Attacks occur more frequently and last longer.

Eventually, patients may develop a chronic polyarticular arthritis, sometimes nearly symmetrical, that can resemble rheumatoid arthritis. Indeed, if a patient presents with a chronic polyarticular arthritis that began as an intermittent arthritis, a crystalline disorder should be considered in the differential diagnosis.

While gout typically causes inflammation in a joint, it also can cause inflammation in other synovial-based structures such as bursas and tendons.

Tophi are collections of uric acid crystals in the soft tissues. They occur in more than half of untreated patients. While the classic location is along the helix of the ear, they can be found in multiple locations, including the fingers, toes, in the olecranon bursae, and along the olecranon, where they can resemble rheumatoid nodules. The finding of a rheumatoid nodule in a patient with a negative rheumatoid factor should prompt the clinician to consider gout in the differential diagnosis. Finding tophi during the first episode of gout is unusual; they tend to develop after 10 years in untreated patients who develop chronic gouty arthritis.

Acute flares of gout can occur in situations that lead to increased levels of serum uric acid, such as the use of alcohol, overindulgence of certain foods, trauma, hemorrhage, or the use of medications that elevate levels of uric acid. Situations that lead to the rapid depletion of adenosine triphosphate (ATP) can result in the accumulation of adenosine 5'-diphosphate, adenosine monophosphate (AMP), and, subsequently uric acid. Alcohol, for example, accelerates the conversion of ATP to AMP. Alcohol also increases lactate relative to pyruvate and thereby reduces the excretion of uric acid. Beer contains guanosine and thereby increases the purine load.

Acute flares of gout also can occur in situations that lead to decreased levels of serum uric acid, such as the use of radiocontrast dye or medications that lower the levels of uric acid.

Patients with gout have a 1000-fold increased incidence of renal stones and therefore may have a history of renal colic. Indeed, renal stones may precede the onset of gout in 40% of patients. While 80% of these patients may have stones composed entirely of uric acid, 20% may develop calcium oxalate or calcium phosphate stones with a

uric acid core. Patients with gout also are prone to develop urate nephropathy, in which uric acid crystals are deposited in the medullary interstitium and pyramids. While patients with gout have a higher incidence of renal impairment, whether hyperuricemia is an independent risk factor for this remains unclear because such patients have a higher incidence of hypertension, diabetes, and other risk factors for renal insufficiency.

Patients with gout often are clustered with the insulin resistance syndrome known as metabolic syndrome or syndrome X: diabetes, hypertension, hypertriglyceridemia, and low high-density lipoproteins. No evidence indicates that gout or hyperuricemia cause any of these other disorders. Because the presence of these associated disorders can lead to coronary artery disease, the incidence of which also is increased in patients with gout, these problems should be sought and treated in patients diagnosed with gout. However, no evidence indicates that gout is an independent risk factor for atherosclerosis.

Importantly, ask about a history of peptic ulcer disease, renal disease, or other conditions that may complicate the use of the medications to treat gout.

Physical examination fidings

During an acute attack, examine all joints to determine if the patient's arthritis is monoarticular or polyarticular. Involved joints show all the signs of inflammation: swelling, warmth, erythema, and tenderness. The erythema over the joint can resemble cellulitis, and the skin may desquamate as the attack subsides. The joint capsule becomes quickly swollen, resulting in a loss of range of motion of the involved joint. During an acute gout attack, patients can have a fever, particularly if it is an attack of polyarticular gout. Look for sites of infection that could have potentially seeded the joint and caused an infectious arthritis that can resemble or coexist with acute gouty arthritis. The presence of tophi suggests long-standing hyperuricemia.

Causes of gout

Gout can develop when excessive stores of uric acid are present. Uric acid is a byproduct of purine metabolism. Lacking uricase, humans remove uric acid primarily by renal excretion. Of patients with primary gout, 90% develop excess stores of uric acid because they are unable to excrete sufficient amounts of uric acid in their urine (underexcretion). The remaining patients produce excessive amounts of uric acid (overpro-

duction). When uric acid levels exceed 6.8 mg/dL, with some variability depending on temperature and pH, uric acid can crystallize.

Individual attacks of gout often are triggered by acute fluxes in uric acid levels that may lead to the exposure or shedding of crystals that are not coated with apo B or apo E. This can result from alcohol ingestion, overindulgence in certain foods, starvation, trauma, hemorrhage, or medications such as diuretics. It also can result from situations that lower levels of uric acid, including the use of radiocontrast dyes and medications such as allopurinol.

Rarely, overproduction of uric acid is due to genetic disorders. These include hypoxanthine-guanine phosphoribosyl transferase deficiency (Lesch-Nyhan syndrome), glucose-6-phosphatase deficiency (von Gierke disease), fructose1-phosphate aldolase deficiency, and PP-ribose-P synthetase variants.

Overproduction of uric acid also can occur secondary to disorders causing high cell turnover. These include myeloproliferative and lymphoproliferative disorders, psoriasis, chemotherapy (tissue lysis), hemolytic anemias, excessive exercise, and obesity.

More common causes of secondary gout include renal insufficiency, lead nephropathy (saturnine gout), starvation or dehydration, hypothyroidism, hyperparathyroidism, drugs (including diuretics and cyclosporine A), and ethanol abuse. These disorders should be identified and corrected if possible.

Lab Studies

- Synovial fluid: When a patient presents with acute inflammatory monoarticular arthritis, aspiration of the involved joint is critical to rule out an infectious arthritis and to attempt to confirm a diagnosis of gout or pseudogout by crystal identification.
- The critical and essential study is synovial fluid analysis to identify urate crystals. Finding intracellular urate crystals by polarizing light microscopy firmly establishes a positive diagnosis of gouty arthritis.

Urate crystals are shaped like needles or toothpicks with pointed ends.

Urate crystals are negatively birefringent. Pragmatically, this means that the crystals are yellow when aligned parallel to the slow ray of the compensator and that they are blue when they are perpendicular.

Pseudogout crystals (calcium pyrophosphate) are rod-shaped with blunt ends.

Pseudogout crystals are positively birefringent. Pragmatically, this means that the colors are the opposite of gout. Thus, pseudogout crystals are blue when aligned parallel to the slow ray of the compensator and yellow when they are perpendicular.

Crystals need to be distinguished from birefringent cartilaginous or other debris. Debris may have fuzzy borders and may be curved, whereas crystals have sharp borders and are straight.

Corticosteroids used to inject joints have a crystalline structure that can be either positively or negatively birefringent. Therefore, interpreting polarized microscopy from a joint that was recently injected with corticosteroids is difficult.

The sensitivity of a synovial fluid analysis for crystals is 84%, with a specificity of 100%. If gout remains a clinical consideration after a negative analysis, the procedure can be repeated in another joint or with a subsequent flare.

While the sensitivity is less, urate crystals can be identified from synovial fluid aspirated from previously inflamed joints that are not currently inflamed. These generally are extracellular.

Minute quantities of fluid in the shaft or hub of the needle are sufficient for synovial fluid analysis.

Once a crystal diagnosis of gout is established, joints do not need repeat aspiration with subsequent flares unless infection is suggested or the flare does not respond appropriately to therapy for acute gout.

For patients with acute monoarticular arthritis, send synovial fluid for Gram stain and culture and sensitivity. The culture also provides sensitivities for antibiotic management.

Synovial fluid also should be sent for cell count.

During acute attacks, the synovial fluid is inflammatory, with a WBC count greater than 2000/microliter (class II fluid) and possibly greater than 50,000/microliter with a predominance of polymorphonuclear neutrophils.

Synovial fluid glucose usually is normal, whereas in septic arthritis and occasionally rheumatoid arthritis, it may be depressed. Measurement of synovial fluid protein has no clinical value.

Crystalline arthritis and infectious arthritis can coexist. Indeed, infectious arthritis is more common in previously damaged joints, which may occur in chronic gouty arthritis.

Serum uric acid

This is the most misused test in the diagnosis of gout.

Five to eight percent of the population has elevated serum uric acid levels (>7 mg/dL), but only 5-20% of patients with hyperuricemia develop gout. Thus, the presence of an elevated level of serum uric acid does not mean the patient has gout or will develop gout. Gout is diagnosed by finding urate crystals in the synovial fluid or soft tissues. More importantly, a number of patients with infectious arthritis present with a hot swollen joint and an elevated serum uric acid level. These patients will be mismanaged if their synovial fluid is not aspirated to determine that they have septic arthritis.

Asymptomatic hyperuricemia should not be treated. However, patients with levels higher than 11 mg/dL and overexcretion of uric acid are at risk for renal stones and renal impairment; therefore, renal function should be monitored in these individuals.

The risk for developing gout increases with the level of serum uric acid. The 5-year risk for developing gout is approximately 0.6% if the level is less than 7.9 mg/dL, 1% if 8-8.9 mg/dL, and 22% if higher than 9 mg/dL.

As many as 10% of patients with gout have normal serum uric acid levels at the time of their attack. Thus, the correct diagnosis of gout can be missed if the joint is not aspirated because their uric acid level is normal. Remember that situations that lower uric acid levels can trigger attacks of gout. However, the patient's prior medical records should reveal prior elevations of uric acid. Elevated levels of serum uric acid can be observed in other disorders such as myeloproliferative disorders, polycythemia vera, psoriasis, sarcoidosis, hyperparathyroidism, hypothyroidism, pernicious anemia, and sickle cell anemia.

Uric acid in 24-hour urine sample.

If patients excrete more than 800 mg of uric acid in 24 hours on a regular diet, they are overexcretors and thus overproducers of uric acid. Patients who excrete more than 1100 mg in 24 hours should have renal function monitored closely because of the risk of stones and urate nephropathy. Patients who are overproducers of uric acid, only

10% of patients with gout, require allopurinol instead of probenecid to lower their uric acid. If the patient already has a contraindication for using probenecid, such as a history of renal stones or renal insufficiency, then a 24-hour urine test of uric acid excretion does not need to be performed because the patient clearly will need allopurinol.

Blood chemistry

Obtaining an estimate of the patient's renal function before deciding on therapy for gout is important. Remember that the serum creatinine alone can overestimate renal function in elderly patients or in patients with low muscle mass. Patients with gout have a higher incidence of diabetes mellitus. Abnormal liver function tests need to be considered when selecting therapy.CBC count: WBC count can be elevated in patients during the acute gouty attack, particularly if it is polyarticular. **Lipids:** Hypertriglyceridemia and low high-density lipoproteins are associated with gout.

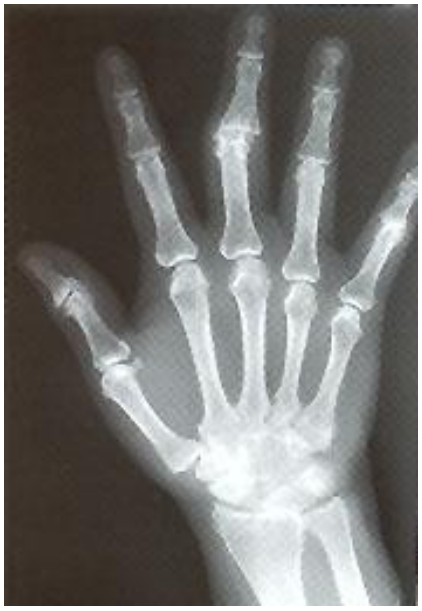
Urinalysis: Patients with gout have a high incidence of renal stones; therefore, patients may have or may have had hematuria.

Imaging Studies

Plain radiographs may show findings consistent with gout, but these findings are not diagnostic. Radiograph examination usually shows sharply "punched-out" bony defects of the distal radius, as indicated Figura 8.

Figura 8

Radiograph showing sharply "punched-out" bony defects of the distal radius and proximal phalange of the middle finger



The most common radiographic finding early in the disease is soft-tissue swelling or a normal radiograph.

- Haziness suggestive of tophi can be seen in late gout, and tophi may calcify.
- Erosions that are not typical of rheumatoid arthritis may suggest gout.
- Erosions with maintenance of the joint space
- Erosions without periarticular osteopenia
- Erosions outside the joint capsule
- Erosions with overhanging edges
- Erosions with sclerotic borders, sometimes called cookie-cutter or punched-out borders
- Erosions that are distributed asymmetrically among the joints, with strong predilection for distal joints, especially in the lower extremities

Procedures

Perform arthrocentesis to rule out an infectious arthritis and to establish a crystal-proven diagnosis of gout. Tophi also may be aspirated for crystal analysis under polarizing microscopy.

Histologic Findings

Tophi have been found in all tissues except the brain. However, uric acid dissolves in formalin; therefore, only the ghosts of uric acid crystals may be seen if formalin is used. Alcohol-fixed tissue is best for identification of uric acid crystals.

Medical Care

There are 3 stages in the management of gout: treating the acute attack, providing prophylaxis to prevent acute flares, and lowering excess stores of uric acid to prevent flares of gouty arthritis and to prevent tissue deposition of uric crystals.

Management of acute gout: Options for treatment of acute gout include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or colchicine (a classic treatment but now rarely indicated). The choice is based primarily on the patient's other health problems, such as renal insufficiency and peptic ulcer disease.

Nonsteroidal anti-inflammatory drugs

NSAIDs are the drugs of choice in most patients without underlying health problems. Indomethacin is the traditional choice unless the patient is elderly, because of the potential for adverse CNS effects in this age group. However, most NSAIDs can be

used. Select an agent with a quick onset of action, but do not use aspirin because it can alter uric acid levels and potentially prolong and intensify an acute attack. Cyclooxygenase-2 (COX-2) inhibitors have been used with success. Start with the highest dose for 2-3 days and taper down over approximately 2 weeks. Patients should be asymptomatic for at least 2 days before discontinuing the NSAID. Avoid NSAIDs in patients who have a history of peptic ulcer disease or GI bleeding, patients with renal insufficiency, patients with abnormal hepatic function, patients taking coumadin (selective COX-2 inhibitors can be used), and patients in the intensive care unit who are predisposed to gastritis.

Corticosteroids

Corticosteroids can be given to those patients who cannot use NSAIDs or colchicine. Some rheumatologists recommend corticosteroids over NSAIDs as the preferred choice for treatment of acute gout. Steroids can be given orally, intravenously, intramuscularly, intra-articularly, or indirectly via adrenocorticotropic hormone (ACTH). Prednisone can be given at a dose of approximately 40 mg for 1-3 days and then tapered over approximately 2 weeks. Tapering more rapidly can result in a rebound flare. Using parenteral corticosteroids confers no advantage unless the patient cannot take oral medications. Intra-articular corticosteroids are particularly useful in patients with a monoarticular flare to help reduce the systemic effect of oral steroids. Ensuring that the joint is not infected prior to injecting intra-articular corticosteroids is particularly important. ACTH at 40 IU IM can be given to induce corticosteroid production by the patient's own adrenal glands. Such a regimen does not depend on the patient to taper prednisone properly.

Colchicine

Colchicine is the classic medication for gout but is not the preferred medication for the treatment of acute gout. It is most effective during the first 12-24 hours of an attack, but its effectiveness declines with the duration of inflammation. Moreover, when used to treat an acute attack, colchicine causes adverse GI effects, particularly diarrhea and vomiting, in 80% of patients. To treat an acute attack colchicine is given orally at 0.5-0.6 mg every hour until the patient has relief, has adverse GI effects, or takes 6 mg (ten 0.6-mg tabs). The total dose and the frequency need to be reduced in patients with renal or hepatic insufficiency, and colchicine generally is not recommended in these situa-

tions. Patients may be able to abort an attack by taking a single colchicine tablet at the first twinge of an attack. Colchicine should not be used if the glomerular filtration rate (GFR) is less than 10 mL/min, and the dose should be decreased by at least half if the GFR is less than 50 mL/min. Colchicine also should be avoided in patients with hepatic dysfunction, biliary obstruction, or an inability to tolerate diarrhea. A clinical response to colchicine is not pathognomonic for gout and can be seen with pseudogout, sarcoid arthropathy, psoriatic arthritis, and calcific tendonitis. Colchicine also can be administered intravenously. While this route of therapy can quickly abort an attack of gout, it should be employed only in unusual circumstances because it is potentially toxic. Indeed, this therapy is banned in some countries due to a 2% fatality rate. IV colchicine should be used cautiously, if at all, in patients with renal insufficiency or hepatic dysfunction. When given intravenously, 1 mg of colchicine is diluted in 20 mL of isotonic sodium chloride solution without glucose and pushed over 10-20 minutes in a secure IV line. A maximum of 4 mg is given over 24 hours, and no further colchicine should be given for the next week. If the medication extravasates, it can cause tissue necrosis. Within the vessels, it also can cause thrombophlebitis. Granulocytopenia is a prime complication of IV colchicine. The WBC count should be measured before infusion. Other complications include disseminated intravascular coagulopathy, renal failure, hepatocellular toxicity, seizures, and shock.

Prophylaxis to prevent acute flares

Lowering uric acid with either allopurinol or probenecid can precipitate attacks of gout. When used prophylactically, colchicine can reduce such flares by 85%. The standard dose for prophylaxis is colchicine at 0.6 mg bid. In patients with renal insufficiency, this dose may need to be decreased to daily or every-other-day administration. Compared with the 80% risk of adverse GI effects in patients using colchicine for the treatment of acute gout, the prophylactic dose of colchicine induces adverse GI effects in only 4% of patients. Long-term use of colchicine can lead to a muscle weakness associated with elevated levels of creatine kinase due to a drug-induced neuromyopathy, particularly in patients with renal insufficiency. In patients who cannot take colchicine, NSAIDs can be used for prophylaxis, such as indomethacin at 25 mg bid.

Prophylaxis with colchicine can be started during the acute attack.

Lowering uric acid levels.

In many cases, patients who have a first attack of gout should undergo therapy with agents that lower uric acid, given the high risk for further inflammatory attacks and the potential for destructive tophaceous deposition in the bone and synovium, even without episodes of acute inflammation. Some rheumatologists advocate waiting for the second attack to begin therapy to lower uric acid levels because not all patients have a second attack and because some patients may need to be convinced they need life-long therapy. This decision is partly dependent on the baseline serum uric acid levels (a level > 9 mg/dL denoting higher risk for recurrent gouty arthritis and tophi). In all cases, the risks and benefits need to be judged based on the individual patient. For instance, in an elderly patient with multiple medical problems and renal insufficiency, the risks of therapy to lower uric acid levels may outweigh the benefits. The goal of therapy is to lower serum uric acid levels to approximately 5-6 mg/dL. The risk of a second attack of gout after the first attack is 62% after 1 year, 78% after 2 years, and 93% after 10 years. Treating patients with colchicine alone may help prevent flares of inflammatory arthritis but does not prevent the accumulation of uric acid in the joints, which can lead to further joint destruction. While using agents that lower uric acid is important, they should not be started during an acute attack. This may lead to a more intense and prolonged attack. Typically, they should be started a few weeks after the attack has resolved and with the protection of colchicine to prevent another attack. If the patient develops a flare of gout when starting on agents that lower uric acid, do not discontinue the agent because this will only cause another flux in the uric acid level that may prolong and intensify the attack.

Probenecid

Some rheumatologists prefer probenecid whenever possible because it has fewer significant adverse effects than allopurinol. Probenecid can be used in the majority of middle-aged, otherwise healthy men with gout. Indications for the use of allopurinol instead of probenecid include renal insufficiency (GFR <50 mL/min), renal stones, use of aspirin (blocks the effect of probenecid), overproduction of uric acid, and unresponsiveness to probenecid. Drug interactions may occur with probenecid. Patients using probe-

necid need to drink 2 L of fluid daily at the inception of therapy to ensure adequate diuresis to decrease the risk of renal stones.

Sulfinpyrazone: Sulfinpyrazone is an alternative uricosuric agent that has antiplatelet activity but is seldom used because of the added risk of bone marrow suppression.

Allopurinol

Allopurinol blocks xanthine oxidase and thus reduces the generation of uric acid. Therefore, it should be used in patients who are overproducers of uric acid and in patients at risk of tumor lysis syndrome to prevent renal toxicity during therapy for malignancies. It is the most effective agent to lower serum uric acid levels. However, alcohol can interfere with the effectiveness of allopurinol. Approximately 3-10% of patients taking allopurinol develop dyspepsia, headache, diarrhea, or pruritic maculopapular rash. More infrequently, patients can develop allopurinol hypersensitivity, which has a mortality rate of 20-30%. Features of allopurinol hypersensitivity include fever, toxic epidermal necrolysis, bone marrow suppression, eosinophilia, leukocytosis, renal failure, hepatic failure, and vasculitis. Corticosteroids often are used to treat allopurinol hypersensitivity. Allopurinol hypersensitivity is more likely to occur in patients with renal insufficiency, patients who are taking a diuretic, and patients begun on 300 mg of allopurinol. Allopurinol should be discontinued in patients who develop a rash. In patients with a history of drug eruptions due to allopurinol, both an oral and IV desensitization regimen are available that can be considered. In most patients, start at 100 mg per day and adjust the dose monthly according to the uric acid level until the goal of a uric acid level of 5-6 mg/dL is achieved.

Beware of drug interactions. For example, allopurinol prolongs the half-life of azathioprine and 6-mercaptopurine. It enhances the toxicity of cyclophosphamide. Patients taking concomitant ampicillin have an increased incidence of rash. Once the target level is achieved and maintained for 6 months, discontinue colchicine prophylaxis. Avoiding the use of medications that elevate uric acid in patients with gout is prudent. Thus, other agents are preferable to a thiazide diuretic to treat hypertension. However, if such a medication is needed, it can be used with appropriate adjustments of allopurinol or probenecid.

Allopurinol can be used in combination with probenecid. However, note that allopurinol increases the half-life of probenecid, whereas probenecid increases the excretion of allopurinol.

Other potential therapeutic options include the following:

Nonrecombinant urate-oxidase (uricase) is used in Europe to prevent severe hyperuricemia induced by chemotherapy in malignant patients, as well as for selected patients with treatment-refractory gout. Recently, the Food and Drug Administration (FDA) approved recombinant Aspergillus flavus uricase for the prevention of tumor lysis syndrome. However, it is highly immunogenic and may cause anaphylaxis. Patients with allopurinol hypersensitivity can often tolerate oxypurinol, which is a metabolite of allopurinol. Benzbromarone is an effective uricosuric agent that may eventually become available. However, it can cause fulminant hepatotoxicity. Febuxostat, a nonpurine selective inhibitor of xanthine oxidase, is a potential alternative to allopurinol for patients with gout. It is orally administered and metabolized mainly in the liver. In contrast, allopurinol and its metabolites are excreted primarily by the kidney. Therefore, febuxostat can be administered in patents with renal insufficiency, with no dosage adjustment. Its efficacy and side-effect profile otherwise appears similar to that of allopurinol. The angiotensin receptor blocker losartan and the triglyceride-lowering agent micronized fenofibrate have moderately potent uricosuric effects. They should therefore be considered in patients with gout who also require treatment for hypertension and hypertriglyceridemia. Vitamin C, with its uricosuric effect, may reduce the serum concentration of uric acid.

Surgical Care

If diagnosed and treated early, patients should not need orthopedic surgery. In patients who are untreated or in those who are treated late in the course of their disease, orthopedic repair may be necessary. Tophi should not be surgically removed unless they are in a critical location or drain chronically. In patients undergoing arthroscopy, the presence of white lesions, sometimes on an erythematous base, should prompt consideration for gout.

Consultations

Rheumatologists should be involved in the care of patients with gout. They can establish the diagnosis by arthrocentesis and synovial fluid analysis for crystals. They also are skilled in the management of this disorder.

Diet

Diet modifications can only improve the serum uric acid levels by 1 mg/dL and rarely are able to lower uric acid levels sufficiently to prevent further attacks and accumulation of uric acid. Patients should avoid alcohol because it elevates levels of uric acid and therefore can precipitate attacks of gout. Indeed, heavy drinkers are much more likely to have recurrent gout attacks, even with allopurinol therapy. Particularly because of the association of gout with atherosclerosis, the diagnosis of gout may be a good time to advise a low-cholesterol, low-fat diet if otherwise appropriate for the patient. While such a diet may help uric acid levels, such advice should be given primarily to help prevent atherosclerosis. Weight reduction in patients who are obese can improve hyperuricemia.

Activity

Patients should avoid using the inflamed joint during the acute attack. Otherwise, they should be active.

Complications

Untreated, gout can lead to severe joint destruction. In those undergoing treatment, the primary problems are toxicity of the medications. Septic arthritis can occur in a gouty joint, and draining tophi can become secondarily infected.

Prognosis

If treated early and properly and if patient compliance is good, the prognosis is excellent.

Part 8.

BEHÇET DISEASE

Behçet disease (BD) is characterized by a triple-symptom complex of recurrent oral aphthous ulcers, genital ulcers, and uveitis. Hippocrates may have described Behçet disease in the fifth century BC; however, the first description of the syndrome was attributed to the Turkish dermatologist Hulusi Behçet in 1924. In 1930, the Greek physician Adamantiades reported a patient with inflammatory arthritis, oral and genital ulcers, phlebitis, and iritis. Since then, the syndrome has been referred to as Behçet disease.

Pathophysiology

Theories behind the pathogenesis of Behçet disease currently point toward an autoimmune etiology. Current research suggests that exposure to an infectious agent may trigger a cross-reactive immune response. Proposed infectious agents have included herpes simplex virus (HSV), Streptococcus species, Staphylococcus species, and Escherichia coli, all of which commonly inhabit the oral cavity. The International Study Group for Behçet's Disease has emphasized the presence of recurrent oral ulcers as a primary consideration in the diagnosis of Behçet disease. In response, the pathogens above have been targeted for study in hopes of establishing a direct link between their presence and disease activity. Unfortunately, researchers have been unable to generalize results across geographic populations so far. The study of heat shock proteins (HSPs) has provided some insight into possible mechanisms that contribute to the development of Behçet disease. Through discovery that HSP 60 and HSP 65 share greater than 50% homology with mycobacterial HSP, enhanced T-cell response has been elicited with exposure to both bacterial and human homogenates in Behçet disease patients compared to controls in UK, Japanese, and Turkish populations. HSP 65 found in high concentrations in oral ulcers and active skin lesions in patients with Behçet disease, has also been demonstrated to stimulate production of antibodies that exhibit cross-reactivity with streptococcal species present in the mouth. These examples provide further support that exposure to an infectious agent may initiate cross-reactive autoimmune responses in persons with Behçet disease.

Systemic involvement of multiple organs is observed in Behçet disease, rooted primarily in the development of vasculitic or vasculopathic lesions in the affected areas.

These areas may demonstrate microscopic evidence of inflammatory tissue infiltration with both T cells and neutrophils. Studies of T lymphocytes have suggested a T-helper type 1 (TH1)–predominant response. Both CD4+ and CD8+ lymphocytes demonstrate higher concentrations in peripheral blood with characteristic and corresponding elevations of cytokines (interleukin-2 [IL-2] and interferon-γ [IFN-γ]). Serum levels of IL-12 have also been shown to be elevated in patients with Behçet disease, possibly helping drive the response.

Attempts at determining if tissue antigens have a role in channeling the immune response have been unsuccessful. Elevated peripheral levels of γδ+ T cells in patients with Behçet disease compared with those in healthy subjects imply a nidus for their production. To support this, an antigen-driven expansion of oligoclonal Vβ+ T-cell receptor (TCR)–specific cell lines has been demonstrated. However, generalization of these results is not applicable because of the high degree of interindividual variability in TCR expression.

Considering the degree of neutrophilic infiltration demonstrated in characteristic Behçet disease lesions, including hypopyon, pustular lesions, and pathergy reactions, activity and function of these cells has been explored extensively. Unfortunately, existing studies offer inconsistent results regarding cell adhesion and chemotactic behavior, superoxide production, and phagocytic properties. Thus, the specific role of neutrophils in Behçet disease has been difficult to characterize. Some studies portend that cytokine release in Behçet disease may, by an unknown mechanism, place neutrophils in a static pre-excitatory "primed" state, eventually triggered into hyperactivity by environmental stimuli at a lower threshold than in individuals who do not have Behçet disease. HLA-B51 has been shown to be more prevalent in Turkish, Middle Eastern, and Japanese populations, corresponding with a higher prevalence of Behçet disease in these populations. However, HLA-B51 has not been shown to affect the severity of symptoms. Presentation in males serves as the only proven predictor of severity, causing many of the complications of Behçet disease in higher proportion to their female counterparts.

Frequency of Behçet disease

The incidence and prevalence of Behçet disease are highest along the old Silk Road, extending from the Middle East to China. Turkey has the highest prevalence of

Behçet disease, with 420 cases per 100,000 population. The prevalence in Japan, Korea, China, Iran, and Saudi Arabia ranges from 13.5-22 cases per 100,000 population. The prevalence in North America and Europe is much less, with 1 case per 15,000-500,000 population.

Mortality and Morbidity

Epidemiology studies have reported that Behçet disease carries an overall mortality rate of up to 16% at 5 years. Coronary/pulmonary arterial aneurysm rupture in association with Behçet disease carries a high mortality rate. Neurologic involvement has been associated with mortality rates up to 20% at 7-year follow-up in one Turkish study. Thrombosis may lead to death. CNS involvement can lead to permanent deficits or death. Eye involvement can result in blindness.

Race, age and sex particularities

The prevalence of Behçet disease is highest among Middle Eastern and Japanese persons.The sexual prevalence varies by country. In the Middle East, Behçet disease is more common among males, with male-to-female ratios of 3.8:1 (Israel), 5.3:1 (Egypt), and 3.4:1 (Turkey). In Germany, Japan, and Brazil, the disease is slightly more common in females. In the United States, Behçet disease is more common in females (5:1 female-to-male ratio). Males are more likely to develop severe presentations of Behçet disease. Pulmonary aneurysms, eye involvement, thrombophlebitis, and neurologic disease are all more common in males. However, females are more likely to develop erythema nodosum–like skin lesions. Behçet disease is most common among persons aged 20-40 years. Cases that develop before age 25 years are more likely to involve eye disease and active clinical disease. The mean age at onset is 25-30 years.

History of Behçet disease

In 1990, the International Study Group (ISG) for Behçet's Disease clarified criteria for the diagnosis of Behçet disease. The ISG group compared the clinical findings of 914 patients with a history of aphthous ulcers with those of controls. Initial criteria for diagnosis require the occurrence of at least 3 episodes of oral herpetiform or aphthous ulcerations within a 12-month period observed directly by a physician or reported by the patient. To confirm the diagnosis, at least 2 of the following must also be demonstrated:

- Recurrent painful genital ulcers that heal with scarring

- Ophthalmic lesions, including anterior or posterior uveitis, hypopyon, or retinal vasculitis
- Skin lesions, including erythema nodosum–like lesions, pseudofolliculitis, or papulopustular or acneiform lesions
- Positive results from pathergy skin testing, defined as the formation of a sterile erythematous papule 2 mm in diameter or larger that appears 48 hours following a skin prick with a sharp sterile needle (22-24 gauge [a dull needle may be used as a control])

Considering the above diagnostic criteria, case presentation often includes the following characteristics:

- Multiorgan system involvement, often beginning with mucocutaneous involvement and usually sparing the liver, kidneys, and heart
- Age of 25-35 years at onset
- Organ-specific manifestations characterized by exacerbations and a relapsing/remitting course
- Pertinent site-specific manifestations include the following:
- Skin and mucous membranes

Painful oral lesions (aphthous or herpetiform) are one of the criteria for diagnosis and may be the first manifestation (70% of cases). Oral lesions are usually not distinguishable from other causes but often have a high recurrence rate (often >5 times/y despite only 3 times/y specified in ISG criteria) and appear as multiple lesions or crops (often >6 simultaneous lesions at a given time). Oral lesions are commonly found in keratinized areas of the oropharynx, often excluding the nonkeratinized surfaces of the dorsal tongue, gums, and hard palate. Skin lesions often occur in the genital region of both sexes. In males, scrotal involvement is most characteristic; however, lesions can also develop on the penile shaft. In females, the labial area is most commonly involved, with lesions occasionally developing in the vagina and on the perineum. Genital ulcerations typically heal with scarring and are more painful in men. Nodules that resemble erythema nodosum are more common in the lower extremities of females. They are tender, erythematous, and nodular and usually resolve after 2-3 weeks but often recur. Acneiform papulopustular lesions are more common in men and are usually found on the

trunk and extremities, although they may develop anywhere on the body. Extragenital ulcerations that heal with scarring are rare and affect only 3% of patients. These are very specific for Behçet disease. They can be found in the axillae, neck, breast, interdigital skin of the feet, and groin. Positive pathergy test findings are more common in Turkish and Japanese populations, as well as patients with ophthalmic and neurologic manifestations.

Ocular lesions

Ocular presentations (anterior or posterior uveitis, hypopyon, retinal vasculitis) represent the first manifestation of disease in 10% of patients with Behçet disease but usually occur following oral ulceration. Symptoms commonly include blurred vision, periorbital pain, photophobia, scleral injection, and excessive lacrimation. Men, particularly of Iranian and Japanese descent, tend to present with more severe eye involvement. Highly recurrent posterior uveitis can lead to blindness. Ocular symptoms usually present in the first years of illness. Cases that cause blindness commonly develop within the first 7 years. The prognosis is better for persons who develop symptoms later in the disease course.

Neurologic manifestations

Collectively, neurologic symptoms tend to be an unusual late manifestation, 1-8 years after disease onset. Memory tends to be affected in most cases, particularly affecting recall and learning. Orientation, arithmetic, and language are often unaffected. Symptoms are usually parenchymal in nature, predominantly with brainstem involvement. Behavioral changes, primarily apathy or disinhibition, occur in 54% of patients. Seizures and bulbar signs with ophthalmoplegia are less common.

Vasculopathy

Behçet disease can cause aneurysms in the pulmonary arterial tree that often prove to be fatal. Pulmonary artery aneurysmal involvement is associated with right-sided cardiac thromboses and can manifest as hemoptysis, cough, chest pain, or dyspnea. Vasculitis of the small and large vessels can cause a panoply of symptoms depending on location of the lesions. Arterial disease predominantly affects males and only rarely occurs in women. Venous involvement (usually in the form of superficial thrombophlebitis) is more common than arterial involvement. Superficial thrombophlebitis presents in

a linear fashion with overlying erythema and is often confused with erythema nodosum. In males, formation of these linear areas of vasculopathy leads to sclerosis and string-like thickening in the affected areas. Symptoms correlate with the vessel involved and may be devastating. For example, extension of an inferior vena caval clot to the hepatic vein may be the mechanism of Budd-Chiari syndrome in Behçet disease.

Arthritis

Arthritis and arthralgias occur in as many as 60% of patients and primarily affect the lower extremities, especially the knee. Ankles, wrists, and elbows can also be primarily involved. The arthritis is nondeforming and asymmetric in nature and can assume a monoarticular, oligoarticular, or polyarticular pattern of involvement. Symptoms relapse and remit and rarely become chronic.

Gastrointestinal/genitourinary manifestations

GI involvement affects 3-16% of patients with Behçet disease. Areas affected often include the esophagus and ileocecal area. Symptoms include abdominal pain, bloating, and GI bleeding. Complications often result from deep ulceration of intestinal sections.

GU involvement can include epididymitis, neurogenic bladder, and sterile urethritis.

Renal manifestations

Renal manifestations may be underreported. A recent study found that 1-29% of patients with Behçet disease developed such manifestations. Associated amyloidosis may develop. The first presentation is often nephritic-range proteinuria found incidentally. Crescenteric and proliferative glomerulonephritis, as well as IgA nephritis, have also been reported in some cases.

Oral ulcers

Oral lesions represent the most common, and often the first, manifestation of Behçet disease. Even when they are not the first manifestation, they are considered a primary criterion for diagnosis and eventually occur in most patients. Ulcers are aphthous or herpetiform in nature and can occur in various keratinized areas of the oral cavity. They can be very painful, can last up to 3-5 weeks, and can vary in size. Large ulcers (>10 mm in diameter) heal with scarring as do their genital counterparts.

Genital ulcers

In females, these lesions commonly appear in the labial folds but can also be found in the vulva and vagina. In males, they are usually scrotal in nature but can also develop in the perianal region and penile shaft. Genital ulcers last longer than oral lesions, are deeper, and typically scar after healing. Ulcerations in women may correlate with menstruation.

Skin disorders

Pseudofolliculitis and acneiform lesions, found more commonly in males with Behçet disease, primarily affect the trunk and extremities. Erythema nodosum, which is more common in females with the disease, are occasionally differentiated from alternate etiologies based on ulceration, which is a characteristic more unique to Behçet disease.

Ocular manifestations

- Anterior uveitis with and without hypopyon formation
- Posterior uveitis that may cause blindness
- Glaucoma
- Synechiae
- Retinal vasculitis
- Infarctions
- Hemorrhage
- Edematous appearance of the disc, with retinal detachment
- Leaky retinal vessels revealed by fluorescein angiography, leading to atrophy and fibrosis in some cases

Neurologic manifestations

Pyramidal tract lesions with spastic paralysis and dementia have been demonstrated in some patients with Behçet disease. Neurologic signs may include mental status changes; seizures; clonus; positive Babinski sign; difficulty with speech, swallowing, and emotional lability; and acute deafness. Apathy or disinhibition is common. Difficulty with recall and learning has been demonstrated. Peripheral nerve involvement is rare.

Vascular manifestations

Lower-extremity superficial thrombophlebitis often presents in a linear fashion with overlying erythema and tenderness. Palpation of sclerosed thrombophlebitis yields subcutaneous stringlike quality.

Deep venous thrombosis (DVT) develops in some cases and typically manifests as local tenderness or as disparity in limb girth. Arterial vasculitis may manifest as claudication symptoms.

Arthritis

- Inflammatory peripheral arthritis is common, occurring in about half of patients with Behçet disease.
- The arthritis has a predominance for the lower extremities but may occur in any pattern.
- Diffuse arthralgias are also common.
- Arthritis is usually not destructive or deforming.
- Joint-fluid content often reflects only inflammatory properties.
- Aseptic necrosis develops in rare cases.

Gastrointestinal manifestations

- Ulcerative lesions can cause abdominal pain, bloody diarrhea, and occasional intestinal perforation.
- GI lesions are indistinguishable from those associated with inflammatory bowel disease but commonly occur in the ileocecal region.

Genitourinary manifestations

- Glomerulonephritis can cause hematuria. The glomerulonephritis can be crescenteric or proliferative. IgA nephritis has also been reported.
- Epididymitis manifests as scrotal tenderness.
- Neurogenic bladder can present with typical symptoms of urinary retention.

Other lesions

Cardiac manifestations include coronary vasculitis and thrombosis, pericarditis, myocarditis, endocarditis with granulomatous changes or fibrosis, regurgitation, and diastolic dysfunction (5-17% of cases). Lung involvement occurs in up to 18% of patients with Behçet disease. Pulmonary vasculitis, hypertension, and pleural effusions have been reported. Aneurysms represent a dreaded complication of Behçet disease and may result in massive hemoptysis.

Causes

The specific etiology of Behçet disease remains elusive, but, as described in Pathophysiology, the interplay between infectious-agent exposure and genetic factors may have a role. An environmentally triggered hyperactive primed state of autoimmunity ensues, resulting in two types of vascular damage. The first is vasculitic lesions that may be widespread. Sequelae depend on the various organ systems affected. Some of the pa-

thologic changes are due to thrombosis and/or clot formation caused by the development of a hypercoagulable state. The mechanism is still undetermined; however, studies have demonstrated excessive thrombin formation and the potential role of impaired fibrinolytic kinetics in the generation of the hypercoagulable/prothrombotic state. Pathologic activation of the procoagulant cascade via endothelial injury has also been demonstrated in patients with Behçet disease.

Lab Studies

- Laboratory findings
  - Laboratory findings are nonspecific and reflect the inflammatory state.
  - C-reactive protein levels, erythrocyte sedimentation rate (ESR), leukocyte count, complement components, and acute-phase reactants may all be elevated during an acute attack.
  - Levels of IgA, IgG, alpha-2 globulin, IgM, and immune complexes are occasionally elevated.
  - None of these findings is specific for the diagnosis of Behçet disease, but such findings can corroborate active disease.
- Antiphospholipid antibodies: These include lupus anticoagulant, dilute Russell viper venom test (DRVVT), and anticardiolipin antibodies. Although uncommon in Behçet disease, they are worth pursuing to rule out alternate causes of thrombosis.
- Up to one third of patients with Behçet disease who have thrombosis are found to have factor V Leiden–deficiency mutations. Therefore, this, APL antibody, and other causes of hypercoagulability should be ruled out as contributing factors to thrombosis formation.
- Antineutrophil cytoplasmic antibody: Occasionally, patients are found with positive test results for perinuclear antineutrophil cytoplasmic (p-ANCA) antibody, although positive or negative results on this test do not change prognosis or therapy.
- Synovial fluid: Synovial fluid usually is cloudy with variable viscosity, and the WBC counts are 300-36,000/μL (either noninflammatory or inflammatory). Polymorphonuclear leukocytes and protein elevations are the predominant findings,

and glucose levels are near normal. Thus, because synovial fluid merely demonstrates general inflammation, examination serves only to rule out the presence of aseptic joint, crystal-induced arthropathy, or other alternate identifiable cause in patients with Behçet disease.

- Cerebrospinal fluid: These findings may show local inflammation with increased WBC counts, lymphocyte predominance, and elevated protein levels, as well as Ig levels and Ig index that reflect local production of Ig. Opening pressures are very high in some patients.

Imaging Studies

- Radiography, MRI, and CT scanning: Sacroiliitis may be observed on a radiograph, MRI, or CT scan.
- Brain CT scanning: Acute areas of ischemia can be identified.
- Brain MRI/magnetic resonance angiography (MRI/MRA): Cerebral vasculopathy and acute/subacute areas of ischemia can be identified.
- Single-photon emission computed tomography (SPECT): This has been used to identify areas of cerebral hypoperfusion in Italian, Spanish, and Turkish studies among pediatric, adolescent, and adult populations.
- Angiography: This test may be used to evaluate for aneurysms.

Other Tests

- Pathergy test: Minor skin trauma induces an inflammatory papule or pustule within 24-48 hours.

Procedures

- As with laboratory studies, samples obtained via arthrocentesis and lumbar puncture are used primarily to rule out alternate causes of disease presentation, as they normally demonstrate nonspecific inflammatory findings.
- Similarly, skin biopsy results often reflect nondiagnostic findings but can be used to differentiate alternate disease entities.

Histologic Findings

Although no specific histologic findings characterize Behçet disease, biopsy samples of affected tissue often reveal leukocytoclastic vasculitis and perivascular infiltration. CNS lesions may demonstrate meningeal and cerebral inflammation, cerebral atro-

phy, and encephalomalacia. Thrombosis commonly develops in affected areas and must be distinguished from vasculitis as a precipitating cause for organ-specific symptoms.

Other organ-system findings include the following:

- Skin - Erythema nodosum lesions with characteristic findings and occasional granulomas; folliculitis; leukocytoclastic vasculitis; dermal inflammation and perivascular infiltrates; fibrosis; and mucosal lesions, including aggregated intravascular conglomerates of neutrophils, endothelial cell swelling, fibrinoid necrosis, and a mixed perivascular infiltrate (Pathergy test reveals mononuclear cell infiltrates and keratinocytes.)
- Eye - Cataracts, posterior and anterior uveitis, retinal vasculitis and thrombosis, cytoid macular degeneration, retinal detachment, and lymphocytic infiltrates in the iris (even during clinical remissions)
- Brain - Infarctions due to vasculitis or thrombosis, meningoencephalitis, lymphocytic meningeal infiltration, or demyelinization
- Joint - Superficial inflammatory synovial infiltrates, mainly polymorphonuclear lymphocytes, and deposition of IgG in the synovium
- GI tract - Ulcerations from the buccal mucosa to the anus, intestinal perforation, peritonitis, infiltration with polymorphonuclear leukocytes and lymphocytes, hepatitis, cholecystitis, and pancreatitis
- Heart - Pericarditis, myocarditis, endocarditis, coronary arteritis, and myocardial fibrosis
- Lung - Serositis and vasculitis
- Kidneys - Glomerulonephritis

Medical Care

Oral ulcerations can be successfully treated with topical steroids or sucralfate solution. Colchicine has also been used to prevent mucocutaneous relapse. For severe mucocutaneous lesions, systemic corticosteroids, azathioprine, pentoxifylline, dapsone, interferon-alpha, colchicine, and thalidomide have demonstrated benefit. For genital ulceration, topical and intralesional steroids can be used. Topical sucralfate also has demonstrated benefit. GI lesions are primarily treated with 5-ASA derivatives, including sulfasalazine or mesalamine. However, upon lack of response, systemic corticosteroids can be used with eventual taper as dictated by decreasing C-reactive protein values on surveillance. Upon development of steroid dependence, azathioprine can be used adjunctively in an attempt to decrease the need for glucocorticoids. Pulmonary arterial aneurysms are treated with cyclophosphamide. Joint involvement may respond to prednisone, local corticosteroid injections, and nonsteroidal anti-inflammatory drugs (NSAIDs). Colchicine, sulfasalazine, and interferon-alpha are also used. Levamisole and aza-

thioprine serve as alternative modes of therapy. Multiple modes of therapy have been studied for ocular symptoms, and a good response has been demonstrated with interferon therapy. TNF-inhibitor therapy with infliximab (Remicade) and etanercept (Enbrel) has also demonstrated favorable response in treating rapidly progressive anterior and posterior uveitis. Cyclosporine has been well supported in the literature as an effective therapeutic measure. Erythema nodosum is a special circumstance and may be treated with colchicine or dapsone. CNS disease is usually treated with systemic corticosteroids, chlorambucil, or cyclophosphamide. Thrombotic events are treated with systemic anticoagulation. TNF-inhibitor therapy with infliximab and etanercept has also demonstrated varying degrees of success in treating cases of severe GI and CNS manifestations of Behçet disease and has been shown to have the added benefit of improving mucocutaneous manifestations and polyarthritis.

Surgical Care

GI presentations that require surgical intervention include intestinal stenosis, lesions unresponsive to medical therapy, fistula formation, perforation, and severe bleeding. Pulmonary aneurysms and areas that incur ischemic damage due to vasculitis or thrombosis may require resection. Ventricular aneurysms, coronary thrombosis, and endocardial fibrosis are occasionally amenable to surgery. Glaucoma, cataracts, and retinal detachment occasionally warrant surgical intervention. Neurosurgery may be required to correct some CNS aneurysms and clots.

Consultations

- Rheumatologist
- Specialist consultations as needed (for specific organ involvement)
    - Urologist for genital and urologic lesions
    - Neurologist for CNS involvement
    - Ophthalmologist for ocular disease
    - Gastroenterologist for intestinal disease
    - Dermatologist for possible help with recurrent skin lesions
    - Surgeon, when indicated
    - Nephrologist for proteinuria or hematuria
    - Pulmonologist or cardiologist in rare cases of intracardiac or pulmonary thrombosis and aneurysms

Diet

No general dietary recommendations exist. Patients with severe bowel involvement are advised to follow GI recommendations given to patients with inflammatory bowel disease, often requiring total parenteral nutrition.

Activity

Activity is suggested as tolerated and may be limited owing to systemic symptoms or arthritis.

Further Inpatient Care

Inpatient care is based on individual organ-system involvement. In general, no further care is needed.

Further Outpatient Care

As disease activity subsides, taper medications to the lowest dose that effectively controls the symptoms and disease activity.

In/Out Patient Meds

Inpatient and outpatient medication are the same. All agents discussed above have been found to be effective in controlling the manifestations of Behçet disease.

Transfer

Individualize the transfer situation for each patient based on the specifics of organ-system involvement.

Deterrence and prevention

Continual use of immunosuppressive medications may be required to suppress disease. Use the lowest dose required to control the manifestations of illness.

Complications

- Aneurysms are especially feared.
- Thrombotic events and vasculitis may lead to ischemia distal to vascular lesions.
- Uncontrolled ophthalmologic involvement in the form of anterior and posterior uveitis can lead to vision loss.
- Neurologic involvement suggests progressive disease and can lead to permanent deficits or even death.

Prognosis

Prognosis is related to the site and severity of involvement.

Part 9.

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS) is a disorder characterized by recurrent venous or arterial thrombosis and/or fetal losses associated with characteristic laboratory abnormalities, such as persistently elevated levels of antibodies directed against membrane anionic phospholipids (ie, anticardiolipin [aCL] antibody, antiphosphatidylserine) or their associated plasma proteins, predominantly beta-2 glycoprotein I (apolipoprotein H), or evidence of a circulating anticoagulant. Multiple terms for APS exist. Unfortunately, some synonyms can be confusing. Lupus anticoagulant (LA) syndrome, for example, is misleading because patients with APS may not necessarily have systemic lupus erythematosus (SLE) and LA is associated with thrombotic rather than hemorrhagic complications. In an attempt to avoid further confusion, APS is currently the preferred term for the clinical syndrome (as described below).

APS can occur in patients without evidence of any definable associated disease or in association with SLE or another rheumatic or autoimmune disorder. Traditionally, this has been referred to as primary or secondary APS, respectively, although, currently, the preferred terminology is APS with or without associated rheumatic disease. Although antiphospholipid (aPL) antibodies are clinically linked to APS, whether they are involved in the pathogenesis or are an epiphenomenon is unclear. (Up to 5% of healthy individuals are known to have aPL antibodies.)

Pathophysiology of antiphospholipid syndrome

In APS, the homeostatic regulation of blood coagulation is altered; however, the mechanisms of thrombosis are not yet defined. One hypothesis postulates a defect in cellular apoptosis, which exposes membrane phospholipids to the binding of various plasma proteins, such as beta-2 glycoprotein I. Once bound, a phospholipid-protein complex is formed and a neoepitope is uncovered, which subsequently becomes the target of autoantibodies. Recent evidence suggests that oxidized beta-2 glycoprotein I is able to bind to and activate dendritic cells in a manner similar to activation triggered by Toll-like receptor 4 (TLR-4), which could amplify the production of autoantibodies. Other proposed mechanisms for the hypercoagulable effect of aPL antibodies, which may or may not depend on beta-2 glycoprotein I, include the following:

- Production of antibodies against coagulation factors, including prothrombin, protein C, protein S, and annexins
- Activation of platelets to enhance endothelial adherence
- Activation of vascular endothelium, which, in turn, facilitates the binding of platelets and monocytes
- Reaction of antibodies to oxidized low-density lipoprotein, thus predisposing to atherosclerosis and myocardial infarction (MI)

Complement activation has been increasingly recognized as a possible significant role in the pathogenesis of APS. Emerging evidence from murine models suggests that APL-mediated complement activation may be a primary event in pregnancy loss. Clinically, the series of events that leads to hypercoagulability and recurrent thrombosis can affect virtually any organ system, including the following:

- Peripheral venous system (deep venous thrombosis [DVT])
- Central nervous system (cerebrovascular accident [CVA], sinus thrombosis)
- Hematologic (thrombocytopenia, hemolytic anemia)
- Obstetric (pregnancy loss, eclampsia)
- Pulmonary (pulmonary embolism [PE], pulmonary hypertension)
- Dermatologic (livedo reticularis, purpura, infarcts/ulceration)
- Cardiac (Libman-Sacks valvulopathy, MI)
- Ocular (amaurosis, retinal thrombosis)
- Adrenal (infarction/hemorrhage)
- Musculoskeletal (avascular necrosis of bone)

Frequency of antiphospholipid syndrome

The actual frequency of APS in the general population is unknown. One to 5% of healthy individuals have aPL antibodies. aCL antibodies tend to be found more frequently in elderly persons; thus, positive titer results should be interpreted with caution in this population. aPL antibodies are found in approximately 30-40% of patients with SLE, but only about 10% have APS. Approximately half of APS cases are not associated with another rheumatic disease. In a study of 100 patients with confirmed venous thrombosis and no history of SLE, aCL antibodies were found in 24% and LA in 4%.

Mortality and Morbidity

APS may contribute to an increased frequency of CVAs or MIs, especially in younger individuals. CVAs may develop secondary to in situ thrombosis or embolization that originates from the valvular lesions of Libman-Sacks (sterile) endocarditis,

which may be seen in patients with APS. Cardiac valvular disease may be severe enough to require valve replacement. Recurrent pulmonary emboli or thrombosis can lead to life-threatening pulmonary hypertension. Catastrophic APS (CAPS) is a rare, serious, and often fatal manifestation (mortality rate of approximately 50%) characterized by multiorgan infarctions over a period of days to weeks. Late spontaneous fetal loss (second or third trimester) is common; however, it can occur at any time during pregnancy. Recurrent early fetal loss (<10 weeks' gestation) is also possible.

Race, sex and age particularities

No defined racial predominance for primary APS has been documented, although SLE is more common in African American and Hispanic populations. A female predominance has been documented, particularly for secondary APS. This parallels the association of APS with SLE and other connective-tissue diseases, which also have a female predominance. APS is more common in young to middle-aged adults; however, it also manifests in children and elderly people. Disease onset has been reported in children as young as 8 months.

History of antiphospholipid syndrome

Antiphospholipid syndrome is a heterogenous disorder in terms of clinical manifestations and range of autoantibodies. In 2006, revised criteria for the diagnosis of APS were published in an international consensus statement. At least one clinical criterion and one laboratory criterion must be present for a patient to be classified as having APS.

The clinical criteria are as follows:

Vascular thrombosis

One or more clinical episodes of arterial, venous, or small-vessel thrombosis in any tissue or organ confirmed by findings from imaging studies, Doppler studies, or histopathology. Thrombosis may involve the cerebral vascular system, coronary arteries, pulmonary system (emboli or thromboses), arterial or venous system in the extremities, hepatic veins, renal veins, ocular arteries or veins, or adrenal glands. Investigation is warranted if a history of DVT, PE, acute ischemia, MI, or CVA (especially when recurrent) is present in a younger individual (males <55 y; females <65 y) or in the absence of other risk factors.

Pregnancy morbidity

- One or more late-term (>10 weeks' gestation) spontaneous abortions.
- One or more premature births of a morphologically healthy neonate at or before 34 weeks' gestation because of severe preeclampsia or eclampsia or severe placental insufficiency.
- Three or more unexplained, consecutive, spontaneous abortions before 10 weeks' gestation.

Laboratory criteria: Patients must have medium to high levels of immunoglobulin G (IgG) or immunoglobulin M (IgM) anticardiolipin (aCL), anti–beta-2 glycoprotein I, or LA on at least 2 occasions at least 12 weeks apart.

Other antiphospholipid (aPL)–associated clinical features recognized by the 2006 consensus statement but not included in the criteria include cardiac valve disease, livedo reticularis, thrombocytopenia, nephropathy, and neurologic manifestations. Thus, history of any of the following should raise the examiner's suspicion for APS:

- Thrombosis (eg, DVT/PE, MI, transient ischemic attack [TIA], or CVA, especially if recurrent, at an earlier age, or in the absence of other known risk factors)
- Miscarriage (especially late trimester or recurrent) or premature birth
- History of heart murmur or cardiac valvular vegetations
- History of hematologic abnormalities, such as thrombocytopenia or hemolytic anemia
- History of nephropathy
- Nonthrombotic neurologic symptoms, such as migraine headaches, chorea, seizures, transverse myelitis, Guillain-Barré syndrome, or dementia (rare)
- Unexplained adrenal insufficiency
- Avascular necrosis of bone in the absence of other risk factors
- Pulmonary hypertension
- Cutaneous signs
    - Livedo reticularis
    - Superficial thrombophlebitis
    - Leg ulcers
    - Painful purpura
    - Splinter hemorrhages
    - Venous thrombosis
- Leg swelling (DVT)
- Ascites (Budd-Chiari syndrome)
- Tachypnea (PE)
- Peripheral edema (renal vein thrombosis)

- Abnormal funduscopic examination results (retinal vein thrombosis)
- Arterial thrombosis
- Abnormal neurologic examination results (eg, CVA)
- Digital ulcers
- Gangrene of distal extremities
- Signs of MI
- Heart murmur (frequently aortic) or mitral insufficiency (Libman-Sacks endocarditis)
- Abnormal funduscopic examination results (retinal artery occlusion)

Causes

APS is an autoimmune disorder of unknown cause. The search for possible triggers has uncovered a wide array of associated autoimmune or rheumatic diseases, infections, and drugs that are associated with the LA or aCL antibodies. These associations may ultimately provide a clue to the etiology of APS. A considerable percentage of persons with certain autoimmune or rheumatic diseases also have aPL antibodies. Note that these represent percentages of patients with aPL antibodies, rather than the clinical syndrome of APS.

- Common autoimmune or rheumatic diseases and the percentage of affected patients with aPL antibodies
    - SLE - 25-50%
    - Sjögren syndrome - 42%
    - Rheumatoid arthritis - 33%
    - Autoimmune thrombocytopenic purpura - 30%
    - Autoimmune hemolytic anemia - Unknown
    - Psoriatic arthritis - 28%
    - Systemic sclerosis - 25%
    - Mixed connective-tissue disease - 22%
    - Polymyalgia rheumatica or giant cell arteritis - 20%
    - Behçet syndrome - 20%
- Infections
    - Syphilis
    - Hepatitis C infection
    - HIV infection
    - Human T-cell lymphotrophic virus type 1 infection
    - Malaria
    - Bacterial septicemia

  Drugs
    - Cardiac - Procainamide, quinidine, propranolol, hydralazine
    - Neuroleptic or psychiatric - Phenytoin, chlorpromazine

- Other - Interferon alfa, quinine, amoxicillin

Genetic predisposition

Familial association: Relatives of persons with known APS are more likely to have aPL antibodies. One study showed a 33% frequency. HLA associations: Recent studies have revealed an association between aCL antibody and groups of individuals who carry certain HLA genes, including *DRw53, DR7* (mostly people of Hispanic origin), and *DR4* (mostly whites).

Lab Studies

The hallmark result from laboratory tests that defines antiphospholipid syndrome (APS) is the presence of antiphospholipid (aPL) antibodies or abnormalities in phospholipid-dependent tests of coagulation. In addition to the clinical criteria, at least one of the following laboratory criteria is necessary for the classification of APS:

- Presence of LA in plasma on 2 or more occasions at least 12 weeks apart (see below)
- Presence of moderate to high levels of anticardiolipin (aCL) (IgG or IgM) in serum or plasma (ie, >40 IgG phospholipid units (GPL)/mL or IgM phospholipid units (MPL)/mL or >99th percentile) on 2 or more occasions at least 12 weeks apart
- Presence of moderate to high levels of anti–beta-2 glycoprotein I antibodies (IgG or IgM) in serum or plasma (>99th percentile) on 2 or more occasions at least 12 weeks apart aCL antibodies react primarily to membrane phospholipids, such as cardiolipin and phosphatidylserine. Of the 3 known isotypes of aCL (ie, IgG, IgM, immunoglobulin A [IgA]), IgG correlates most strongly with thrombotic events.
- Cardiolipin is the dominant antigen used in most serologic tests for syphilis; consequently, these patients may have a false-positive test result for syphilis. Recent literature suggests that an abnormal LA finding is the laboratory test result that confers the strongest risk for thrombosis. LA is directed against plasma coagulation molecules. In vitro, this interaction results in the paradoxical prolongation of clotting assays, such as activated partial thromboplastin time (aPTT), kaolin clotting time, and dilute Russell viper venom time (DRVVT). The presence of LA is

confirmed by mixing normal platelet-poor plasma with the patient's plasma. If a clotting factor is deficient, the addition of normal plasma corrects the prolonged clotting time. If the clotting time does not normalize during mixing studies, an inhibitor is present; the absence of a specific clotting factor inhibitor confirms that a LA is present.

Patients with APS may have one or more abnormal results from these laboratory tests; the following laboratory tests should be considered in a patient suspected of having APS:

- aCL antibodies (IgG, IgM)
- Anti–beta-2 glycoprotein I antibodies (IgG, IgM)
- Activated partial thromboplastin time (aPTT)
- LA tests such as DRVVT
- Serologic test for syphilis (false-positive result)
- CBC count (thrombocytopenia, hemolytic anemia)

Thrombocytopenia is fairly common in persons with APS (22% at presentation, 30% cumulatively) and is therefore associated with paradoxical thrombosis. However, patients with platelet counts of less than 50,000/μL may have an increased risk of bleeding. Hemolytic anemia has been well described in patients with APS and is associated with the presence of IgM aCL antibodies. A low antinuclear antibody level may be present and does not necessarily imply coexisting SLE.

Additional antibodies directed against phospholipid/phospholipid-protein complexes that may be useful in selected cases include the following:

- IgA aCL
- IgA beta-2 glycoprotein I
- anti-phosphatidylserine antibodies
- anti-phosphatidylethanolamine antibodies
- anti-prothrombin antibodies
- antibodies against the phosphatidylserine-prothrombin complex

Imaging Studies

- Imaging studies are helpful for confirming a thrombotic event. A good example is the use of CT scanning or MRI of the brain (CVA), chest (PE), or abdomen (Budd-Chiari syndrome).
- Doppler ultrasound studies are recommended for possible detection of DVT.
- Two-dimensional echocardiography findings may demonstrate asymptomatic valve thickening, vegetations, or valvular insufficiency; aortic or mitral insufficiency is the most common valvular defect found in persons with Libman-Sacks endocarditis.

Procedures of antiphospholipid syndrome

- Individualize appropriate procedures to evaluate specific thrombotic events.

Histologic Findings of antiphospholipid syndrome

Unlike inflammatory autoimmune diseases, histologic studies of skin or other involved tissue reveal a noninflammatory bland thrombosis with no signs of perivascular inflammation or leukocytoclastic vasculitis. Similarly, biopsy samples from affected kidneys demonstrate glomerular and small arterial microthrombi.

Medical Care of antiphospholipid syndrome

Patients with antiphospholipid syndrome (APS) may be evaluated in an outpatient setting. Inpatient evaluation is required if the patient presents with a significant clinical event. Patients with CAPS require intense observation and treatment, often in an intensive care unit. In general, treatment regimens for APS must be individualized according to the patient's current clinical status and history of thrombotic events. Asymptomatic individuals in whom blood test findings are positive do not require specific treatment.

Prophylactic therapy of antiphospholipid syndrome

Eliminate other risk factors, such as oral contraceptives, smoking, hypertension, or hyperlipidemia. Low-dose aspirin is used widely in this setting; however, the effectiveness of low-dose aspirin as primary prevention for APS remains unproven. Clopidogrel has anecdotally been reported to be helpful in persons with APS and may be useful in patients allergic to aspirin. In patients with SLE, consider hydroxychloroquine, which may have intrinsic antithrombotic properties. Consider the use of statins, especially in patients with hyperlipidemia.

Thrombosis

Perform full anticoagulation with intravenous or subcutaneous heparin followed by warfarin therapy. Based on the most recent evidence, a reasonable target for the international normalized ratio (INR) is 2.0-3.0 for venous thrombosis and 3.0 for arterial thrombosis. Patients with recurrent thrombotic events, while well maintained on the above regimens, may require an INR of 3.0-4.0. For severe or refractory cases, a combination of warfarin and aspirin may be used. Treatment for significant thrombotic events in patients with APS is generally lifelong.

Obstetric considerations

Patients with pregnancy loss receive a prophylactic dose of subcutaneous heparin (preferably low–molecular-weight heparin [LMWH]) and low-dose aspirin. Therapy is withheld at the time of delivery and is restarted after delivery, continuing for 6-12 weeks postpartum. Most authors avoid warfarin (Coumadin) because it is contraindicated in pregnancy. Patients with a history of thrombosis receive therapeutic doses of heparin during pregnancy; long-term anticoagulation is then continued postpartum. Corticosteroids have not been proven effective for persons with primary APS, and they have been shown to increase maternal morbidity and fetal prematurity rates. Breastfeeding women may use heparin and warfarin.

CAPS

These patients generally are very ill, often with active SLE. Treatment with intensive anticoagulation, plasma exchange, and corticosteroids appears beneficial, but no controlled trials have been performed. Intravenous immunoglobulin may be of some benefit and cyclophosphamide may be considered in selected cases, especially in SLE-associated CAPS.

Surgical Care

Recurrent DVT may necessitate placement of an inferior vena cava filter.

Consultations

- Rheumatologist
- Hematologist
- Neurologist, cardiologist, pulmonologist, hepatologist, ophthalmologist (depending on clinical presentation)
- Obstetrician with experience in high-risk pregnancies

Diet

If warfarin therapy is instituted, instruct the patient to avoid excessive consumption of foods that contain vitamin K.

Activity

No specific limitations on activity are necessary. Individualize the activity according to the clinical setting. Instruct the patient to avoid sports with excessive contact if taking warfarin. Limit activity in patients with acute DVT. Instruct the patient to avoid prolonged immobilization.

Further Inpatient Care

Intensive observation is warranted for patients with CAPS.

Further Outpatient Care

Carefully monitor medication doses and the INR if applicable. Closely observe the patient for clinical events. Ensure the care of any underlying connective-tissue disease.

In/Out Patient Meds

The suggested medications include heparin, warfarin, aspirin, and, in selected cases, hydroxychloroquine, intravenous immunoglobulin, and corticosteroids. Corticosteroids are rarely used for the treatment of recurrent fetal loss because of the increased risk of maternal morbidity. Generally, the use of corticosteroids is reserved for specific nonthrombotic manifestations, such as associated thrombocytopenia, autoimmune hemolytic anemia, or the treatment of an underlying connective-tissue disease. Prescribe antihypertensive drugs when necessary. Administer antihyperlipidemic agents including statins when appropriate.

Transfer

When treating seriously ill patients with CAPS, transfer the patient to a setting where plasma exchange can be performed or where intravenous immunoglobulin or cyclophosphamide can be administered if needed.

Deterrence/Prevention

Instruct the patient to avoid smoking. Inform the patient to avoid oral contraceptives or estrogen replacement therapy. Ensure that the patient avoids any prolonged immobilization.

Complications

Permanent functional disability can occur at a relatively young age. This may include the following:

- Cardiovascular accident
- MI
- Pulmonary hypertension
- Renal failure
- Death

Prognosis

With appropriate medication and lifestyle modifications, most individuals with primary antiphospholipid syndrome (APS) lead normal healthy lives. However, subsets of patients continue to have thrombotic events despite aggressive therapies. In these patients and in patients with CAPS, the disease course can be devastating, often leading to significant morbidity or early death. Patients with secondary APS carry a similar prognosis; however, morbidity and mortality may also be influenced by these patients' underlying autoimmune or rheumatic condition. In patients with SLE and APS, antiphospholipid (aPL) antibodies have been associated with neuropsychiatric disease and have been recognized as a major predictor of irreversible organ damage. Women with aPL antibodies who experience recurrent miscarriages may have favorable prognoses in subsequent pregnancies if treated with aspirin and heparin.

Patient Education

Stress the importance of early recognition of a possible clinical event. Educate the patient about anticoagulation therapy. Discuss the importance of planned pregnancies so that long-term warfarin can be switched to aspirin and heparin before pregnancy is attempted.

Part 10.

DERMATOMYOSITIS

Dermatomyositis (DM) is an idiopathic inflammatory myopathy (IIM) with characteristic cutaneous findings. In 1975, Bohan and Peter first suggested a set of criteria to aid in the diagnosis and classification of dermatomyositis and polymyositis (PM). Four of the 5 criteria are related to the muscle disease, as follows: progressive proximal symmetrical weakness, elevated muscle enzymes, an abnormal finding on electromyogram, and an abnormal finding on the muscle biopsy sample. The fifth criterion was compatible cutaneous disease. The association between dermatomyositis (and possibly polymyositis) and malignancy has been recognized for a long time. Dermatomyositis is a systemic disorder that frequently affects the esophagus and lungs and, less commonly, may affect the heart. Calcinosis is a complication that is observed most often in children or adolescents. Therapy of the muscle component involves the use of corticosteroids with or without an immunosuppressive agent. The skin disease is treated with sun avoidance, sunscreens, topical corticosteroids, antimalarial agents, methotrexate, mycophenolate mofetil and/or intravenous immune globulin. Some of the newer biologic agents may prove useful for either component of the disease or for both components. The prognosis depends on the severity of the myopathy, the presence of a malignancy, and/or the presence of cardiopulmonary involvement.

Pathophysiology of dermatomyositis

The pathogenesis of the cutaneous disease is poorly understood. Bohan and Peter (1975) suggested 5 subsets of myositis, as follows: dermatomyositis, polymyositis, myositis with malignancy, childhood dermatomyositis/polymyositis, and myositis overlapping with another collagen-vascular disorder. In a subsequent publication, Bohan et al (1975) noted that cutaneous disease may precede the development of the myopathy. The existence of another subset of patients with disease that only affects the skin (called amyopathic dermatomyositis [ADM] or dermatomyositis-sine myositis) was only recently recognized. Lastly, a group of patients exists whose myopathy is controlled but who continue to have severe and sometimes debilitating skin disease; these patients' conditions have been termed postmyopathic dermatomyositis. Recent studies of the pa-

thogenesis of the myopathy have been controversial. Some suggest that the myopathy in dermatomyositis and polymyositis is pathogenetically different. Dermatomyositis is probably caused by complement-mediated (terminal attack complex) vascular inflammation, while polymyositis is caused by the direct cytotoxic effect of $CD8^+$ lymphocytes on muscle. However, other studies of cytokines suggest that some of the inflammatory processes may be similar. A recent report has linked tumor necrosis factor (TNF) abnormalities with dermatomyositis.

Frequency of dermatomyositis or polymyositis

The incidence of dermatomyositis/polymyositis has been estimated at 5.5 cases per million people, and the incidence is apparently increasing.

Mortality and morbidity of dermatomyositis or polymyositis

Dermatomyositis may cause death because of muscle weakness or cardiopulmonary involvement. Patients with an associated malignancy may die from the malignancy. Most patients with dermatomyositis survive, in which case they may develop residual weakness and disability. In children with severe disease, contractures can develop. Calcinosis may complicate dermatomyositis. It is very rare in adults, but is more common in children and has been linked to delay in diagnosis and to less aggressive therapy.

Race, sex and age particularities of dermatomyositis or polymyositis

No racial predilection exists for dermatomyositis or polymyositis. Women are affected twice as often as men. Dermatomyositis can occur in people of any age. Two peak ages of onset exist. In adults, the peak age of onset is approximately 50 years, and, in children, the peak age is approximately 5-10 years

History of dermatomyositis or polymyositis

Patients often present with skin disease as one of the initial manifestations. Sometimes, perhaps in as many as 40% of the patients, the skin disease may be the sole manifestation at the onset. Muscle disease may occur concurrently, may precede the skin disease, or may follow the skin disease by weeks to years. Patients often notice an eruption on exposed surfaces. The rash is often pruritic, and intense pruritus may disturb sleep patterns. Patients may also report a scaly scalp or diffuse hair loss. Muscle involvement is manifested by proximal muscle weakness. Patients often begin to note fa-

tigue of their muscles or weakness when climbing stairs, walking, rising from a sitting position, combing their hair, or reaching for items in cabinets that are above their shoulders. Muscle tenderness may occur, but tenderness is not a regular feature of the disease. Systemic manifestations may occur; therefore, the review of systems should assess for the presence of arthralgia, arthritis, dyspnea, dysphagia, arrhythmia, and dysphonia. Malignancy is possible in any patient with dermatomyositis, but it occurs more frequently in adults older than 60 years. Only a few children with dermatomyositis and malignancy have been reported. The history should include a thorough review of systems and an assessment for previous malignancy. Children with dermatomyositis may have an insidious onset that defies diagnosis until the dermatologic disease is clearly observed and diagnosed. Calcinosis is a complication of juvenile dermatomyositis but is rarely observed at the onset of disease. Ask questions about hard nodules of the skin during the initial examination.

Physical findings

Dermatomyositis is a disease that primarily affects the skin and the muscles but may affect other organ systems. The characteristic, and possibly pathognomonic, cutaneous features of dermatomyositis are heliotrope rash and Gottron papules. Several other cutaneous features, including malar erythema, poikiloderma (ie, variegated telangiectasia, hyperpigmentation) in a photosensitive distribution, violaceous erythema on the extensor surfaces, and periungual and cuticular changes, are characteristic of the disease even though they are not pathognomonic. Muscle findings typically include proximal weakness and, sometimes, tenderness. Other systemic features include joint swelling, changes associated with Raynaud phenomenon, and abnormalities on cardiopulmonary examination. The heliotrope rash consists of a violaceous-to-dusky erythematous rash with or without edema in a symmetrical distribution involving periorbital skin. Sometimes, this sign is subtle and may involve only a mild discoloration along the eyelid margin. A heliotrope rash is rarely observed in other disorders; thus, its presence is highly suggestive of dermatomyositis. The Gottron papules are found over bony prominences, particularly the metacarpophalangeal joints, the proximal interphalangeal joints, and/or the distal interphalangeal joints. Papules may also be found overlying the elbows, knees, and/or feet. The lesions consist of slightly elevated violaceous papules and

plaques. A slight scale and, occasionally, a thick psoriasiform scale may be present. These lesions may resemble lesions of lupus erythematosus (LE), psoriasis, or lichen planus (LP). Nailfold changes consist of periungual telangiectases and/or a characteristic cuticular change with hypertrophy of the cuticle and small hemorrhagic infarcts with this hypertrophic area. Periungual telangiectases may be apparent clinically or may be visible only on capillary microscopy. Poikiloderma may occur on exposed skin, such as the extensor surfaces of the arm, and may appear in a V-shaped distribution over the anterior neck and upper chest and back (ie, shawl sign). With the exception of the heliotrope rash, the eruption of dermatomyositis is photodistributed and photoexacerbated. Despite the prominent photodistribution of the rash, patients rarely report photosensitivity. Facial erythema may also occur in dermatomyositis. This change must be differentiated from LE, rosacea, seborrheic dermatitis, or atopic dermatitis. Scalp involvement in dermatomyositis is relatively common and is manifested by an erythematous-to-violaceous psoriasiform dermatitis. Clinical distinction from seborrheic dermatitis or psoriasis is occasionally difficult. Nonscarring alopecia may occur in some patients and often follows a flare of systemic disease. Dermatomyositis-sine myositis, also known as ADM, is diagnosed in patients with typical cutaneous disease, no clinical evidence of muscle weakness, and normal serum muscle enzyme levels for at least 2 years. Patients who have undergone disease-modifying therapies such as corticosteroids or immunosuppressive agents are not classified as having ADM. Some patients with ADM have abnormal findings on sonogram, MRI, or muscle biopsy sample. These patients have subclinical muscle involvement, but their condition still may be classified as ADM. Because many ADM patients are not evaluated beyond clinical and enzymatic studies, many think that ADM represents a systemic process requiring systemic therapies. Some patients have myositis that resolves following therapy, but the skin disease remains an active important feature of the disease. Although the skin disease is the major, and often only, manifestation of the disease, these patients are not diagnosed with ADM. In addition, a small subset of patients never develop myositis despite having prominent cutaneous changes. Rare cutaneous manifestations include vesiculobullous erosive lesions and exfoliative erythroderma. Biopsy tissue samples from these patients reveal an interface dermatitis (ie, inflammation at the dermal-epidermal junction) similar to biopsy tissue

samples from heliotrope rash, Gottron papules, poikiloderma, or scalp lesions. These cutaneous manifestations may be more common in patients with an associated malignancy. Various other cutaneous lesions have been described in patients with dermatomyositis or polymyositis that do not reflect the interface changes observed histopathologically with the pathognomonic or characteristic lesions. Panniculitis, urticaria, and hyperkeratosis of the palms (known as mechanic's hands) are examples of these cutaneous lesions. Other findings include cutaneous mucinosis, follicular hyperkeratosis, hyperpigmentation, ichthyosis, white plaques on the buccal mucosa, cutaneous vasculitis, and flagellate erythema. Muscle disease manifests as a proximal symmetrical muscle weakness. Patients may have difficulty rising from a chair or squatting and raising themselves from this position. In an effort to rise, patients sometimes use other muscles that are not as affected. The careful examiner may note this finding. Testing of the muscle strength is part of each assessment of the patient. Often, the extensor muscles of the arms are more affected than the flexors. Distal strength is almost always maintained. Muscle tenderness is a variable finding. Calcinosis of the skin or muscle is unusual in adults but may occur in as many as 40% of children or adolescents with dermatomyositis. Calcinosis cutis is manifested by firm, yellow- or flesh-colored nodules, often over bony prominences. Occasionally, the nodules can extrude through the surface of the skin, in which case secondary infection may occur. Joint swelling occurs in some patients with dermatomyositis. The small joints of the hands are most frequently involved. The arthritis associated with dermatomyositis is not erosive or deforming. Patients with pulmonary disease may have abnormal breath sounds (crackles from interstitial fibrosis or pneumonitis). Patients with an associated malignancy may have physical findings relevant to the affected organs.

Causes

The cause of dermatomyositis is unknown; however, the following factors have been implicated:

- A genetic predisposition may exist. Dermatomyositis rarely occurs in multiple family members, but it may be linked to certain human leukocyte antigen (HLA) types (eg, DR3, DR5, DR7). In addition, polymorphisms of TNF-alpha have been linked to photosensitivity in patients with dermatomyositis.

- Immunological abnormalities are common in patients with dermatomyositis. Patients frequently have circulating autoantibodies. Abnormal T-cell activity may be involved in the pathogenesis of both the skin and the muscle disease. In addition, family members may have other diseases associated with autoimmunity.
- Autoantibodies to nuclear antigens (ANA) and cytoplasmic (ie, antitransfer RNA synthetases) antigens may be present. Although their presence may help to define subtypes of dermatomyositis and polymyositis, their role in pathogenesis is uncertain.
- Infectious agents, including viruses (eg, coxsackievirus, parvovirus, echovirus, human T-cell lymphotrophic virus type 1 [HTLV-1], HIV) and Toxoplasma and Borrelia species, have been suggested as possible triggers of the disease.
- Several cases of drug-induced disease have been reported. Dermatomyositislike skin changes have been reported with hydroxyurea in patients with chronic myelogenous leukemia or essential thrombocytosis. Other agents that may trigger the disease include penicillamine, statin drugs, quinidine, and phenylbutazone.
- Dermatomyositis may be initiated or exacerbated by silicon breast implants or collagen injections, but the evidence for this is anecdotal and has not been verified in case-control studies. A recent report detailed HLA differences among women in whom inflammatory myopathy develops after they received silicone implants.

Lab Studies

Muscle enzyme levels are often abnormal during the course of dermatomyositis, except in patients with the amyopathic variant. The most sensitive/specific enzyme is an elevated creatine kinase (CK), but aldolase levels and other tests (eg, aspartate aminotransferase [AST], lactic dehydrogenase [LDH]) may also yield abnormal results. At times, the elevation of the enzymes precedes clinical evidence of myositis. Thus, if a patient who is presumably stable develops an elevation of an enzyme previously within the reference range, the clinician should assess the possibility of a flare of the muscle disease. Several serologic abnormalities have been identified and may be helpful in the classification of subtypes for prognosis, but they are not used for routine diagnosis. As a group, these antibodies have been termed myositis-specific antibodies (MSAs). These autoantibodies occur in about 30% of all patients with dermatomyositis or polymyositis.

- A positive ANA finding is common in patients with dermatomyositis.
- Anti–Mi-2 antibodies are highly specific for dermatomyositis but lack sensitivity because only 25% of the patients with dermatomyositis demonstrate them. They are associated with acute-onset classic dermatomyositis with the V-shaped and shawl rash (poikiloderma) and a relatively good prognosis.
- Anti–Jo-1 (antihistidyl transfer RNA [t-RNA] synthetase) is more frequent in patients with polymyositis than in patients with dermatomyositis. It is associated

with pulmonary involvement (interstitial lung disease), Raynaud phenomenon, arthritis, and mechanic's hands.
- Other MSAs include antisignal recognition protein (anti-SRP), associated with severe polymyositis, and anti–PM-Scl and anti-Ku, which are associated with overlapping features of myositis and scleroderma.

Imaging Studies

- Magnetic resonance imaging
    - MRI may be useful for assessing the presence of an inflammatory myopathy in patients without weakness.
    - MRI is useful in differentiating a steroid myopathy from continued inflammation.
    - MRI imaging may serve as a guide in selecting a muscle biopsy site.
- Chest radiographs should be obtained at the time of diagnosis and when symptoms develop.
- A barium swallow allows evaluation of esophageal dysmotility.
- Ultrasonography of the muscles has been suggested for evaluation, but it has not been widely accepted.
- Electromyography is a means of detecting muscle inflammation and damage and, at times, has been useful in selecting a muscle biopsy site. This test is obtained less commonly since the introduction of MRI of muscle.
- CT scans are useful in the evaluation of potential malignancy that might be associated with inflammatory myopathy.

Other Tests

- Pulmonary function studies
- Electrocardiography
- Esophageal manometry - May be obtained in select patients

Procedures

A muscle biopsy sample, obtained either open or by a needle, may enhance the clinician's ability to diagnose dermatomyositis. The results of this biopsy may be useful in differentiating steroid myopathy from active inflammatory myopathy when patients have been on corticosteroid therapy but are still weak.

Histologic Findings

A skin biopsy sample reveals an interface dermatitis that is difficult to differentiate from LE. Vacuolar changes of the columnar epithelium and lymphocytic inflammatory infiltrates at the dermal-epidermal junction basement membrane can occur. Muscle biopsy samples in patients with dermatomyositis reveal perivascular and inter-

fascicular inflammatory infiltrates with adjoining groups of muscle fiber degeneration/regeneration. This contrasts with polymyositis infiltrates, which are mainly intrafascicular (endomysial inflammation) with scattered individual muscle fiber necrosis.

Medical Care

The therapy of dermatomyositis involves general measures and measures to control both the muscle disease and the skin disease. In addition, some patients may need treatment for other systemic manifestations or complications.

General treatments

Bedrest is often valuable for those patients with severe muscle inflammation. In patients with muscle weakness, especially children, a program of physical therapy is useful to help prevent contractures that can complicate the disease when patients do not fully move their joints. For patients with dysphagia, recommending elevating the head of their bed and not eating before bedtime is useful, possibly preventing aspiration pneumonitis. Occasionally, nasogastric tube feeding may be needed to increase caloric input.

Treatments for muscle disease

The mainstay of therapy for the muscle disease is systemically administered corticosteroids. Traditionally, prednisone (1-2 mg/kg/d) is administered as initial therapy. Taper slowly to avoid relapse of the disease. Because most patients develop steroid-related toxic effects, many authorities begin an immunosuppressive or cytotoxic agent early in the course. Most clinical and published experience is with the use of methotrexate as a steroid-sparing agent, but azathioprine and mycophenolate mofetil have been used. Results with cyclophosphamide in severe cases have been disappointing. In patients for whom these measures fail, the use of monthly high-dose intravenous immunoglobulin (IVIG) for 6 months has proved beneficial in the short term. A recent report has suggested that rituximab, a chimeric antibody directed against $CD20^+$ B cells, may be effective. However, other reports have failed to produce positive results.

Treatments for skin disease

Therapy of the cutaneous disease is often difficult. Some patients present primarily with skin disease (ie, amyopathic dermatomyositis), while other patients present with a muscle component that is controlled but with significant ongoing skin disease. First-line therapy is to recognize that the patient is photosensitive and to prescribe sun avoidance

and sun protective measures, including broad-spectrum sunscreens. Hydroxychloroquine and chloroquine have been beneficial in small, open-label case studies; however, roughly 20% of patients with dermatomyositis who are treated with an antimalarial agent develop a drug eruption. Methotrexate is useful. Recently, mycophenolate mofetil has been reported to be useful. Sirolimus may also be of use in some patients. IVIG not only benefits the muscle but also clears the skin lesions.

Calcinosis

This complication of the disease affects children and adolescents. Some believe that aggressive early treatment of the myositis may aid in preventing this complication. Once established, the process is debilitating in many patients. Although spontaneous remission is a possibility, it often occurs after many years. The use of the calcium channel blocker diltiazem (240 mg bid) is reportedly associated with gradual resolution of calcinosis in a small number of cases.

Surgical Care

Surgical care is usually not necessary. Some patients may request surgical removal of local areas of calcinosis.

Consultations

- Rheumatologist
- Dermatologist
- Neurologist
- Medical or surgical oncologist (for patients with cancer)
- Internal medicine specialist or pediatrician (depending on patient age)
- Pulmonologist

Diet

A well-balanced diet is useful. Patients with severe muscle inflammation may need extra protein to balance their loss. Patients with dysphagia should avoid eating before bedtime. They may require a special diet depending on the severity of the esophageal dysfunction.

Activity

Activity should be maintained as much as possible; however, avoid vigorous physical training when the myositis is active. Use exercises to maintain the patient's

range of motion. Recommend sun avoidance and sun protective measures in patients with skin lesions.

Further Inpatient Care

Inpatient care is needed for patients with fulminant disease.

Further Outpatient Care

Monitoring disease activity is necessary at least on a monthly basis. Repeat measurements of muscle enzymes may aid in assessment of the activity of the myositis, along with clinical assessment of patients' strength. Machines are available that can aid in the quantification of strength, but they are not used widely. Skin disease is assessed with physical examination in conjunction with history. A system for judging the activity and damage associated with dermatomyositis is being developed. Annual physical examinations are useful to monitor for potential toxicity from therapy or for the presence of a malignancy. Malignancy evaluations should be conducted for at least the first 3 years following diagnosis. A report by Hill et al (2001) suggested that the risk of malignancy never returns to baseline, even after 3 years; thus, vigilance is still warranted. The testing selected should be chosen based upon the patient's age, sex, race, and other symptoms or findings. Female patients should be screened for ovarian cancer. After 3 years, patients should be monitored as any other person of their same age, race, and sex.

In/Out Patient Meds

Prednisone is a first-line therapy. The dose is altered depending on the response of the patient's condition. Immunosuppressive/cytotoxic agents are used as steroid-sparing agents for the muscle disease. Methotrexate has been demonstrated to be useful for the skin disease even in the absence of significant muscle disease. Mycophenolate mofetil may also be useful for cutaneous disease. Antimalarials, particularly hydroxychloroquine, may be useful for the cutaneous disease. An increased risk of drug eruptions may exist in patients with dermatomyositis.

Intravenous immunoglobulin is used in patients for whom therapy with corticosteroids and immunosuppressives fails. This agent is useful for both the skin and the muscles. Biologic therapies including rituximab and TNF antagonists might be useful. However, their widespread use is discouraged until adequate, preferably controlled studies demonstrate efficacy and safety.

Transfer

Patients may be served better by a physician or a team of physicians who have experience in managing this relatively rare disorder. Transfer to a tertiary center is often warranted for initial care and even for follow-up care.

Deterrence/Prevention

Skin disease is exacerbated by sunlight and other sources of ultraviolet light. In addition, the muscle disease may be exacerbated. Sunscreens and sun protective measures are helpful in avoiding flares of the disease.

Complications

Calcinosis may complicate dermatomyositis in children and adolescents. Contractures can occur if the patient is immobile.

Prognosis

Patients with dermatomyositis who have malignancy, cardiac involvement, or pulmonary involvement or who are elderly (ie, >60 y) have a poorer prognosis. The disease may spontaneously remit in as many as 20% of the patients. About 5% of patients have a fulminant progressive course with eventual death. Therefore, many patients require long-term therapy.

Part 11.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a chronic, multifaceted inflammatory disease that can affect every organ system of the body. SLE is protean in its manifestations and follows a relapsing and remitting course. This article addresses what is known regarding the etiology, pathophysiology, clinical features, and treatment of SLE.

Pathophysiology

SLE is an autoimmune disorder that involves multisystem microvascular inflammation with the generation of autoantibodies. Although the specific cause of SLE is unknown, multiple factors are associated with the development of the disease. These include genetic, racial, hormonal, and environmental factors. Many immune disturbances, both innate and acquired, occur in SLE. One proposed mechanism for the development of autoantibodies involves a defect in apoptosis that causes increased cell death and a disturbance in immune tolerance. The redistribution of cellular antigens during apoptosis leads to a display of plasma and nuclear antigens on the cell surface. Thus, dysregulated (intolerant) lymphocytes begin targeting normally protected intracellular antigens. Immune complexes form in the microvasculature, leading to complement activation and inflammation. Moreover, antibody-antigen complexes deposit on the basement membranes of skin and kidneys. In active SLE, this process has been confirmed based on the presence of complexes of nuclear antigens such as DNA, immunoglobulins, and complement proteins at these sites. Antinuclear antibodies (ANAs) are present in the serum in virtually all patients with active SLE, and antibodies to native double-stranded DNA (dsDNA) are relatively specific for the diagnosis of SLE.

Frequency

Worldwide, the prevalence of SLE is variable, from 12 cases per 100,000 population in Britain to 39 cases per 100,000 population in Sweden. Although African Americans have a high prevalence of this disease, SLE is exceedingly rare among blacks who live in Africa. In New Zealand, disease prevalence is 50 cases per 100,000 population among Polynesians, compared with only 14.6 cases per 100,000 in the white population. The prevalence of SLE in US is approximately 1 case per 2000 population. The annual incidence averages 1 case per 10,000 population. Frequency varies with ethnicity.

Mortality and morbidity

The natural history of SLE varies from relatively benign disease to rapidly progressive and even fatal disease. Most patients are diagnosed at ages 14-64 years, and the disease often waxes and wanes in individual patients throughout life. Patients with isolated skin and musculoskeletal involvement have higher survival rates than those with renal and central nervous system (CNS) disease. Despite improvements in overall survival rates, patients with SLE still have a death rate that is 3 times that of the general population.

The 10-year survival rate now approaches 90%; prior to 1955, the 5-year survival rate was less than 50%. Decreased mortality rates can be attributed to earlier diagnosis (including milder cases), improvement in disease-specific treatments, and advances in general medical care. One third of SLE-related deaths in the United States occur in patients younger than 45 years, making this a serious issue despite declining overall mortality rates.

Specific SLE-related deaths, such as those due to nephritis, usually occur within the first 5 years of symptom onset. Infectious complications related to active SLE and immunosuppressive treatment are now the most common cause of death in early active SLE. Cardiovascular disease and malignancy, which may be related to chronic inflammation and cytoxic therapies, are common etiologies of late mortality.

The Framingham Offspring Study demonstrated that women aged 35-44 with SLE had a 50-fold greater risk of myocardial infarction than healthy women. Causes of accelerated coronary artery disease (CAD) are likely multifactorial, including endothelial dysfunction, inflammatory mediators, corticosteroid-induced atherogenesis, and dyslipidemia related to renal disease. Active lupus (34%), infection (22%), cardiovascular disease (16%), and cancer (6%) accounted for deaths in 144 of 408 patients with SLE who were monitored over 11 years.

Race

Worldwide, different races appear to have varying rates of disease. However, because of different prevalence rates among people of the same race in different geographical locations, a clear conclusion cannot yet be drawn. A higher prevalence of SLE occurs in African American women (2.5- to 6-fold higher relative risk) in the United

States than in white women. Black women in the United States tend to have a higher frequency of antibodies to dsDNA, with an associated higher rate of renal involvement. The influence of race on prognosis has been widely debated because black and Hispanic patients often have a poorer prognosis in the United States than whites do. However, links between socioeconomic status and prognosis suggest this association may be confounded. The essential nonexistence of SLE in West and Central Africa in contrast to high prevalence of the disease among African American women provides strong support for the importance of environmental influences.

Sex

SLE occurs predominantly in women of childbearing age, suggesting a role for hormonal factors in the pathogenesis of the disease. A hormonal influence hypothesis is supported by the 6- to 10- fold higher incidence of SLE in women of reproductive age and a higher prevalence of SLE in men with Klinefelter disease. Additionally, pregnancy and administration of exogenous estrogen often precipitate exacerbations of SLE. Men at all ages have a risk of disease similar to that of women who are prepubertal or postmenopausal.

Age

A correlation between age and incidence of SLE mirrors peak years of female sex hormone production. Disease incidence is highest among women aged 14-64 years. Males do not have an age-related peak in incidence.

History

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect almost any organ system. Its presentation and course is highly variable, ranging from indolent to fulminant.

- Constitutional

Nonspecific fatigue, fever, arthralgia and weight changes are the most frequent symptoms in new cases or recurrent active SLE flares. Fatigue, the most common constitutional symptom, can be due to active SLE, medications, lifestyle habits, or affective disorders. Fatigue due to active SLE generally occurs in concert with other clinical and laboratory markers. Fever, another common yet nonspecific symptom, may also be due to many causes. Active SLE, infection, and drug fever are the most common etiologies. Careful history taking may help to differentiate these. Weight loss may occur with ac-

tive disease. Weight gain may also be due to corticosteroid treatment or active disease such as nephrotic syndrome anasarca.

- Musculoskeletal

Arthralgia, myalgia, and arthritis represent the most common presenting symptoms in SLE. Small joints of the hands, wrists, and knees are involved most frequently. Migratory asymmetrical pain is often out of proportion with swelling.

- Dermatologic

Cutaneous manifestations of SLE comprise 3 diagnostic criteria and multiple other clues to a potential diagnosis of lupus. Malar rash describes an erythematous rash over the cheeks and nasal bridge that lasts from days to weeks and is occasionally painful or pruritic. A report of a photosensitive rash may be elicited from patients if they are asked if they have any unusual rash or symptom exacerbation after sun exposure. Discoid lesions often also develop in sun-exposed areas but are plaquelike lesions with follicular plugging and scarring. They may be part of systemic lupus or may represent discoid lupus without organ involvement, which is a separate diagnostic entity. Alopecia is a common yet less specific feature of SLE that often affects the temporal regions or creates a patchlike pattern of hair loss. Asking patients if they note any hand color change or pain with cold exposure may yield a history of Raynaud phenomenon. A painful triphasic blue, white, and red color change is a classic description. Although it is not a specific finding for SLE, Raynaud phenomenon may be seen in up to 20-30% of patients with SLE. Other skin lesions related to but not specific to SLE include livedo reticularis, panniculitis (lupus profundus), bullous lesions, vasculitic purpura, and urticaria.

- Renal

The kidney is the most commonly involved visceral organ in SLE. Although only approximately 50% of patients develop clinically evident renal disease, biopsy studies demonstrate some degree of renal involvement in almost all patients. Glomerular disease usually develops within the first few years after onset and is usually asymptomatic. Acute nephritic disease may manifest as hypertension and hematuria. Nephrotic syndrome may cause edema, weight gain, or hyperlipidemia. Acute or chronic renal failure may cause symptoms related to uremia and fluid overload.

- Neuropsychiatric

Widely varying nomenclature has been used to describe SLE-related CNS manifestations, although broader syndromes are commonly reported. Headache is the most common neurological symptom, often with migraine or complex migraine features, although a clear association with SLE is debated. Mood disorders such as anxiety and depression are frequently reported. Cognitive disorders may be variably apparent in patients with SLE. Formal neuropsychiatric testing reveals deficits in 21-67% of patients with SLE. Whether this represents true encephalopathy, neurological damage, medication effects, depression, or some other process is unclear. Psychosis related to SLE may manifest as paranoia or hallucinations. Delirium represents a spectrum of fluctuating altered consciousness characteristic of SLE. Delirium may be caused by CNS vasculitis, encephalopathy, or the manifestations previously called organic brain syndrome. Seizures related to SLE may be generalized or partial and may precipitate status epilepticus. Stroke and transient ischemic attack (TIA) may be related to antiphospholipid antibody syndrome or vasculitis. Movement disorders include chorea and parkinsonism; additionally, transverse myelitis with spastic paraparesis is a rare but serious complication of SLE. Myelopathy, optic neuropathy, or other demyelinating disorders may occur. Mononeuritis may result in focal peripheral deficits such as foot drop. Sensory neuropathy or mixed polyneuropathy may also be reported. Aseptic meningitis may occur.

- Pulmonary

Pulmonary manifestations of SLE may manifest acutely or indolently, representing many different complications. Pleurisy with pleuritic chest pain with or without pleural effusions is the most common feature of acute pulmonary involvement. Shortness of breath or dyspnea may be due to many causes. Serositis due to pericardial or pulmonary effusions, pulmonary embolism, lupus pneumonitis, chronic lupus interstitial lung disease, complement-mediated pulmonary leukoaggregation, or infection may be related to lupus disease. Pulmonary hypertension without underlying parenchymal lung disease rarely occurs with symptomatic dyspnea or right heart failure. Hemoptysis may herald diffuse alveolar hemorrhage, a rare, acute, life-threatening pulmonary complication of SLE.

- Gastrointestinal

Gastrointestinal symptoms secondary to primary SLE and adverse effects of medication are common among persons with SLE. Abdominal pain in SLE is significant because it may be directly related to active lupus, including peritonitis, pancreatitis, mesenteric vasculitis, and bowel infarction. Nausea and dyspepsia are frequent symptoms in patients with active SLE and are sometimes difficult to correlate with objective evidence of gastrointestinal involvement. Jaundice due to autoimmune hepatitis may be reported.

- Cardiac

Heart failure or chest pain symptoms must be carefully examined in patients with SLE. Pericarditis that manifests as chest pain is the most common cardiac manifestation of SLE and may occur with or without a detectable pericardial effusion. Libman-Sacks endocarditis is noninfectious but may manifest with symptoms similar to those of infectious endocarditis. Myocarditis may occur in SLE with heart failure symptomatology. Accelerated ischemic CAD is associated with SLE and may present as atypical anginal equivalents in this predominantly female population. Coronary vasculitis that manifests as angina or infarction is rarely reported. Coronary thrombosis related to antiphospholipid antibodies is also rare.

- Hematologic

History of multiple cytopenias such as leucopenia, lymphopenia, anemia, or thrombocytopenia may suggest SLE, among other etiologies. Leukopenia and, more specifically, lymphopenia are common in SLE; this and hypocomplementemia may predispose persons with SLE to frequent infections. Thrombocytopenia may be mild or part of a thrombotic thrombocytopenic purpura (TTP)–like syndrome. Anemia is occasionally overlooked in young menstruating women.

- Other

History of recurrent early miscarriages or a single late pregnancy loss may be clues to lupus, or isolated antiphospholipid antibody syndrome. Family history of autoimmune disease should also raise further suspicion of SLE.

Physical

As discussed above, almost any organ system can be involved in active SLE. The constellation of several physical findings may suggest a diagnosis of SLE. For the American College of Rheumatology (ACR) diagnostic criteria.

- Constitutional
  - Fever may signal infection or an acute SLE flare.
  - Lymphadenopathy or splenomegaly may be found.
- Skin
  - Malar rash describes an erythematous rash over the cheeks and nasal bridge with classic nasolabial fold sparing, as seen in Image 2.
  - Photosensitive rash is often macular or diffusely erythematous in sun-exposed areas of the face, arms, or hands, as in Image 3.
  - Discoid lesions are plaquelike lesions with follicular plugging, which may create scarring. Again, these may represent limited discoid lupus or systemic SLE.
  - Erythema annular centrifugum describes unique nonscarring erythematous papules or plaques with central sparing or a more confluent appearance similar to that of psoriasis or lichen planus.
  - Alopecia in SLE often affects the temporal regions or creates a patchy pattern.
  - Livedo reticularis describes a lacy, mottled, erythematous skin pattern that develops in some patients with SLE or antiphospholipid antibody syndrome.
  - Raynaud phenomenon may be observed with blue, white, and red color change at the distal digital tips. Capillaroscopy can be performed with an ophthalmoscope to look for dilated capillary nailfold loops.
  - Oral ulcers may be noted, with palatal ulcers being most specific for SLE.
  - Panniculitis, bullous lesions, vasculitic purpura, and urticaria are other skin lesions that are sometimes seen in SLE.
- Musculoskeletal
  - Jaccoud arthropathy is the term for the nonerosive hand deformities due to chronic arthritis and tendonitis that develop in 10% of patients with SLE. This may mimic rheumatoid arthritis (RA) ulnar deviation and phalangeal subluxations.
  - Small-joint arthritis of the hands and wrists is most frequent, followed by arthritis of the knees. Pain reports may be out of proportion to synovitis or swelling upon examination.
  - Myositis that manifests as weakness rarely occurs and is more commonly related to overlap syndromes or corticosteroid-induced myopathy.
  - Fibromyalgia may be concomitant with SLE, causing generalized widespread pain, arthralgia, and myalgia.
- Renal
  - Hypertension or hematuria may signal nephritic disease.
  - Edema of periorbital or peripheral regions and anasarca are common physical findings related to nephrotic syndrome or volume overload with renal failure.
- Neuropsychiatric
  - Altered mental status may be secondary to aseptic meningitis, seizures, psychosis, or organic brain syndrome.
  - Focal neurological deficits may represent stroke, TIA, or mononeuritis.

- Mononeuritis manifests with the functional loss of one or a few isolated peripheral nerves. Mononeuritis is observed in some patients with SLE vasculitis or antiphospholipid disease.

- Cardiopulmonary
  - Pleuropericardial friction rubs and signs of effusions may be found.
  - Hypoxia, tachypnea, crackles, or gross hemoptysis may be signs of pneumonitis or diffuse intrapulmonary hemorrhage.
  - Hemodynamic instability and hypoxia may suggest pulmonary embolism.
  - Heart failure signs or arrhythmias may point to ischemia or inflammatory myocarditis.
  - Murmurs may represent Libman-Sacks endocarditis, superimposed infectious endocarditis, or thromboembolic disease.
  - Ischemic chest pain due to CAD may be observed in a patient with lupus with otherwise inactive disease.
- Gastrointestinal
  - Abdominal tenderness and pain may be observed in peritonitis, pancreatitis, mesenteric vasculitis, or non–lupus-related processes.
  - Lupus peritonitis is a less common serositis that may be present, even in the absence of ascites.

Causes

Although the specific cause of SLE is unknown, immune system dysregulation and immune complex tissue damage at sites such as the skin and kidneys, as well as direct antibody-mediated cytotoxicity that causes thrombocytopenia and hemolytic anemia, are suspected causes. Multiple immune disturbances may predispose to SLE.

- At least 10 different gene loci are known to increase the risk for SLE.
  - A genetic predisposition is supported by the 10-fold increase in concordance among monozygotic twins versus dizygotic twins.
  - Studies of the human leukocyte antigens (HLA) reveal that HLA-DR2 and HLA-DR3 occur more often in people with SLE than in the general population.
  - The presence of the null complement alleles and congenital deficiencies of complement (especially C4, C2, and other early components) are also associated with an increased risk of SLE.
  - The multitude of distinct genetic associations suggests a complex genetic predisposition for the disease, perhaps explaining the variable clinical courses and organ system involvement

Lab Studies

Systemic lupus erythematosus (SLE) is a diagnosis that must be based on the proper constellation of clinical findings and laboratory evidence. Familiarity with the diagnostic criteria helps clinicians to recognize SLE and to subclassify patients with this com-

plex disease based on their pattern of target organ manifestations. The American College of Rheumatology (ACR) criteria summarize features necessary to diagnose SLE; they are summarized below with a useful mnemonic. The presence of 4 of the 11 criteria holds a sensitivity of 85% and a specificity of 95%. Keep in mind that individual features are variably sensitive and specific. Patients may present with any combination of clinical features and serologic evidence of lupus, ranging from indolent mild disease to fulminant acute initial presentations. The following is the ACR diagnostic criteria in SLE, presented in the "SOAP BRAIN MD" acronym:

- Serositis - Pleurisy, pericarditis
- Oral ulcers - Oral or nasopharyngeal, usually painless; palate is most specific
- Arthritis - Nonerosive Jaccoud type
- Photosensitivity - Unusual skin reaction to light exposure
- Blood disorders - Leukopenia, lymphopenia, thrombocytopenia, Coombs test–positive anemia
- Renal involvement - Proteinuria (>0.5 g/d or positive on dipstick testing; cellular casts)
- Antinuclear antibodies (ANAs) - Higher titers generally more specific (>1:160)
- Immunologic phenomena - Lupus erythematosus (LE) cells; anti–double-stranded DNA (dsDNA); anti-Smith (Sm) antibodies; antiphospholipid antibodies (anticardiolipin immunoglobulin G [IgG] or immunoglobulin M [IgM] or lupus anticoagulant); biologic false-positive serologic test results for syphilis
- Neurologic disorder - Seizures or psychosis
- Malar rash - Fixed erythema over the cheeks and nasal bridge
- Discoid rash - Raised rimmed lesions with keratotic scaling and follicular plugging

- In patients with high clinical suspicion or high ANA titers, additional testing is indicated. This may commonly include evaluation of antibodies to dsDNA, complement, and ANA subtypes such as Sm, SSA, SSB, and ribonucleoprotein (RNP) (often called the ENA panel). Screening laboratory studies to diagnose possible SLE should include a CBC count with differential, serum creatinine, urinalysis with microscopy, ANA, and, perhaps, basic inflammatory markers. The following are autoantibody tests used in SLE diagnosis:
  - ANA - Screening test; sensitivity 95%; not diagnostic without clinical features
  - Anti-dsDNA - High specificity; sensitivity only 70%; level variable based on disease activity
    - Anti-Sm - Most specific antibody for SLE; only 30-40% sensitivity
    - Anti-SSA (Ro) or Anti-SSB (La) - Present in 15% of patients with SLE and other connective tissue diseases such as Sjögren syndrome; associated with neonatal lupus

- Anti-ribosomal P - Uncommon antibodies that may correlate with lupus cerebritis
- Anti-RNP - Included with anti-Sm, SSA, and SSB in the ENA profile; may indicate mixed connective tissue disease with overlap SLE, scleroderma, and myositis
- Anticardiolipin - IgG/IgM variants measured with enzyme-linked immunoassay (ELISA) among the antiphospholipid antibodies used to screen for antiphospholipid antibody syndrome
- Lupus anticoagulant - Multiple tests (eg, Direct Russell Viper Venom test) to screen for inhibitors in the clotting cascade in antiphospholipid antibody syndrome
- Coombs test - Coombs test–positive anemia to denote antibodies on RBCs
- Anti-histone - Drug-induced lupus (DIL) ANA antibodies often this type (eg, with procainamide or hydralazine; perinuclear antineutrophil cytoplasmic antibody [p-ANCA]–positive in minocycline-induced DIL)

- Other laboratory tests include the following:
  - Inflammatory markers: Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels may be elevated in any inflammatory condition, including SLE; CRP levels change more acutely, and ESR lags behind disease changes.
  - Complement levels: C3 and C4 levels are often depressed in patients with active SLE because of consumption by immune complex–induced inflammation. In addition, some patients have congenital complement deficiency that predisposes them to SLE.
  - Complete blood count: Including differential diagnoses, CBC count may help to screen for leucopenia, lymphopenia, anemia, and thrombocytopenia.
  - Urinalysis/urine protein: Screening tests are used to evaluate for proteinuria (>0.5 g/d or positive on dipstick testing), hematuria, casts, or pyuria.
  - Creatinine: Creatinine evaluation is useful to monitor kidney disease activity.
  - Liver function tests: These may be mildly elevated in acute SLE or in response to therapies such as azathioprine or nonsteroidal anti-inflammatory drugs (NSAIDS).
  - Creatinine kinase: Creatinine kinase levels may be elevated in myositis or overlap syndromes.

Imaging Studies

Joint radiography often provides little evidence of SLE given the absence of erosions, even in the presence of Jaccoud arthropathy with deformity or subluxations. The most common radiographic changes include periarticular osteopenia and soft tissue swelling. Chest radiography and chest CT scans can be used to monitor interstitial lung disease

and to assess for pneumonitis, pulmonary emboli, and alveolar hemorrhage. Brain MRI/magnetic resonance angiography (MRA) is used to evaluate CNS lupus for white-matter changes, vasculitis, or stroke, although findings are often nonspecific. Echocardiography is used to assess for pericardial effusion, pulmonary hypertension, or verrucous Libman-Sacks endocarditis.

Procedures

Lumbar puncture may be performed to exclude infection with fever or neurologic symptoms. Nonspecific elevations in cell count and protein level and decrease in glucose level may be found in the cerebrospinal fluid of patients with CNS lupus. Renal biopsy is used to identify the specific type of glomerulonephritis, to aid in prognosis, and to guide treatment. Another benefit of renal biopsy is to distinguish renal lupus from renal thrombosis, which may complicate antiphospholipid antibody syndrome and require anticoagulation rather than immunomodulatory therapy. Skin biopsy can help to diagnose SLE or unusual rashes in patients with SLE. Many different rashes may herald SLE, making review by a dermatopathologist important.

Histologic Findings

Renal biopsy confirms the presence of lupus nephritis, aids classification of SLE nephritis, and guides therapeutic decisions. The World Health Organization classification for lupus nephritis is based on light microscopy, electron microscopy, and immunofluorescence findings. The following is the International Society of Nephrology 2003 revised classification of SLE nephritis (Table 10):

Table 10

Classification of SLE nephritis accordingly International Society of Nephrology (2003)

Class	Stage	Microscopy findings
Class I	Minimal mesangial	Normal light microscopy findings; abnormal electron microscopy findings
Class II	Mesangial proliferative	Hypercellular on light microscopy
Class III	Focal proliferative	<50% of glomeruli involved
Class IV	Diffuse proliferative	>50% of glomeruli involved; classified segmental or global; aggressively treated
Class V	Membranous	Predominantly nephrotic disease
Class VI	Advanced sclerosing	Chronic lesions and sclerosis

Lupus skin rash often demonstrates inflammatory infiltrates at the dermoepidermal junction and vacuolar change in the basal columnar cells. Discoid lesions demonstrate more significant skin inflammation, with hyperkeratosis, follicular plugging, edema, and mononuclear cell infiltration at the dermoepidermal junction. In many SLE rashes, immunofluorescent stains demonstrate immunoglobulin and complement deposits at the dermoepidermal basement membrane.

Medical Care

Care of patients with systemic lupus erythematosus (SLE) depends on disease severity. Periodic follow-up and laboratory testing, including urinalyses, are imperative to detect signs and symptoms of new organ system involvement and to monitor response or adverse reactions to therapies. CBC count with differential, creatinine, and urinalyses aid in detection of new organ system involvement and in monitoring response to therapies. At least quarterly visits are recommended in most cases. Fever, skin, musculoskeletal, and serositis represent milder disease manifestations, which may wax and wane with disease activity. These are often controlled with low-potency medications or short steroid courses. CNS involvement and renal disease must be recognized as more severe disease manifestations and are often treated with more aggressive immunosuppression.

Acute emergencies in SLE include severe neurologic involvement, systemic vasculitis, profound thrombocytopenia with a TTP-like syndrome, rapidly progressive glomerulonephritis, or diffuse alveolar hemorrhage. Rare serious manifestations such as TTP, diffuse alveolar hemorrhage, or profound steroid-refractory thrombocytopenia may require plasma exchange or intravenous immunoglobulin (IVIG), respectively.

Preventative care measures are necessary to minimize the risks of steroid-induced osteoporosis and accelerated atherosclerotic disease. The ACR Guidelines for the prevention of glucocorticoid-induced osteoporosis suggest traditional steps and the consideration of prophylactic bisphosphonate therapy. Recently, numerous authors have also advocated drafting cardiovascular prevention guidelines that equate SLE as a "CAD risk-equivalent" similar to diabetes mellitus. This is based on a 10-year coronary event rate of 13-15% in patients with active SLE compared with a 10-year event rate of 18.8% in patients with known pre-existing coronary heart disease. The European League Against

Rheumatism (EULAR) recently released new recommendations for the treatment of SLE.

Consultations

The multisystemic nature of this chronic disease often requires involvement of consultants, depending on the organ system involved. Consultation with any of the following specialists may be necessary:

- Rheumatologist
- Infectious disease specialist
- Neurologist
- Pulmonologist
- Cardiologist
- Gastroenterologist
- Nephrologist
- Dermatologist
- Hematologist

Diet

No diet-based treatment of SLE has been proven effective.

Activity

Patients should be reminded that activity may need to be modified as tolerated. Specifically, stress such as physical illness may precipitate SLE flares. Additionally, persons with SLE should wear sunscreen and protective clothing or avoid sun exposure to limit photosensitive rash or disease flares.

Further Inpatient Care

Fever in patients with systemic lupus erythematosus (SLE) is grounds for inpatient admission because of the difficulty of distinguishing a disease flare from infection in these immunocompromised hosts. Patients with SLE are often complement deficient and at risk for encapsulated organisms. For example, meningococcemia in young females with lupus may be catastrophic. Stress-dose steroid protocols should be used in patients receiving maintenance corticosteroids who are admitted with infectious or perioperative stress.

Further Outpatient Care

Periodic follow-up and laboratory testing, including urinalyses, are imperative to detect signs and symptoms of new organ system involvement and to monitor response and ad-

verse reactions to therapies. Perform at least 1 screening urinalysis per year to assess for nephritis. Immunization against encapsulated organisms is advised. This may include meningococcal vaccination, Pneumovax, and routine Haemophilus influenzae childhood vaccination. Annual influenza vaccine is also encouraged.

Transfer

TTP should prompt transfer to a center capable of offering plasma exchange therapy. CNS lupus with depressed consciousness may prompt ICU transfer and consideration of protective intubation.

Deterrence/Prevention

Avoid ultraviolet light and sun exposure to minimize worsening symptoms due to photosensitivity. Antimalarial therapy (hydroxychloroquine) has been shown to prevent relapses and to improve mortality. Estrogen therapies have typically been avoided to prevent disease flares; progesterone contraception has been encouraged. However, recent literature suggests that oral contraceptives may not be associated with disease flares or thrombosis risk in mild lupus without antiphospholipid antibodies. High rates of sulfa allergy and anecdotal reports of disease flares have also led to avoidance of sulfa-based medications in patients with SLE. Aggressive blood pressure and lipid goals may help to prevent CAD or renal disease progression. Angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers may be useful in patients with chronic renal disease. Calcium, vitamin D, and prophylactic bisphosphonates may reduce the risk of glucocorticoid-induced osteoporosis.

Complications

Opportunistic infections can develop, most often in patients receiving chronic immunosuppressive therapy. Osteonecrosis, especially of the hips and knees, is not uncommon and is related to prolonged high-dose corticosteroid usage. Premature atherosclerotic disease and myocardial infarction are possible complications.

Prognosis

Prognosis for SLE is highly variable. Renal and CNS involvement tend to be associated with a poorer prognosis.

Part 12.

SYSTEMIC SCLEROSIS

Systemic sclerosis (SSc) is a systemic connective tissue disease. Characteristics of systemic sclerosis include essential vasomotor disturbances; fibrosis; subsequent atrophy of the skin, subcutaneous tissue, muscles, and internal organs (eg, alimentary tract, lungs, heart, kidney, CNS); and immunologic disturbances accompany these findings.

Definition.

The term systemic sclerosis is used to describe a systemic disease characterized by skin induration and thickening accompanied by various degrees of tissue fibrosis and chronic inflammatory infiltration in numerous visceral organs, prominent fibroproliferative vasculopathy, and humoral and cellular immune alterations.

The American College of Rheumatology (ACR) criteria for the classification of systemic sclerosis require one major criterion or two minor criteria, as follows:

- Major criterion: Proximal scleroderma is characterized by symmetric thickening, tightening, and induration of the skin of the fingers and the skin that is proximal to the metacarpophalangeal or metatarsophalangeal joints. These changes may affect the entire extremity, face, neck, and trunk.
- Minor criteria
    - Sclerodactyly includes the above major criterion characteristics but is limited to only the fingers.
    - Digital pitting scars or a loss of substance from the finger pad: As a result of ischemia, depressed areas of the fingertips or a loss of digital pad tissue occurs.
    - Bibasilar pulmonary fibrosis includes a bilateral reticular pattern of linear or lineonodular densities most pronounced in basilar portions of the lungs on standard chest roentgenograms. These densities may assume the appearance of diffuse mottling or a honeycomb lung and are not attributable to primary lung disease.

Pathophysiology

Excessive collagen deposition causes skin and internal organ changes. Many factors, including environmental factors, can lead to immunologic system disturbances and vascular changes. Endothelial alterations may lead to a cascade of stimulatory changes that involve many cells, including fibroblasts, T lymphocytes, macrophages, and mast cells. In turn, the activated cells secrete a variety of substances, including cytokines and

their soluble receptors and enzymes and their inhibitors. These substances lead to changes in the extracellular matrix compounds, including fibronectin; proteoglycans; and collagen types I, III, V, and VII. Increased collagen deposition in tissues is a characteristic feature of systemic sclerosis. Increased collagen production or disturbances in its degradation can cause excessive collagen deposition in tissues.

Fibrosis can be caused by profibrotic cytokines, including transforming growth factor-beta (TGF-beta), interleukin-4 (IL-4), platelet-derived growth factor (PDGF), and connective-tissue growth factor. The vasculopathy may be linked to TGF-beta and PDGF, while the diminution of lesional cutaneous blood vessels can be attributed to antiendothelial cell autoantibodies. The activation of the immune system is of paramount importance in the pathogenesis of systemic sclerosis. Antigen-activated T cells, activated infiltrate early, infiltrate the skin, and produce the profibrotic cytokine IL-4. B cells may contribute to fibrosis, as deficiency of CD19, a B-cell transduction molecule, results in decreased fibrosis in animal models.

Different factors, including genetic, environmental, vascular, autoimmunologic, and microchimeric factors are involved in systemic sclerosis pathogenesis. One theory states that antigens from the human leukocyte antigen (HLA) histocompatability complex, including HLA-B8, HLA-DR5, HLA-DR3, HLA-DR52, and HLA-DQB2, are involved in systemic sclerosis. Some data suggest that apoptosis and the generation of free radicals may be involved in the pathogenesis of systemic sclerosis. In systemic sclerosis, affected organs and systems include the skin, lungs, heart, digestive system, kidneys, muscles, joints, and nervous system.

Frequency

Systemic sclerosis is estimated to occur in 2.3-10 people per 1 million. Systemic sclerosis is rare in the resident population of Japan and China. Systemic sclerosis is a rare disease. Systemic sclerosis is diagnosed in approximately 67 male patients and 265 female patients per 100,000 people each year.

Mortality and morbidity

The mortality rate is increasing in the United States and Europe; as many as 3.08 persons are affected per 1 million. Generally, renal and lung changes are responsible for death in patients with systemic sclerosis. Pulmonary hypertension leads to 12% of sys-

temic sclerosis–related deaths. Lung fibrosis and heart changes are responsible for 9% of systemic sclerosis – related deaths.

Race, sex and age particularities

No apparent racial predominance exists. However, systemic sclerosis is rare in the resident population of Japan and China. Diffuse systemic sclerosis (dSSc) occurs more often in black women than in white women. Overall, a substantial female predominance exists, with a female-to-male ratio of 3-6:1. However, dSSc occurs equally in males and females. The limited form of systemic sclerosis (lSSc) has a strong female predominance, with a female-to-male ratio of 10:1. Systemic sclerosis usually appears in women aged 30-40 years, and it occurs in slightly older men. In approximately 85% of cases, systemic sclerosis develops in individuals aged 20-60 years. Cases also are observed in children and in the elderly population.

History of Systemic sclerosis

Systemic sclerosis can have many different presentations. It involves the skin and many internal organs. Therefore, the presenting symptoms may differ among patients.

- Cutaneous pruritus is common.
- Raynaud phenomenon, or whitening of the hands on exposure to cold, is a common finding. Pain in the affected digits, blanching, cyanosis, and hyperemia can follow.
- Difficulty in swallowing solid foods can be followed by difficulty with swallowing liquids and subsequent nausea, vomiting, weight loss, abdominal cramps, blotting diarrhea, and fecal incontinence.
- The patient can have shortness of breath on exertion and, subsequently, at rest.
- Palpitations may occur without characteristic pain in thoracic cavity.
- The patient may have a nonproductive cough.
- Atypical chest pain, fatigue, dyspnea, and hypertension may be present.
- Joint pain, limitation of movement, joint swelling, and muscle pain may be present. Systemic sclerosis begins as joint pain in 15% of patients. It begins as inflammatory myopathy in 10% of patients.
- Weakness is present in 80% of patients.
- Medical signs and symptoms associated with disability, pain, and psychosocial adjustment in systemic sclerosis were assessed. In one study, 114 patients underwent examination, including a determination of skin thickening. Signs and symptoms were a significant correlate of all outcomes. Patient-reported dependent edema significantly correlated with all outcomes. For disability, significant correlates were physician-determined joint tenderness and number of tender points and patient-reported joint pain with motion, joint contracture, extremity ulcers other than digital, and dyspnea.

Physicalexamination findings

- According to the American College of Rheumatology (ACR), features characteristic for scleroderma are divided into 2 groups:
- Major features include centrally located skin sclerosis that affects the arms, face, and/or neck.
- Minor features include sclerodactyly, erosions, atrophia of the fingertips, and bilateral lung fibrosis.
- Systemic sclerosis is diagnosed when a patient has 1 major and 2 minor criteria.

Cutaneous involvement has 3 phases: edematous, indurative, and atrophic. Skin becomes thickened and tight. Systemic sclerosis is divided into 5 forms: dSSc, lSSc, transitory form (dSSc/lSSc), systemic scleroderma sine scleroderma, and malignant scleroderma. The principal forms are dSSc and lSSc. In addition to the following features, dSSc is characterized by Raynaud phenomenon that precedes the development of skin changes by approximately 1 year:

- Generalized skin fibrosis of the chest and limbs
- Areas of skin hyperpigmentation and hypopigmentation
- Tendon friction rubs
- Early involvement of the lungs, kidneys, digestive system, and heart
- Antibodies against topoisomerase I DNA (Scl 70) in approximately 30% of patients
- Nail-fold capillary dilatation and capillary destruction

lSSc is characterized by sclerotic changes of the hands, face, feet, and forearms in addition to the following features:

- Atrophic changes of the ala nasi and lips, facial amimia
- Telangiectasia of the skin
- Late involvement of the lungs and late development of pulmonary hypertension
- Anticentromere antibodies in approximately 70-80% of patients
- Dilated capillary loops in nail folds
- Cutaneous calcification
- dSSc and/or lSSc are described in a few cases in which internal organ changes preceded or simultaneously occurred with cutaneous changes.
- Systemic scleroderma sine scleroderma is difficult to diagnose because only internal organs are involved. Systemic scleroderma sine scleroderma usually is diagnosed after the patient's death.
- Malignant scleroderma most often occurs in men, usually in elderly men. An accelerated course of malignant scleroderma leads to death.

Causes

Systemic sclerosis is an autoimmunologic disease, but the pathogenesis is only partially understood. Certain factors are well known to trigger occurrence of the disease or

create a similar clinical appearance. Environmental factors include exposure to the following:

- Vibration injury (similar vascular changes)
- Silica
- Organic solvents (eg, toluene, benzene, xylene)
- Aliphatic hydrocarbons (eg, hexane, vinyl chloride, trichloroethylene)
- Epoxy resin
- Amino acid compound L-5-hydroxytryptophan
- Pesticides
- Drugs (eg, bleomycin, carbidopa, pentazocine, cocaine, penicillamine, vitamin K): A limited form of cutaneous systemic sclerosis has been described with paclitaxel in with the setting of breast cancer.
- Appetite suppressants (eg, phenylethylamine derivatives)
- Substances used in cosmetic procedures (eg, silicone or paraffin implants)

Lab Studies

The role of the immune system in the pathogenesis of systemic sclerosis remains unclear; however, patients have specific humoral and cell-mediated immunity abnormalities. Antinuclear antibodies are present in about 95% of the patients, usually with a speckled or homogenous pattern. A nucleolar pattern, although less common, is more specific for systemic sclerosis. Cell-mediated abnormalities involve lymphocytes, mononuclear phagocytes, and mast cells. Topoisomerase I antibodies (formerly Scl-70) are present in approximately 30% of patients with diffuse disease (absent in limited disease) and are associated with pulmonary fibrosis. Anticentromere antibodies are present in about 60-90% of patients with limited disease and are rare in patients with diffuse disease. Fibrillarin antibodies and antibodies to U3 ribonucleoprotein (RNP) may be present. Anti-U3RNP is present mostly in patients with diffuse disease with overlap syndromes. In addition, these antibodies are more common in patients with skeletal muscle involvement and pulmonary disease. Anti-ThRNP is present mostly in limited disease and is associated with more extensive visceral disease. Anti-PM-Scl is present in limited and overlap states and is associated with myositis and renal involvement. A microangiopathic hematologic picture may precede renal crisis. Current studies report new autoantibodies in systemic sclerosis that may play a role in its pathogenesis; these autoantibodies include antiendothelial cell (AECA), anti-fibrillin (FBN1), anti–matrix

metalloproteinase (MMP)–1 and anti–MMP-3, and anti–platelet-derived growth factor receptor (PDGFr).

Imaging Studies

CT scan: HRCT scan is required to evaluate pulmonary fibrosis. Imaging may reveal a ground-glass appearance, possibly indicating active alveolitis. Ground-glass appearance on HRCT scan is the first abnormality observed during the development of lung fibrosis and is subsequently replaced by honeycombing and traction bronchiectasis or bronchiolectasis. HRCT scanning should be performed every 6 months if active alveolitis or interstitial pulmonary fibrosis is present and every year if these abnormalities are not present.

Radiography: Chest radiography is a very insensitive imaging procedure that shows only late findings of pulmonary fibrosis, such as increased interstitial markings. Extremity radiography should be performed to reveal calcinosis and resorption of the distal tufts of the digits.

Echocardiography: Conduct this test to evaluate the patient's pulmonary artery pressure and to assess septal fibrosis or pericardial effusions. Roughly 30% of patients have asymptomatic pericardial effusions.

Right-heart catheterization: This remains the standard criterion for diagnosing pulmonary hypertension and is performed after an elevated pulmonary artery pressure is found on echocardiographic screening.

Esophagraphy: Perform this test to document esophageal dysmotility and incompetent LES.

Other Tests

- Pulmonary function testing (every 6 months)

Conduct this test to evaluate the DLCO, forced vital capacity (FVC) and total lung capacity (TLC). A FVC/DLCO of greater than 1.6 increases the likelihood of pulmonary hypertension. This is a very sensitive technique for detecting early fibrotic changes, alveolitis, and pulmonary hypertension. An isolated reduction in the DLCO is the best predictor of pulmonary hypertension.

Serum N-terminal pro-brain natriuretic peptide (NT-proBNP): Elevation of NT-proBNP levels may correlate with early pulmonary hypertension.

Cardiac rhythm monitoring: Perform 24-hour ambulatory Holter monitoring to evaluate arrhythmias and serious conduction defects. Esophagogastroduodenoscopy, esophageal manometry, and pH monitoring studies: Conduct these studies to survey and evaluate the upper GI system.

Procedures

- Nail fold capillary microscopy.
- Bronchoscopy with bronchoalveolar lavage to assess active lung inflammation

Histologic Findings

Systemic sclerosis is characterized by excessive fibrosis in the skin and other affected organs. The skin and lungs also show prominent T-lymphocyte infiltration. A severe fibroproliferative vasculopathy that affects small arteries and arterioles is universally present in affected organs. Platelet microthrombi are often found in the lumen of the narrowed vessels.

Medical Care

Skin thickening can be treated with D-penicillamine and other experimental drugs or interventions (interferon-gamma, mycophenolate mofetil, cyclophosphamide, photopheresis, allogeneic bone marrow transplantation). However, the US Food and Drug Administration (FDA) has not approved any therapies for systemic sclerosis. No placebo-controlled studies have demonstrated superiority, although some large uncontrolled series suggest beneficial effect from D-penicillamine. Interferon-gamma is effective, but its use is limited because it activates inflammatory and endothelial cells.

Pruritus can be treated with moisturizers, histamine 1 (H1) and histamine 2 (H2) blockers, tricyclic antidepressants, and trazodone.

Raynaud phenomenon can be treated with calcium channel blockers (to tolerance), prazosin, prostaglandin derivatives such as prostaglandin E1, dipyridamole, aspirin, and topical nitrates. In the event of thrombosis and vascular flow compromise, a tissue plasminogen activator, heparin, and urokinase may be necessary. In very severe cases, patients may benefit from a pharmacologic cervical sympathectomy or from surgical digital sympathectomy. Bosentan, a dual endothelin receptor antagonist, is under investigation and may decrease new digital ulcer formation. Sildenafil has also been shown

to be effective and tolerated in patients with primary Raynaud and is currently approved to treat pulmonary hypertension.

GI symptoms may be treated with antacids, H2 blockers, reflux and aspiration precautions, proton pump inhibitors, prokinetic agents, octreotide, smaller meals, and laxatives.

Pulmonary fibrosing alveolitis may be treated with cyclophosphamide, either orally or in intravenous pulses. Pulmonary hypertension may require supplemental oxygen. Bosentan is effective in treating primary (idiopathic) pulmonary hypertension, as well as pulmonary hypertension associated with systemic sclerosis, and has demonstrated substantial clinical and hemodynamic improvement in patients with systemic sclerosis–associated pulmonary hypertension. Numerous newer agents are available to treat pulmonary hypertension or are currently being tested in open and randomized controlled trials. These newer agents include other endothelin receptor antagonists such as sitaxsentan and ambrisentan; prostaglandin derivatives such as epoprostenol, treprostinil, beraprost and iloprost; and phosphodiesterase type 5 (PDE-5) inhibitors such as sildenafil. Preliminary nonrandomized studies have also shown benefit from mycophenolate mofetil.

Renal crisis episodes are best prevented and treated with the aggressive use of ACE inhibitors at the earliest signs of hypertension.

Myositis may be treated cautiously with steroids (first choice), methotrexate, and azathioprine. Doses of prednisone greater than 40 mg/d are associated with a higher incidence of sclerodermal renal crisis.

Arthralgias can be treated with acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs).

Proteinuria is not uncommon in patients with scleroderma who are receiving D-penicillamine.

Surgical Care

Digital sympathectomy may be used in patients with severe Raynaud phenomenon who have an unrelenting acute attack and who are threatened by digital loss. Debridement or amputation may be required in severe ischemic or infected digital lesions. Hand surgery may be performed to correct severe flexion contractures. Removal of severely painful or draining of infected calcinotic deposits is occasionally required.

Consultations

Ensure that all patients with systemic sclerosis are treated in conjunction with an experienced rheumatologist who has a full understanding of the disease, the complications of the therapies, and the frequently serious adverse effects.

Diet

Instruct the patient to avoid large does of vitamin C (>1000 mg/d) because it stimulates collagen formation and may enhance its deposition.

Activity

Ensure that the patient maintains a core body temperature to try to minimize the Raynaud phenomenon. Assist the patient in avoiding contamination of any skin wound caused by ischemic lesions or calcinosis. Digital ulcers must be kept clean and dry. Instruct the patient to perform continuous physical and occupational therapy to maintain range of motion and to minimize or delay contractures.

Further Inpatient Care

Patients may need to be treated by other subspecialists depending on their symptoms (eg, cardiologist, pulmonologist, gastroenterologist, nephrologist, hand surgeon). The value of serology testing is for initial diagnosis and assessment of associated conditions, but it is of little use for monitoring disease activity. Instruct the patient to maintain a core body temperature to minimize the risk of Raynaud phenomenon flare. Renal and lung transplantation are performed in specialized centers for patients with end-stage renal or lung involvement. Current studies of autologous stem cell transplantation are ongoing and may lead to disease remission.

Further Outpatient Care

Instruct the patient to avoid digital or skin trauma, cold exposure to the skin, and smoking and follow up for other complications. Evaluate the patient every 3-6 months, depending on the disease activity and progression. Serial skin scoring (also known as modified Rodnan skin score) is useful for monitoring skin changes over time. New techniques such as durometry, a technique for objectively measuring skin involvement, are currently being studied.

Deterrence/Prevention

Instruct the patient to stop smoking, to avoid cold exposure, and to treat skin ulcerations prior to tissue breakdown.

Complications

- Digital infarctions
- Pulmonary hypertension
- Myositis
- Renal failure
- Wound infections

Prognosis

For patients with limited involvement, 10-year survival rates are roughly 60-70%. For patients with diffuse disease, 10-year survival rates are 20%. Factors that imply a more severe prognosis are as follows:

- Youth
- African descent
- Rapid progression of skin symptoms
- Extent of skin involvement
- Anemia
- Elevated erythrocyte sedimentation rate (ESR)
- Pulmonary and renal involvement

Part 13.

RAYNAUD PHENOMENON

Raynaud phenomenon refers to reversible ischemia of peripheral arterioles. This can be in response to various stimuli but is most commonly caused by exposure to cold or stress. Raynaud phenomenon (secondary Raynaud) should be distinguished from Raynaud disease (primary Raynaud). They are distinct disorders that share a similar name. Raynaud disease is the occurrence of the vasospasm alone, with no association with another illness. Raynaud phenomenon is usually used in the context of vasospasm associated with another illness, most commonly an autoimmune disease. Other terms used for this distinction are primary Raynaud (disease) and secondary Raynaud (phenomenon).

Young female patients who have had Raynaud phenomenon alone for more than 2 years and have not developed any additional manifestations are at low risk for developing an autoimmune disease. Most of these patients are considered to have primary Raynaud. These patients do not exhibit capillary nailfold changes. If such changes are noted on nailfold capillaroscopy, other autoimmune diseases should be considered in the differential diagnoses. The same should be said for older and male patients who have Raynaud phenomenon, as vasospastic symptoms may predate systemic disease by as much as 20 years. In some studies, 46-81% of patients have secondary Raynaud.

Although Raynaud phenomenon has been described with various autoimmune diseases, the most common association is with progressive systemic sclerosis (scleroderma; 90% prevalence) and mixed connective-tissue disease (85% prevalence). Raynaud phenomenon has also been described with such diverse diseases as systemic lupus erythematosus and other disorders not classified as autoimmune, including frostbite, vibration injury, polyvinyl chloride exposure, and cryoglobulinemia.

Pathophysiology

One or more body parts experience intense vasospasm with associated pallor and, often, cyanosis. This is often followed by a hyperemic phase with associated erythema. The affected body parts are usually those most susceptible to cold injury. A clear line of demarcation exists between the ischemic and unaffected areas. These effects are reversible, and they must be distinguished from irreversible causes of ischemia such as vascu-

litis or thrombosis. Rarely, tissue necrosis occurs distal to the affected vessel. This usually happens in the periphery of the vasculature. It most commonly affects the digits of the fingers but may affect the toes, nose, and ears. Occasionally, even the tongue is involved.

Evidence exist that, even under normal conditions, patients with primary or secondary Raynaud have abnormal blood flow to the affected digits and an abnormal recovery to cold stimuli. The decreased blood flow may be a result of increased blood viscosity, abnormalities of the vasculature (specifically the endothelium), or unusually intense vessel constriction. Patients with cryoglobulins or Waldenstrцm macroglobulinemia have hyperviscosity syndromes that make blood flow in their peripheral vessels even more difficult, leading to this manifestation. Release of von Willebrand factor, nitric oxide synthesis, and local inflammation and cytokine production have all been implicated.

In patients with scleroderma, secondary Raynaud is associated with narrowing of the blood vessels from proliferation in the subintimal area. This fixed lesion causes a certain amount of baseline ischemia and hypoxia. The endothelial cell has been implicated as one of the early targets for scleroderma. Vasospasm occurs on top of the background hypoxia. It has also been associated with an increase in endothelin-1, a vasoconstrictor substance. Endothelin-1 has not been noted in patients with primary or secondary Raynaud that is not associated with scleroderma. It is believed to be a product of abnormal endothelial cells that are present in the skin of these patients.

Medications have been associated with exacerbations of primary or secondary Raynaud. Most of these medications promote vasoconstriction and include ergot alkaloids, nonspecific beta-adrenergic antagonists, and birth control pills. Some chemotherapeutic agents that are associated with fibrosis and may decrease blood flow, specifically bleomycin and the vinca alkaloids, have been associated with the development of secondary Raynaud.

Frostbite leads to vasomotor instability that may last for many years after the freezing episode. Patients with primary Raynaud have successfully been treated by blocking alpha2-adrenergic receptors, but the precise mechanism for this positive response is unclear.

U1-RNP antibodies may represent a marker for the vascular process that causes Raynaud phenomenon. It can also be considered a marker for associated structural vasculopathy. Originally, anti–U1-RNP was mostly associated with MCTD; however, subsequent studies have revealed that up to 29 % of patients may have undifferentiated connective-tissue disease (UCTD). Patients with scleroderma may express this in up to 21% of cases, while patients with SLE may develop antibodies up to 30% of the time. Neurologic influences, both locally and systemically, have been implicated.

Frequency

The prevalence of primary Raynaud varies among different populations, from 4.9-20.1% in women to 3.8-13.5% in men. The commonly accepted rate remains about 3-4%.

Mortality/Morbidity

Primary Raynaud does not usually cause death or serious morbidity. However, ischemia of the affected body part can result in necrosis. This is a very rare occurrence. Secondary Raynaud is important as a possible marker for other diseases that may lead to morbidity and mortality. Examples of this include scleroderma (progressive systemic sclerosis), systemic lupus erythematosus, and hyperviscosity syndromes.

Race, sex and age particularities

Primary Raynaud shows no racial predilection. Secondary Raynaud approximates the racial prevalence of the underlying disease.Prevalence of primary Raynaud varies in different populations, ranging from 4.9-20.1% in women to 3.8-13.5% in men.Primary Raynaud usually occurs in the second or third decade of life. Secondary Raynaud simultaneously begins with the underlying disorder.

History

- Numbness and pain in the affected area(s) may be present.
- Affected areas show at least 2 color changes: white (pallor), blue (cyanosis), and red (hyperemia).
    - The color changes are usually in the order noted but not always.
    - These changes should be reversible but may, in severe cases, lead to local ischemia and ulceration.
- Any history of associated symptoms should raise suspicion of an underlying disorder. History of other vasospastic symptoms such as migraines may be useful.
- Obtain occupational history.
    - Secondary Raynaud has been associated with the frequent use of vibrating tools such as jackhammers and sanders.

- Industrial exposure to polyvinyl chloride has been implicated.
- Any history of injury or frostbite may leave the involved limb vulnerable to vasospasm.

- Syndromes associated with Raynaud phenomenon include the following:
  - Autoimmune disorders
    - Progressive systemic sclerosis (scleroderma) including the diffuse and limited (formerly called CREST syndrome)
    - Systemic lupus erythematosus
    - Mixed connective-tissue disease (and other overlap syndromes)
    - Dermatomyositis and polymyositis
    - Rheumatoid arthritis
    - Sjögren syndrome
    - Vasculitis
    - Primary pulmonary hypertension
  - Infectious syndromes
    - Hepatitis B and C (especially associated with mixed or type 3 cryoglobulinemia)
    - *Mycoplasma* infections (with cold agglutinins)
  - Neoplastic syndromes
    - Lymphoma
    - Leukemia
    - Myeloma
    - Waldenström macroglobulinemia
    - Polycythemia
    - Monoclonal or type 1 cryoglobulinemia
    - Lung adenocarcinoma
    - Other paraneoplastic disorders
  - Environmental associations
    - Vibration injury
    - Vinyl chloride exposure
    - Frostbite
    - Lead exposure
    - Arsenic exposure
  - Metabolic/endocrine syndromes
    - Acromegaly
    - Myxedema
    - Diabetes mellitus
    - Pheochromocytoma
    - Fabry disease
  - Hematologic syndromes
    - Paroxysmal nocturnal hemoglobinuria
    - Polycythemia
    - Cryofibrinogenemia
  - Drug-related associations
    - Oral contraceptives
    - Ergot alkaloids

        - Bromocriptine
        - Beta-adrenergic blocking drugs
        - Antineoplastics (eg, vinca alkaloids, bleomycin, cisplatin)
        - Cyclosporine
        - Alfa-interferon
- Syndromes that may be confused with Raynaud phenomenon are as follows:
    - Anatomic syndromes
        - Carpal tunnel syndrome
        - Reflex sympathetic dystrophy syndromes
        - Thoracic outlet syndrome
    - Miscellaneous circulatory syndromes
        - Atherosclerosis
        - Thromboangiitis obliterans
        - Vasculitis
        - Thromboembolic disease
    - Vasospastic syndromes
        - Livedo reticularis
        - Acrocyanosis
        - Chilblains

Physical examination findings of primary and secondary Raynaud

- Carefully examine digits if either primary or secondary Raynaud is suspected.
    - Observe for sclerodactyly, calcinosis, or digital ulcers.
    - Examine nailfold capillaries under magnification from a dissecting microscope or ophthalmoscope to help diagnose underlying autoimmune disorders.
    - Abnormalities often appear in patients with early scleroderma. The normally regular pattern of capillary loops is replaced with abnormally large loops, alternating with areas without any capillaries.
- Evaluate any signs or symptoms of other syndromes associated with secondary Raynaud.
    - Bone pain may suggest a paraneoplastic syndrome associated with a hyperviscosity syndrome.
    - The presence of nephritis, malar erythema, and arthritis suggests systemic lupus erythematosus.
- Persistent cyanosis or necrotic distal tissue suggests an underlying disorder or permanent ischemia. Livedo reticularis suggests an autoimmune disorder or coagulation abnormality.
- Carpal tunnel syndrome has been associated with an increased frequency of Raynaud.

Causes of primary and secondary Raynaud

- The cause of primary Raynaud remains unknown.
- Possible causes for secondary Raynaud can be divided into several broad categories that include the following:
    - Occupational

    - Hematologic
    - Collagen-vascular (autoimmune)
    - Medication-induced
    - Miscellaneous syndromes such as Fabry disease, pheochromocytoma, lung adenocarcinoma, acromegaly, carpal tunnel syndrome, and myxedema
- Although the following entities do not usually have the same inciting causes, nor do they encompass the usual color changes associated with Raynaud phenomenon, they can easily be mistaken for Raynaud phenomenon:
    - Vasculitis
    - Carpal tunnel syndrome
    - Reflex sympathetic dystrophy
    - Thromboembolic disease
    - Thoracic outlet syndrome(s)

Lab Studies

- Complete blood cell count - To evaluate polycythemic disorders, underlying malignancies, or autoimmune disorders
- Blood urea nitrogen - To evaluate possible renal impairment or dehydration
- Creatinine - To evaluate possible renal impairment
- Prothrombin time - To observe for any evidence of hepatic dysfunction
- Activated partial thromboplastin time - To observe for any evidence of antiphospholipid antibody disorder or hepatic dysfunction
- Serum glucose - To evaluate patient for diabetic disease
- Thyroid-stimulating hormone - To observe for thyroid disorders
- Optional laboratory tests
    - Antinuclear antibody - May be positive in autoimmune disorders and should be ordered in patients with features of these disorders
    - Serum viscosity - Elevated in hyperviscosity syndromes such as paraproteinemias
    - Serum creatine kinase - Elevated in muscle damage such as polymyositis and dermatomyositis
    - Rheumatoid factor - May be elevated in rheumatoid arthritis, other autoimmune disorders, and some forms of cryoglobulinemia (monoclonal proteins in multiple myeloma and Waldenström macroglobulinemia have an increased frequency of rheumatoid factor activity)
    - Hepatitis panel - Positive for B or C infection in many patients with cryoglobulinemia
    - Cold agglutinins - Present in Mycoplasma infections and lymphomas
    - Heavy metal screen - To observe for patients with neuropathic pain from poisoning
    - Growth hormone - To evaluate patients for acromegaly
    - Serum vanillylmandelic acid - To evaluate for pheochromocytoma
    - Metanephrine - To observe for pheochromocytoma in appropriate patients
    - Catecholamines - To observe for pheochromocytoma
    - Leukocyte alkaline phosphatase - To evaluate for leukemias in appropriate patients

- Antiphospholipid antibodies studies - Including dilute Russell viper venom studies, anticardiolipin antibodies, and anti-beta-1-glycoprotein-2 antibodies.

Imaging Studies

Thermography, isotope studies, and arteriography have all been used, but none has proven superior to clinical assessment in office practice. A fixed, nonreversible, cyanotic lesion requires further evaluation of the vasculature.

Other Tests

- Acid hemolysis test
- Sucrose lysis test

Procedures

- Serum protein electrophoresis
- Liver or kidney biopsy
- Measurement of digital blood pressures before and after immersion in cold water (The difference should be less than 30 mm Hg.).

Medical Care

General measures. These include education, warming of local body part, and cessation of vasoconstricting agents such as nicotine.

Primary Raynaud

Use calcium channel blockers, especially those that cause vasodilation. The most commonly used drug is nifedipine. Use the lowest dose of a long-acting preparation and titrate up as tolerated. If adverse effects occur, decrease dosage or use another agent such as nicardipine, amlodipine, or diltiazem.

Angiotensin-converting enzyme inhibitors and intravenous prostaglandins have been advocated, and clinical trials have indicated some benefit. The selective serotonin uptake inhibitor fluoxetine has also been shown effective in at least one study.

Therapy with antiplatelet agents has been tried but has not been proven effective, and anticoagulation is not indicated. The angiotensin-receptor antagonist losartan at 50 mg/d has been found effective in patients with primary Raynaud and scleroderma.

Secondary Raynaud

Therapy must be tailored to the underlying disorder. If associated with occupational or toxic exposure, the patient should avoid the inciting environment. Patients with hyperviscosity syndromes and cryoglobulinemia improve with treatments that decrease

the viscosity and improve the rheologic properties of their blood (eg, plasmapheresis). Unfortunately, patients with autoimmune disorders and associated Raynaud phenomenon do not usually respond well to therapy.

Infections such as hepatitis B, hepatitis C, and Mycoplasma infections need to be addressed. In older patients with new-onset Raynaud and no obvious underlying cause, malignancy must be considered.

Surgical Care

Cervical sympathectomy still is considered controversial and may offer only temporary relief. Digital sympathectomy has been gaining support for patients with severe or tissue-threatening disease. This may be used in patients with either primary or secondary disease, but it is more commonly necessary with the secondary forms.

Consultations

- Typically, primary Raynaud does not require any consultations.
- Secondary Raynaud can require consultations.
    - Consult a rheumatologist or hematologist to delineate associated syndromes.
    - Fixed (nonreversible) lesions are not Raynaud phenomenon and may require referral to a rheumatologist, vascular surgeon, orthopedist, or other specialist.

Diet

Fish oils containing omega-3-fatty acids may be beneficial to some patients with primary Raynaud.

Activity

- Nondrug therapy may be all that is required for mild cases of primary Raynaud phenomenon. Therapies can include the following:
    - Biofeedback and relaxation
    - Avoiding inciting environmental factors such as direct contact with frozen foods or cold drinks
    - Insulation against cold and local warming, including electric and chemical warming devices
    - Removing any drugs from the medical regimen that may provoke vasospasm
    - Avoiding smoking
- With time, most patients learn to incorporate these therapies on their own

Further Inpatient Care

Primary Raynaud phenomenon is usually treatable on an outpatient basis. Although the same drugs and maneuvers are used for the phenomenon itself, treatment of secondary Raynaud phenomenon depends on the underlying disease.

Further Outpatient Care

Patients should check their systemic blood pressure regularly and may want to keep a log of the number and severity of attacks. This may help in evaluating the efficacy of therapeutic management.

Transfer

Transfer is not usually necessary.

Deterrence/Prevention

Avoid cold and stressful situations that precipitate attacks.

Complications

Rarely, digital ulceration and tissue loss may result from primary Raynaud phenomenon. The complications associated with secondary Raynaud are usually related to the underlying disease. The direst of these are loss of tissue pulp in the distal phalanx, ulceration, and digital gangrene. Critical digital ischemia necessitates aggressive management. It is considered a medical emergency that requires hospitalization. Warm temperature and bed rest are used to decrease trauma and activity and to control pain.

Local infiltration of lidocaine or bupivacaine at the base of the involved digits decreases sympathomimetic input, reduces ischemic pain, and improves blood flow. Rapidly advancing ischemic tissue anticoagulant therapy may be necessary. No algorithms or studies exist for the use of heparin.

Intravenous iloprost, alprostadil, or epoprostenol can be used if anticoagulant therapy fails or if the ischemia rapidly worsens. Failure of all these therapies might warrant surgical intervention with distal digital sympathectomy and arterial reconstruction. Further workup for vasculitis, thrombosis, arthrosclerosis, among other conditions, must be performed while treatment is in place.

Prognosis

Prognosis of primary Raynaud is usually very good, with no mortality and little morbidity. Prognosis of secondary Raynaud is related to the underlying disease. Prognosis for

the involved digit in these patients is related to the severity of the ischemia and the effectiveness of maneuvers to restore blood flow

Part 14.

SJÖGREN SYNDROME

Sjögren syndrome (SS) is characterized by lymphocytic infiltrates in exocrine organs. Typically, most patients present with sicca symptoms, such as xerophthalmia (dry eyes), xerostomia (dry mouth), and parotid gland enlargement. However, numerous extraglandular features may also be present, such as arthralgia, arthritis, Raynaud phenomenon, myalgia, pulmonary disease, gastrointestinal disease, leukopenia, anemia, lymphadenopathy, neuropathy, vasculitis, renal tubular acidosis, and lymphoma.

Sjögren syndrome is sometimes called primary Sjögren syndrome when no other underlying rheumatic disorder is present, whereas SS is sometimes called secondary SS if it is associated with another underlying rheumatic disease, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), or scleroderma (Scl). Given the overlap of Sjögren syndrome with many other rheumatic disorders, determining whether a clinical manifestation is solely a consequence of Sjögren syndrome or is due to one of its overlapping disorders is sometimes difficult. Importantly, classic clinical features of SS may also be seen in viral infections with hepatitis C, human immunodeficiency virus (HIV), and human T-cell lymphotrophic virus. Treatment for SS is largely based on symptoms, but patients must be watched carefully for the potential development of lymphoma.

Pathophysiology of Sjögren syndrome

The pathophysiology of Sjögren syndrome is not well understood. A genetic predisposition exists for the disease, and, interestingly, the genetic association varies among ethnic groups. In white persons, for instance, a linkage exists to human leukocyte antigen (HLA)–B8, HLA-Dw3, and HLA-DR3; whereas the linkage is to HLA-DRw53 in Japanese persons and to HLA-DR5 in Greek and Israeli persons. Some evidence indicates that the true association of Sjögren syndrome may be with HLA-DQA1, which is in linkage disequilibrium with HLA-DR3 and HLA-DR5.

Whereas major histocompatibility complex (MHC) class II molecules are normally expressed on activated immune cells, these HLA-DR molecules are also expressed at high levels on salivary gland epithelial cells. What triggers these epithelial cells to express MHC class II molecules remains unclear. Viruses are a viable candidate, and some evidence suggests involvement by retroviruses. Alternatively, this enhanced expression

could be triggered by cytokines, such as interferon gamma. T_H1 cytokines are overexpressed in patients with Sjögren syndrome. Therefore, these salivary gland epithelial cells that express MHC class II molecules could conceivably act as nonprofessional antigen-presenting cells to $CD4^+$ T cells, which then infiltrate the salivary gland and subsequently interfere with its normal glandular function. Although more information is available about the minor salivary gland because of its accessibility, these events could also occur in other exocrine organs. Another feature of Sjögren syndrome is hypergammaglobulinemia and autoantibody formation, especially antinuclear antibody (ANA) and rheumatoid factor (RF). This may be due to polyclonal B-cell activation, but the cause of this activation is not known.

Recent studies suggest that Sjögren syndrome has neuroendocrine component to the disease process. Normal salivary and lacrimal output is maintained in animals and humans until the gland is more than 90% destroyed. However, salivary gland biopsy samples from patients with Sjögren syndrome typically retain 40- 50% of their viable glandular structure. Therefore, inflammatory destruction of salivary and lacrimal glands may not fully account for the symptoms of Sjögren syndrome. Proinflammatory cytokines released by epithelial cells and lymphocytes may impair neural release of acetylcholine. Moreover, a recent investigation reports that M3 muscarinic receptor antibodies may cause autonomic dysfunction in patients with Sjögren syndrome. Current studies also focused on the role of apoptotic mechanisms in the pathogenesis of primary Sjögren syndrome. A defect in Fas-mediated apoptosis, which is necessary for downregulation of the immune response, can result in a chronic inflammatory destruction of the salivary gland, resembling Sjögren syndrome.

Frequency

Sjögren syndrome is observed throughout the world and it affects 0.1-3% of the population. This wide range, in part, reflects the lack of uniform diagnostic criteria.

Mortality and morbidity of Sjögren syndrome

Morbidity is mainly associated with the gradually decreased function of exocrine organs, which become infiltrated with lymphocytes. Increased mortality is primarily related to disorders commonly associated with Sjögren syndrome, such as SLE, RA, and

primary biliary cirrhosis. Patients with primary Sjögren syndrome have a normal life expectancy, unless they develop a lymphoproliferative disorder.

Race, sex and age particularities of Sjögren syndrome

Persons of all races are affected.The female-to-male ratio is 9:1. Sjögren syndrome can affect patients of any age but is most common in elderly people. Onset typically occurs in the fourth to fifth decade of life.

History

Sicca symptoms (dry eyes and dry mouth)

While dry eyes and dry mouth are the most common symptoms in patients with SS, most patients who report these symptoms have other underlying causes. Indeed, more than a third of elderly persons have sicca symptoms. The incidence of sicca symptoms increases with age; however, whether this is a part of the normal aging process (associated with fibrosis and atrophy observed on some lip biopsy studies) or due to the accumulation of associated illnesses and medications is unclear. A common explanation for sicca symptoms in any age group is the use of medications, such as antidepressants, anticholinergics, beta-blockers, diuretics, and antihistamines. Also remember that anxiety can lead to sicca symptoms.

Patients may report dry mouth in the following ways:

- Inability to eat dry food, such as crackers, because it sticks on the roof the mouth
- Tongue sticking to the roof of the mouth
- Putting a glass of water on their bed stand to drink at night
- Difficulty speaking for long periods of time or the development of hoarseness
- Higher incidence of dental caries and periodontal disease
- Altered sense of taste
- Difficulty wearing dentures
- Development of oral candidiasis with angular cheilitis, which can cause mouth pain

Dry eyes may be red, itchy, and painful. However, the most typical complaint is a gritty or sandy sensation in the eyes. Symptoms typically worsen throughout the day, probably due to evaporation of the aqueous layer. Occasionally, patients may awaken with matting in their eyes and, when severe, have difficulty opening their eyes in the

morning. Blepharitis can also cause similar morning symptoms. Patients can also have difficulty with dry skin and a dry vagina that can lead to dyspareunia.

Parotitis

Patients may have a history of recurrent parotitis, often bilateral. Occasionally, the parotid glands are large enough that patients may report this as a problem. More often, the examining physician discovers them.

Pulmonary symptoms

Patients with Sjögren syndrome can develop dryness of the tracheobronchial mucosa (xerotrachea), which can manifest as a dry cough. Less often, patients develop dyspnea from an interstitial lung disease that is typically mild. Patients may develop recurrent bronchitis or even pneumonitis (infectious or noninfectious).

Gastrointestinal symptoms

Dryness of the pharynx and esophagus frequently leads to difficulty with swallowing (deglutition), in which patients usually describe food becoming stuck in the upper throat. The lack of saliva may lead to impaired clearance of acid and result in gastroesophageal reflux and esophagitis. Abdominal pain and diarrhea can occur. Rarely, patients develop acute or chronic pancreatitis and malabsorption due to pancreatic insufficiency. However, be cautious when interpreting the results from laboratory studies because an elevated amylase level may arise from the parotid gland.

Skin and related symptoms

Palpable purpura develops in some patients with Sjögren syndrome, especially those with hypergammaglobulinemia or cryoglobulinemia. Raynaud phenomenon is observed in approximately 20% of patients.

Neurologic symptoms

The occurrence of central nervous system involvement in Sjögren syndrome is controversial. While one center reports a high incidence of a variety of central neurological problems associated with SS, including seizures and dementia, this has not been observed in other studies. Symmetric, peripheral, sensory neuropathies are found in up to 10% of patients. Cranial neuropathies can develop, particularly trigeminal neuropathy or facial nerve palsy. Mononeuritis multiplex should prompt a search for a vasculitis.

Other symptoms

SS is associated with a wide variety of other disorders; therefore, a careful review of systems is needed to detect problems such as RA, SLE, scleroderma, polymyositis, chronic active hepatitis, idiopathic pulmonary fibrosis, and primary biliary cirrhosis, among others. Patients with Sjögren syndrome may report fatigue, joint pain, and, sometimes, joint swelling. Women with Sjögren syndrome may have a history of recurrent miscarriages or stillbirths, and women and men may have a history of venous or arterial thrombosis. These are related to the presence of antiphospholipid antibodies (eg, lupus anticoagulant or anticardiolipin antibodies).

Physical examination findings

- **Eye examination**

While looking for corneal lesions and a decreased tear pool in the lower conjunctiva during physical examination is important, patients should be referred to an ophthalmologist for more formal testing for keratoconjuctivitis sicca. Patients may have dilation of the conjunctival vessels. Pericorneal injection and dullness or irregularity of the corneal image may be present. Blepharitis may be present as an alternate or additional problem, particularly if the lower eyelid is inflamed. Mucinous threads and filamentary keratosis can be detected during a slit-lamp examination. The relative lack of the aqueous layer also leads to rapid tear breakup. In a Schirmer test, a bent piece of Whatman No. 41 filter paper is placed in the lower conjunctiva, and the amount of tearing on the filter paper is recorded. Normal wetting is greater than 15 mm after 5 minutes, whereas a definitive positive result is less than 5 mm after 5 minutes. This test can be useful to help exclude or confirm significant dryness of the eyes, but it is not disease-specific. Furthermore, false-positive results occur. Indeed, in one study of asymptomatic patients, 41% had an abnormal Schirmer test result but had normal findings after minor salivary gland biopsy.

Mouth examination

Look for a decreased sublingual salivary pool. The tongue may stick to the tongue depressor. Patients may develop frequent caries, sometimes in unusual locations such as the incisor surface and the gum line. Periodontal disease can lead to loss of teeth. Patients are prone to develop oral candidiasis. In addition to white patches, watch for petechial lesions, loss of tongue papilla, erythema and fissuring of the tongue, erythema

on other mucosal surfaces, and angular cheilosis. Oral candidiasis can be seen under dentures.

Ear, nose, and throat examination

Bilateral parotid gland enlargement is common in persons with SS. Some waxing and waning of size may occur. Exudates from the parotid gland are largely lymphocytes. Submandibular glands can be enlarged. Rock hard or unilateral parotid gland enlargement should prompt a referral to an otolaryngologist for biopsy to exclude a tumor. Other causes of parotid enlargement include diabetes, sarcoidosis, amyloidosis, diffuse infiltrative lymphocytic syndrome (DILS) of HIV disease, hepatitis C, and alcoholism. Acute unilateral parotitis can be due to Sjögren syndrome, infection, or obstruction, although the latter two conditions are more often associated with a very tender parotid gland and accompanying fever.

Joint examination

Arthritis may be a component of primary or secondary Sjögren syndrome. Symmetric, polyarticular, inflammatory arthritis suggests underlying RA or a connective tissue disease such as SLE or scleroderma. The arthritis in patients with primary Sjögren syndrome is typically nonerosive and mild. One third of patients with RA have Sjögren syndrome.

Pulmonary examination.

Bibasilar rales can be heard in patients with interstitial lung disease.

Skin examination

Patients with Sjögren syndrome can develop a nonpalpable or palpable vasculitic purpura with lesions that are typically 2-3 mm in diameter and located on the lower extremities. They occur most often in patients with hypergammaglobulinemia or cryoglobulinemia. The lesions usually develop on the lower extremities and can ulcerate. Patients can also develop urticarial vasculitis, erythema multiforme–like lesions, digital vasculitis, petechiae, erythema nodosum, and annular erythematous plaques.

Other findings

Signs of another connective tissue disease (secondary Sjögren syndrome) may be present, such as SLE, scleroderma, or polymyositis. The patient may have signs of autoimmune liver disease such as primary biliary cirrhosis or autoimmune hepatitis.

Causes of Sjögren syndrome

As with many rheumatic disorders, the etiology of SS is not known but appears to derive from interactions between MHC and non-MHC genetic factors with unknown environmental stimuli. Sex hormones may also play a role because Sjögren syndrome is much more common in women.

Lab Studies

- CBC count
    - The CBC count is most often within reference ranges, but anemia of chronic disease may be present.
    - Pernicious anemia may possibly be associated with the atrophic gastritis.
    - An abnormal WBC count, especially with an abnormal differential count, should prompt concerns for a lymphoreticular tumor.
    - Low platelet or WBC count can occur in persons with primary Sjögren syndrome but should also prompt consideration for coexisting SLE.
- Chemistry
    - A high total protein level or a low albumin level should prompt the clinician to perform serum protein electrophoresis.
    - A high alkaline phosphatase level should prompt consideration for primary biliary cirrhosis.
    - With elevated transaminase levels, consider the possibility of chronic active hepatitis, which can be associated with sicca symptoms, or hepatitis C, which can cause mild salivary gland enlargement. However, mild (<2-fold) increases in transaminase levels are observed in 5-10% of patients with SS.
    - Consider evaluating patients with a low bicarbonate level for type I (distal) renal tubular acidosis (RTA). Less commonly, patients can also develop proximal RTA with Fanconi syndrome.
    - Hypokalemia, occasionally severe enough to lead to periodic paralysis, can be observed in patients with type I RTA but can also be observed in patients who have Sjögren syndrome without RTA.
- Serum protein electrophoresis
    - Patients with Sjögren syndrome often have a polyclonal gammopathy.
    - Loss of a previously detected polyclonal gammopathy can be observed in some patients with SS who develop lymphoma.
    - Development of a monoclonal gammopathy can also signal the development of a lymphoma.
- The sedimentation rate is often elevated, but this finding is nonspecific.
- Rheumatoid factor

- Positive RF findings are typically found in most patients with Sjögren syndrome S, even when they do not have RA. Consider a diagnosis of RA if the patient has symmetric polyarticular synovitis.
- Loss of a previously positive RF finding can be observed in some patients with Sjögren syndrome who develop lymphoma.

- ANA: ANAs are typically present in patients with SS. Consider the diagnosis of SLE only if symptoms and signs typical of this disorder are present.
- Antibodies to SS antigen A (SS-A/Ro) and SS antigen B (SS-B/La)
  - Although measuring these autoantibodies can help in the diagnosis of Sjögren syndrome, they are not necessary and can sometimes be misleading.
  - Antibodies against SS-A/Ro are found in approximately 50% of patients with the disease (75% of patients with primary Sjögren syndrome and 15% of patients with secondary Sjögren syndrome). Thus, the absence of anti-SS-A/Ro antibodies does not eliminate the diagnosis of primary or secondary SS.
  - Antibodies against SS-A/Ro are present in 50% of patients with SLE and are sometimes found in healthy individuals. Thus, by itself, the presence of antibody against SS-A/Ro cannot establish a diagnosis of SS.
  - Finding antibodies against SS-B/La in patients without antibodies against SS-A/Ro is unusual, but this combination has occurred in patients with primary biliary cirrhosis and autoimmune hepatitis.
  - Antibodies against SS-B/La are present in 40-50% of patients with primary Sjögren syndrome and in 15% of patients with SLE.
  - Titers of these antibodies do not reflect disease activity. More recent enzyme-linked immunosorbent assay tests for antibodies to SS-A/Ro and SS-B/La are more sensitive than previous tests. Thus, the specificity is lower.
  - Antibodies against SS-A/Ro are also associated with the annular erythematous lesions of subacute cutaneous lupus. They are also found in the mothers of newborns with neonatal lupus syndromes (ie, rash, congenital heart block), and some of these mothers have or will develop SS.
- Antiphospholipid antibodies: Patients with primary Sjögren syndrome may have positive test results for lupus anticoagulant and/or anticardiolipin antibodies, and some develop clinical events (ie, fetal wastage, arterial and/or venous thrombosis) associated with antiphospholipid syndrome.
- Cryoglobulins: Type II cryoglobulins are noted, particularly in patients with palpable and nonpalpable vasculitic purpura. Hepatitis C should be sought in these patients.
- Thyroid-stimulating hormone: In some studies, patients with Sjögren syndrome have an increased frequency of autoimmune thyroid disease with hypothyroidism (10-15%). Lymphocytic infiltration can be observed in the thyroid gland.

Imaging Studies

- Sialography

- In this test, radiopaque material is injected into the salivary glands. Sialography is useful to exclude the presence of obstructions or strictures, but the diffuse sialectasis of SS is seen in a variety of other diseases and, therefore, is not specific.
- Oil-based contrast medium may not be adequately cleared in patients with Sjögren syndrome and, consequently, may damage adjacent tissues and lead to a chronic granulomatous reaction. Performing this procedure with oil-based contrast should be avoided, especially during episodes of acute swelling.

- Salivary scintigraphy: In this technique, the uptake and secretion of sodium pertechnetate technetium Tc 99m is a gauge of the salivary flow rates and can provide a good measurement of salivary gland dysfunction. However, the finding of low flow rates is not specific to Sjögren syndrome.

Other Tests

- Rose bengal staining
  - Rose bengal is an aniline dye that stains devitalized cells and is more sensitive than fluorescein staining.
  - Conjunctival staining can be detected with the naked eye.
  - Slit-lamp examination is performed after rose bengal staining to detect abnormal uptake in the cornea.
- Sialometry: Like the Schirmer test, sialometry is a good measure of the degree of decreased salivary flow and helps establishes xerostomia, but the findings do not narrow the differential diagnoses.
- Sialochemistry: Saliva from patients with Sjögren syndrome has elevated levels of sodium, chloride, lactoferrin, and immunoglobulin A, but these findings are not specific.

Procedures

Minor salivary gland biopsy. In this procedure, an incision is made on the inner lip, and some minor salivary glands are removed for examination. Obtaining the biopsy sample from below normal-appearing mucosa is important in order to avoid false-positive results. At least 4 salivary gland lobules should be obtained for analysis. Currently, this is the best single test to establish a diagnosis of Sjögren syndrome. While this is the most definitive test, performing it is not absolutely necessary from a clinical standpoint. Patients with Sjögren syndrome are essentially treated symptomatically and observed for the development of other rheumatic disorders or lymphoma. This can be initiated without performing a biopsy. If the diagnosis is in doubt or if a definitive diagnosis is needed, then this is the best test. Biopsy can also help in the differential diagnosis because noncaseating granulomas of sarcoidosis can be found.

Histologic Findings

Although pathologists use different classification systems, the characteristic findings after minor salivary gland biopsy in a person with Sjögren syndrome include the following:

- Focal aggregates of at least 50 lymphocytes are seen and, to a lesser extent, plasma cells and macrophages.
- More than 1 focal aggregate is seen per 4 mm^2.
- T cells are present that are predominantly $CD4^+$ cells, unlike the predominately $CD8^+$ T cells seen in the salivary gland biopsy samples from patients with DILS associated with HIV disease.
- Lymphocytic replacement of the normal acini occurs.
- Focal aggregates are seen in almost all glands.
- Ten percent of the lymphocytes are $CD5^+$ B cells that produce immunoglobulin M and immunoglobulin G antibodies, often with a monoclonal or oligoclonal pattern.
- Large foci are present, possibly showing germinal centers.
- Epimyoepithelial islands are uncommon in the minor salivary gland but can be seen in the major salivary glands.

Lymphocytic infiltrates are also seen in other organs. Findings from a gastric mucosal biopsy may show lymphocytic infiltrates with atrophic gastritis. The results of a kidney biopsy may show interstitial lymphocytic infiltration. Lung biopsy can reveal infiltrating $CD4^+$ T cells of a lymphocytic interstitial pneumonitis. Salivary gland biopsy can help detect pseudolymphoma or lymphoma and the noncaseating granulomas of sarcoidosis.

Classification criteria

A number of classification criteria for Sjögren syndrome were designed primarily for clinical research studies but are also often used to help guide clinicians in the diagnosis of their patients. The American-European Consensus criteria for the classification of Sjögren syndrome are outlined below. These criteria allow the classification of Sjögren syndrome in patients without sicca symptoms or who have note undergone a biopsy. According to the American-European Consensus criteria, diagnosis of primary

Sjögren syndrome requires 4 of 6 of the below criteria; in addition, either criterion number 5 or criterion number 6 must be included. Diagnosis of Sjögren syndrome can be made in patients who have no sicca symptoms if 3 of 4 objective criteria are fulfilled. The criteria are as follows:

1. Ocular symptoms

- Dry eyes for more than 3 months
- Foreign-body sensation
- Tear substitutes are used more than 3 times per day

2. Oral symptoms

- Feeling of dry mouth
- Recurrently swollen salivary glands
- Liquids are frequently used to aid swallowing

3. Ocular signs

- Schirmer test performed without anesthesia (J5 mm in 5 min)
- Positive vital dye staining results

4. Oral signs

- Abnormal salivary scintigraphy findings
- Abnormal parotid sialography findings
- Abnormal sialometry findings (unstimulated salivary flow <0.1 mL/min

5. Positive lip biopsy findings

6. Positive anti–SS-A or anti–SS-B antibody results

Medical Care

Dry eyes

Artificial tears should be applied liberally. Patients may need to apply artificial tears more often if they enter an environment with low humidity (ie, air conditioning, airplanes). Artificial tears with hydroxymethylcellulose or dextran are more viscous and can last longer before reapplication is needed. Encourage patients to try various preparations to determine what works best for them. If artificial tears burn when they are instilled, the preservative in the artificial tears is likely irritating the eye. If artificial tears are used more often than every 4 hours, patients should use a preservative-free preparation to avoid eye irritation from the preservatives. If patients wake up in the morning with severe matting in the eyes, then they should use a more viscous preparation, such as Lacri-Lube, at night. While the more viscous preparations can be applied less often,

they can make patients' vision filmy. Therefore, they are best used at night. The more viscous preparations can occasionally lead to blepharitis, which can exacerbate sicca symptoms.

Temporary plugging of the lacrimal puncta can increase the amount of tears that remain in the eyes. Electrocautery and other techniques can be used for permanent punctal occlusion. Patients should avoid medications with anticholinergic and antihistamine effects. The use of humidifiers may help. If living in an area with hard water, using distilled water is best. Glasses fitted with moisture shields can decrease evaporation.

Dry mouth

Patients can liberally drink sips of water and take bottled water with them on trips. They can also place a glass of water at their bedside for nighttime use as needed. Sugar-free lemon drops can also be used as needed to stimulate salivary secretion. Artificial saliva can be used as needed, although patient tolerance is variable. Preparations include Salivart, Saliment, Saliva Substitute, MouthKote, and Xero-Lube. Patients should be seen regularly by a dentist, who might advise fluoride treatments. Toothpaste without detergents can reduce mouth irritation in patients with Sjögren syndrome.

Brands include Biotene toothpaste, Biotene mouth rinse, Dental Care toothpaste, and Oral Balance gel. Patients should avoid medications with anticholinergic and antihistamine effects. Watch for and treat oral candidiasis and angular cheilitis with topical antifungal agents, such as nystatin troches. Oral fluconazole may be needed occasionally. Patients also need to be sure to disinfect their dentures. Sinusitis and sinus blockade should be treated because these problems may contribute to mouth breathing. Emphasize the use of isotonic sodium chloride solution nasal sprays to avoid using antihistamines. Use of humidifiers may help. For patients living in an area with hard water, using distilled water is best. Pilocarpine or cevimeline tablets are options. Some small studies suggest that interferon alfa may be a useful therapy in the future.

Skin and vaginal dryness

Patients should use skin creams, such as Eucerin, or skin lotions, such as Lubriderm, to help with dry skin. Patients should use vaginal lubricants, such as Replens, for vaginal dryness. Vaginal estrogen creams can be considered in postmenopausal women. Watch for and treat vaginal yeast infections.

Arthralgias and arthritis

Acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) can be taken for arthralgias. Consider hydroxychloroquine if NSAIDs are not sufficient for the synovitis occasionally associated with primary Sjögren syndrome. This medication, however, does not relieve sicca symptoms. Patients with RA associated with Sjögren syndrome likely require other disease-modifying agents.

Other drugs

In patients with major organ involvement, such as lymphocytic interstitial lung disease, consider therapy with steroids and immunosuppressive agents, such as cyclophosphamide. While cyclophosphamide and similar agents may be helpful to treat serious manifestations of Sjögren syndrome or disorders associated with Sjögren syndrome, clinicians should understand that these agents are also associated with the development of lymphomas.Anticoagulation: Long-term anticoagulation may be needed in those patients with vascular thrombosis related to antiphospholipid antibody syndrome.

Surgical Care

Perform a minor salivary gland biopsy for diagnostic purposes. Perform a biopsy on the parotid gland if malignancy is suggested. Perform a biopsy on an enlarged lymph node to help rule out pseudolymphoma or lymphoma. Occlusion of the lacrimal puncta can be corrected surgically. Electrocautery and other techniques can be used for permanent punctal occlusion. During surgery, the anesthesiologist should use as little anticholinergic medications as possible and use humidified oxygen to help avoid inspissation of pulmonary secretions. Good postoperative respiratory therapy should also be provided. Patients are at higher risk for corneal abrasions, so ocular lubricants should be considered.

Consultations

Internal medicine specialist: Sjögren syndrome and its associated disorders necessitate a total patient perspective that is often best provided by an internist.

Rheumatologist: With specific training and experience in this disorder and its associated disorders, a rheumatologist is a key person in the management of patients with Sjögren syndrome .

Ophthalmologist: Involve ophthalmologists early in the care of patients for rose bengal and fluorescein staining to help establish the diagnosis and to assess the degree of damage to the eye.

Otolaryngologist: consultation may be needed early to perform a minor or major salivary gland biopsy if this is deemed necessary to establish a diagnosis. The specialist may also need to perform a parotid biopsy if malignant transformation is suggested.

Dentist: Good oral prophylaxis and therapy is necessary.

Other subspecialists: Depending on the problems, patients may need to be seen by other specialists, including the following:

- Nephrologist to help manage RTA
- Pulmonologist to help manage interstitial lung disease
- Hematologist/oncologist if pseudolymphoma or lymphoma develops

Activity

Encourage patients to be active.

Further Outpatient Care

Most patients can be monitored at follow-up visits every 3 months and, if the patient is stable, up to every 6 months. If patients have active problems or in case of concern about an emerging associated illness, patients can be seen as often as monthly.

Complications

Emergence of other associated disorders such as SLE and RA Infection of the parotid gland, typically due to staphylococci, streptococci, or pneumococci: clues include unilateral worsening of symptoms along with tenderness, warmth, and erythema.

Emergence of parotid tumors

Watch for unusually hard or unilateral parotid enlargement. Emergence of pseudolymphomas (pleomorphic cells that do not meet the criteria for malignancy) and non-Hodgkin B-cell lymphomas. Patients with Sjögren syndrome have a 44-fold increased risk of developing lymphoma, with an overall frequency of 5-8%. However, the increased risk has not been found in all studies. The mean time to development of non-Hodgkin lymphoma is 7.5 years. Watch for regional or generalized lymphadenopathy, hepatosplenomegaly, palpable purpura, leukopenia, renal insufficiency, loss of a pre-

viously positive polyclonal gammopathy or RF, development of a monoclonal gammopathy, or the development of a monoclonal cryoglobulinemia.

Neonatal lupus and congenital heart block.

Children born to mothers with antibodies against SS-A/Ro have an increased risk of developing neonatal lupus and congenital heart block. If one child develops congenital heart block, the risk for congenital heart block during a subsequent pregnancy is 15%.

Antiphospholipid syndrome.

Patients with Sjögren syndrome who have antiphospholipid antibodies can develop the clinical features of this syndrome. These include increased fetal wastage and vascular thromboses.

Prognosis of Sjögren syndrome

The prognosis is generally good. If patients develop an associated disorder, the prognosis is more closely related to the associated disorder (eg, SLE, lymphoma).

Part 15.

MIXED CONNECTIVE-TISSUE DISEASE

Mixed connective-tissue disease (MCTD) was first recognized by Sharp and colleagues (1972) among a group of patients with overlapping clinical features of systemic lupus erythematosus (SLE), scleroderma, and myositis, with the presence of a distinctive antibody against what now is known to be U1-ribonucleoprotein (RNP). MCTD has been more completely characterized in recent years and is now recognized to consist of the following core clinical and laboratory features: Raynaud phenomenon, swollen hands, arthritis/arthralgia, acrosclerosis, esophageal dysmotility, myositis, pulmonary hypertension, high level of anti–U1-RNP antibodies, and antibodies against U1-70 kd small nuclear ribonucleoprotein (snRNP).

Pathophysiology

Pathophysiologic abnormalities that are believed to play a role in MCTD include the following:

- B-lymphocyte hyperactivity, resulting in high levels of anti–U1-RNP and anti–U1-70 kd autoantibodies
- T-lymphocyte activation with the presence of anti–U1-70 kd–reactive T lymphocytes circulating in the peripheral blood
- Apoptotic modification of the U1-70 kd antigen
- Immune response against apoptotically modified self-antigens
- Genetic association with major histocompatibility genes human leukocyte antigen (HLA)–DRB1*04/*15[2]
- Vascular endothelial proliferation with widespread lymphocytic and plasmacytic infiltration of tissues
- Activation of Toll-like receptors in a pattern that may differ from that of lupus

Frequency

Careful epidemiological studies have not been performed in the United States. MCTD appears to be more prevalent than dermatomyositis (1-2 cases per 100,000 population) but is less prevalent than SLE (15-50 cases per 100,000 population). In an epidemiological survey in Japan, MCTD has a reported prevalence of 2.7 cases per 100,000 population.

Mortality and morbidity

Recent long-term outcome studies have established pulmonary hypertension as the most common disease-related cause of death. Immunoglobulin G (IgG) anticardiolipin

antibodies are a marker for development of pulmonary hypertension. Infections are a major cause of death.

Race, sex and age particularities

MCTD has been reported in all races. The clinical manifestations of MCTD are similar among various ethnic groups. The female-to-male ratio of MCTD is approximately 10:1. The onset of MCTD can occur at any age but typically occurs in people aged 15-25 years.

History

Manifestations of mixed connective-tissue disease (MCTD) can be protean. Most patients experience Raynaud phenomenon, arthralgia/arthritis, swollen hands, sclerodactyly or acrosclerosis, and mild myositis. The following may be revealed by history or physical examination:

- Raynaud phenomenon (96% cumulatively, 74% at presentation)
- Arthralgia/arthritis (96% cumulatively, 68% at presentation)
- Esophageal hypomotility (66% cumulatively, 9% at presentation)
- Pulmonary dysfunction (66% cumulatively, rare at presentation)
- Swollen hands (66% cumulatively, 45% at presentation)
- Myositis (51% cumulatively, 2% at presentation)
- Rash (53% cumulatively, 13% at presentation)
- Leukopenia (53% cumulatively, 9% at presentation)
- Sclerodactyly (49% cumulatively, 11% at presentation)
- Pleuritis/pericarditis (43% cumulatively, 19% at presentation)
- Pulmonary hypertension (23% cumulatively, rare at presentation)

Physical examination fidings in patients with MCTD

Physical examination is helpful in confirming or identifying features of MCTD. Seek the following features on examination:

- Fever should prompt a careful search for infection. However, infection may be present in the absence of fever and is one of the primary disease-related causes of mortality and/or morbidity in MCTD. The use of corticosteroids and immunosuppressive agents further increases the risk of infection.
- Corticosteroids may mask serious intra-abdominal processes, including appendicitis, vasculitis, pancreatitis, and bowel perforation.
- Cardiopulmonary symptoms or findings should prompt a careful evaluation for pulmonary hypertension.
- Capillary microscopy can assist in finding sclerodermatous-type nailfold changes.
- Severe Raynaud phenomenon may result in digital vascular infarcts and ulcerations.
- Pericarditis may be occult and can progress rapidly to cardiac tamponade.

- Trigeminal neuralgia is common in MCTD.
- Secondary Sjögren syndrome occurs in 25% of patients with MCTD and may cause both ocular symptoms and oral dryness.

Causes of MCTD

The fundamental cause of MCTD remains unknown. Autoimmunity to components of the U1-70 kd snRNP are a hallmark of disease. Anti-RNP antibodies can precede overt clinical manifestations of MCTD, but overt disease generally develops within one year of anti-RNP antibody induction. The loss of T-lymphocyte and B-lymphocyte tolerance, due to cryptic self-antigens, abnormalities of apoptosis, or molecular mimicry by infectious agents, and driven by U1-RNA-induced innate immune responses, are proposed current theories of pathogenesis.

Lab Studies

- CBC count
- Urinalysis
- Routine blood chemistry
- Muscle enzymes if myositis is suspected clinically
- Antinuclear antibodies
    - High-titer speckled pattern fluorescent antinuclear antibody (FANA) is typical of mixed connective-tissue disease (MCTD).
    - FANA is not specific to MCTD.
- High titers of anti–U1-RNP antibodies
    - Anti-RNP antibodies are required for diagnosis of MCTD.
    - The presence of anti–U1-70 kd is characteristic of MCTD.
- Other immune studies
    - Antiphospholipid antibodies (including anticardiolipin antibodies and lupus anticoagulant) may be associated with pulmonary hypertension. In MCTD, however, the presence of these antibodies has not been associated with clotting events.
    - Rheumatoid factor is frequently detected.
    - Other lupus-specific antibodies (eg, anti–double-stranded DNA antibodies) are absent.
    - Scleroderma-specific antibodies, including anticentromere, anti–Scl-70 (topoisomerase), and anti–PM-1 (Pm-Scl), are absent.
    - C3 and C4 complement levels are more likely to be depleted in lupus than in MCTD
- Amylase and lipase - To assess for pancreatitis if clinically indicated

Imaging Studies

- Chest radiography - To assess for infiltrates, effusion, or cardiomegaly
- Echocardiography - Used to evaluate for effusion, chest pain, pulmonary hypertension, or valvular disease (An exercise echocardiography may increase the sensitivity to identify pulmonary hypertension.)
- Ultrasonography/CT scanning - Used to evaluate abdominal pain (indicated for evidence of serositis, pancreatitis, or visceral perforation related to vasculitis)
- MRI - Used to assess neuropsychiatric signs or symptoms

Other Tests

- Pulmonary function testing - To screen for declining diffusing capacity of lung for carbon monoxide (DLCO), possibly indicating pulmonary hypertension
- ECG and/or cardiac enzymes - To assess for myocardial ischemia and myocarditis
- Cerebral spinal fluid (CFS) analysis - To monitor for infection, stroke, or neuropsychiatric manifestations
- Six-minute walk - To assess for cardiopulmonary insufficiency, possibly indicating pulmonary hypertension

Procedures

Right-sided heart catheterization is the criterion standard for diagnosis of pulmonary hypertension.

Staging

MCTD can enter sustained remission later in the clinical course. Anti-RNP autoantibodies typically become undetectable in patients in remission.

Medical Care

The overall goal of therapy is to control symptoms and to maintain function. Target medical therapy to specific organ involvement and extent of disease activity. Monitoring for development of complications, such as pulmonary hypertension or infection, is important.

Consultations

Whenever possible, a rheumatologist experienced in diagnosis and treatment of the disease should co-manage all patients with mixed connective-tissue disease (MCTD). Consultation with other specialists or subspecialists may be indicated for the evaluation and/or treatment of specific aspects of disease, such as pulmonary hypertension.

Diet and activity

Patients with hypertension, esophageal reflux, malabsorption, or other sclerodermatous-type bowel involvement may need special consideration. Because atherosclerotic heart disease remains a major risk in all patients, advocate a heart-healthy diet. However, no specific dietary manipulations have been demonstrated to be effective in treating MCTD. Convincing data support the value of an active lifestyle and an exercise program tailored to the needs of patients with arthritis of various types. This approach also appears to be appropriate in MCTD.

Further Inpatient Care

Patients with mixed connective-tissue disease (MCTD) may require admission pending assessment for suspected infection or complications related to disease or treatment. Admit patients to appropriate service with rheumatology care, if available. Obtain subspecialty consultations as indicated.

Further Outpatient Care

See patients with stable disease and no recent changes in medications approximately every 2-4 months and perform routine laboratory evaluation, including CBC count and chemistry studies. Patients with active disease are typically seen approximately every 3-6 weeks, depending on the severity of disease.

Prognosis

Cases of MCTD with typical clinical or serologic features occasionally evolve into scleroderma, SLE, or another rheumatic disease. Most patients with MCTD have a favorable outcome. Pulmonary hypertension is the most common disease-associated cause of death. Careful monitoring and aggressive treatment may improve the outcome of pulmonary hypertension.

Patient Education

Education about MCTD and its treatment is essential. Active participation in the decision-making process empowers patients in their own care. Education about disease decreases the risk of patients developing learned helplessness and improves functional outcomes.

Part16.

POLYMYALGIA RHEUMATICA

Polymyalgia rheumatica (PMR) is a relatively common clinical syndrome of unknown etiology. It is characterized by proximal myalgia of the hip and shoulder girdles with accompanying morning stiffness that lasts for more than 1 hour. Approximately 15% of patients with polymyalgia rheumatica develop giant cell arteritis (GCA), and approximately 50% of patients with giant cell arteritis have associated polymyalgia rheumatica.

Pathophysiology of Polymyalgia rheumatica

The cause of polymyalgia rheumatica is unknown. HLA-DR4 is found with increased frequency in persons with polymyalgia rheumatica and in those with giant cell arteritis, and systemic monocyte activation is characteristic of both conditions. Both diseases show a sequence polymorphism encoded within the second hypervariable region of the *HLA-DRB1* gene. The pattern of T-cell–derived cytokines distinguishes the two patient populations. Patients with polymyalgia rheumatica often have elevated interleukin-2 (IL-2) and interleukin-6 (IL-6) levels. One hypothesis holds that, in a genetically predisposed patient, an environmental factor, possibly a virus, causes monocyte activation, which helps determine the production of cytokines that induce manifestations characteristic of polymyalgia rheumatica and giant cell arteritis. The prevalence of antibodies to adenovirus and respiratory syncytial virus was reportedly higher in patients with polymyalgia rheumatica. Occurrence in siblings suggests a genetic role in the pathophysiology of the disease.

Frequency of Polymyalgia rheumatica

The frequency varies by country; highest rates occur in northern Europe. For example, in Italy, the incidence is 12.7 cases per 100,000 persons. In US the average annual incidence is 52.5 cases per 100,000 persons aged 50 years and older. The prevalence is approximately 0.5-0.7%.

Mortality and Morbidity of Polymyalgia rheumatica

With appropriate treatment, the survival rate is similar to that of unaffected persons of the same age; however, some reports document increased mortality from vascular disease among men with polymyalgia rheumatica after the initial 2 years following diagno-

sis. Polymyalgia rheumatica is self-limited and often remits in 1-3 years. Untreated patients, however, often feel unwell and have an impaired quality of life.

Race, sex and age particularities of Polymyalgia rheumatica

Polymyalgia rheumatica almost always affects whites but is also occasionally reported in African American persons. Polymyalgia rheumatica is twice as common in females. The incidence increases with advancing age. Polymyalgia rheumatica rarely affects persons younger than 50 years. The median age at diagnosis is 72 years.

History of Polymyalgia rheumatica

Patients are often in good health prior to disease onset, which is abrupt in about 50% of patients. In most patients, the shoulder girdle is first to become symptomatic. In the remainder, the hip or neck is involved at onset. At presentation, symptoms may be unilateral but usually become bilateral within a few weeks.

- Criteria for diagnosis
    - Age 50 years or older at onset
    - Bilateral aching and morning stiffness for at least 1 month and involving at least 2 of 3 areas: neck or torso, shoulders or arms, hips or thighs
    - Westergren erythrocyte sedimentation rate (ESR) 40 mm/h or greater
    - Prompt response of symptoms to corticosteroids (15 mg/d)
- Systemic sings
    - Low-grade fever and weight loss
    - Malaise, fatigue, and depression
    - Difficulty rising from bed in the morning
    - Difficulty getting up from the toilet
    - Difficulty completing daily life activities
    - High, spiking fevers (rare)
- Musculoskeletal sings
    - Morning stiffness for more than 1 hour, often more prolonged
    - Muscle stiffness after prolonged inactivity
    - Carpal tunnel syndrome (in about 15% of patients)
    - Distal extremity swelling (uncommon)
    - Possible development of arthralgia and myalgia up to 6 months after onset of systemic symptoms

Physical examination fidings

Polymyalgia rheumatica is a clinical diagnosis based on the complex of presenting symptoms and exclusion of the other potential diseases.

- General
    - Fatigued appearance

- Low-grade temperature
- Distal extremity swelling with pitting edema, which should be distinguished from remitting seronegative symmetrical synovitis with pitting edema (RS3PE)

- Musculoskeletal
  - Normal muscle strength
  - Pain in the shoulder and hip with movement without significant clinical swelling
  - Transient synovitis of the knee, wrist, and sternoclavicular joints
  - Tenderness to palpation with decreased active range of motion in the proximal hip/leg and/or shoulder/arm girdle musculature
  - In later stages: Disuse muscle atrophy with proximal muscle weakness and even contractures of the shoulder capsule may lead to limitation of passive and active movement.

Causes of Polymyalgia rheumatica

Exact causes are unknown. The disease is more common among northern Europeans, which may indicate a genetic predisposition. An autoimmune process may play a role in polymyalgia rheumatica development. Polymyalgia rheumatica is associated with the HLA-DR4 haplotype. High levels of IL-2 are associated with polymyalgia rheumatica, and high serum levels of IL-6 correlate with increased disease activity. T2-weighted MRI of the shoulders may reveal subdeltoid, subacromial, and bicipital tenosynovitis. These findings have led many investigators to believe that nonerosive synovitis and tenosynovitis are responsible for many symptoms of polymyalgia rheumatica.

Lab Studies

- Erythrocyte sedimentation rate
  - ESR is the most sensitive diagnostic study for polymyalgia rheumatica, although it is not specific.
  - The ESR is frequently elevated and greater than 40 mm/h, but the rate can exceed 100 mm/h.
  - In 20% of patients, the ESR is mildly elevated or, occasionally, normal, which may occur in patients with limited disease activity. In these cases, diagnosis is based on rapid positive response to low-dose oral corticosteroids (10-15 mg/d).
- C-reactive protein
  - The C-reactive protein level is often elevated and may parallel the ESR.
  - Longitudinal studies suggest that it may be a more sensitive test than ESR for the diagnosis of polymyalgia rheumatica.[4]
- CBC count with differential

- CBC count reveals mild normocytic, normochromic anemia.
- The WBC count may be normal or mildly elevated. Platelet counts are often increased.

- Other laboratory tests
  - Liver function tests reveal normal transaminase enzyme levels, the alkaline phosphatase may be mildly increased. Serum albumin levels may be slightly decreased.
  - The creatine kinase level is normal and helps differentiate the disease from polymyositis and other primary myopathic disorders.
  - Antinuclear antibodies and rheumatoid factor levels are usually normal.
  - Serum IL-6 levels are elevated and often closely parallel inflammatory activity of the disease.

Imaging Studies

- Radiography: Radiographs of the painful joints rarely show abnormalities such as osteopenia, joint space narrowing, or erosions.
- MRI
  - MRI is not necessary for diagnosis.
  - MRI of the shoulder reveals subacromial and subdeltoid bursitis and glenohumeral joint synovitis in the vast majority of patients.
  - MRI of the hands and feet demonstrates inflammation of the tendon sheaths in many patients.
  - T2-weighted MRI of the shoulders may reveal subdeltoid, subacromial, ad bicipital tenosynovitis. These findings have led many investigators to believe that nonerosive synovitis and tenosynovitis are responsible for many symptoms of polymyalgia rheumatica.
- Bursa ultrasonography
  - This study may reveal an effusion within the shoulder bursae.
  - The ultrasonography findings and those of MRI usually correlate well.
  - Ultrasonography is very operator-dependent and may be useful when the diagnosis is uncertain.

Procedures

- Occasionally, synovitis with effusions may be observed. In these cases, synovial fluid analysis reveals signs of mild inflammation, including poor mucin clotting. WBC counts are usually 1000-20,000 cells/μL, with 40-50% polymorphonuclear leukocytes.
- Temporal artery biopsy
  - Temporal artery biopsy (TAB) has a very low yield in patients with isolated polymyalgia rheumatica and is therefore usually unnecessary in patients with polymyalgia rheumatica without symptoms of giant cell arteritis.
  - TAB is not indicated in patients with mild symptoms of polymyalgia rheumatica that is of recent onset or in patients who have remained stable over a long

period (1 y or longer without current or previous clinical evidence of arteritis).

- Patients should be monitored for symptoms or signs of arteritis after treatment initiation because low-dose corticosteroids do not prevent progression of polymyalgia rheumatica to giant cell arteritis. If clinical signs of vasculitis develop, TAB should be performed.
- TAB may also be warranted in patients with polymyalgia rheumatica who are receiving low-dose corticosteroids if the clinical response is incomplete or if the ESR remains elevated or rises despite symptom resolution on corticosteroid therapy. Low-dose corticosteroids do not appear to affect biopsy yield.

Histologic Findings

- Synovitis is histologically mild and is characterized by a predominance of macrophages and CD4+ helper cells.

Medical Care

Polymyalgia rheumatica is a chronic, self-limited disorder. Therapy is based on empiric experiences because few randomized clinical trials are available to guide treatment decisions. The therapeutic goals are to control painful myalgia, to improve muscle stiffness, and to resolve constitutional features of the disease. Corticosteroids are considered the treatment of choice because they often cause complete or near-complete symptom resolution and reduction of the ESR to normal. However, no definite evidence demonstrates that corticosteroids (or any other therapy) alter the natural history of polymyalgia rheumatica. The low-dose corticosteroids used in polymyalgia rheumatica are almost certainly ineffective in the prevention of vasculitis progression. Nonsteroidal anti-inflammatory drugs (NSAIDs) can be administered to some patients with mild symptoms; however, most patients require corticosteroids for total control of symptoms. NSAIDs may be helpful in later stages of corticosteroid dosage tapering. NSAIDs generally have no effect on ESR. Methotrexate, azathioprine, and other immunosuppressive drugs have been used in some centers in an effort to limit dosage and duration of corticosteroid therapy. At present, no clear-cut data suggest that any of these drugs is superior to corticosteroid therapy. They are seldom indicated for the vast majority of patients with polymyalgia rheumatica who do not have giant cell arteritis because these patients generally respond to low doses of corticosteroids. In fact, symptomatic palliation of pain with analgesic therapy alone may be preferable in situations of corticosteroid intolerance (eg, uncontrolled diabetes mellitus, severe symptomatic osteoporosis, psychosis).

Consultations

Diagnosis and treatment involve the primary care physician and rheumatologist. Ophthalmologists, pathologists, and surgeons may be consulted on an as-needed basis. In coordination with the primary care physician, the rheumatologist plays an important role in diagnosis, treatment, and follow-up care. Consult with an ophthalmologist if concomitant giant cell arteritis may be causing decreased vision. In order to perform TAB, a consultation with a surgeon is essential if the presence of giant cell arteritis is in doubt.

Diet and activity

Ensure adequate calcium and vitamin D intake with corticosteroid use. Generally, activity restriction is unnecessary.

Further Outpatient Care

Polymyalgia rheumatica is typically treated in an outpatient setting. Objective means of determining prognosis and decisions concerning duration of treatment remain empiric and often need careful supervision. Calcium and vitamin D supplementation should be initiated in all patients with polymyalgia rheumatica who are starting corticosteroid therapy. Osteopenia or osteoporosis discovered with a bone mineral density study (eg, dual-energy x-ray absorptiometry [DEXA] scan) is an indication to start antiresorptive therapy. An isolated increase of ESR without symptoms during the course of treatment is not a valid reason to increase corticosteroid dose; however, a temporary delay in dosage reduction may be necessary. Because relapses are more likely to occur during the initial 18 months of therapy and within 1 year of corticosteroid withdrawal, all patients should be monitored for symptom recurrence throughout corticosteroid tapering and until 12 months after cessation of therapy. Approximately 50-75% of patients can discontinue corticosteroid therapy after 2 years of treatment.

In/Out Patient Meds

If not contraindicated, NSAIDs may provide supplemental pain relief. They may be used alone in the treatment of patients with mild symptoms. Methotrexate and other immunosuppressive therapies are seldom used in polymyalgia rheumatica treatment. Occasionally, they may be considered in patients with corticosteroid intolerance or as corticosteroid-sparing agents.

Deterrence and prevention

No method or strategy is known to be effective in preventing polymyalgia rheumatica.

Complications

Polymyalgia rheumatica usually has a limited course of several months to 5 years. Untreated patients often feel unwell and have an impaired quality of life. Generally, polymyalgia rheumatica is not associated with serious complications. Patients treated with corticosteroids are at risk for long-term complications of corticosteroid therapy. Relapses are common and may occur in up to 25% of all treated patients. Arteritic relapse in a patient who presented exclusively with polymyalgia rheumatica is unusual. Every patient should be considered at risk for giant cell arteritis. Several cases of systemic amyloidosis-associated polymyalgia rheumatica have been reported.

Prognosis

Polymyalgia rheumatica is usually self-limited. With prompt diagnosis and adequate therapy, the condition has an excellent prognosis.

Part 17.

UNDIFFERENTIATED CONNECTIVE-TISSUE DISEASE

Many connective-tissue diseases (CTDs) share common signs and symptoms, which frequently makes the diagnosis of a specific rheumatic disease difficult. Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis (PM), dermatomyositis (DM), mixed connective-tissue disease (MCTD), and Sjögren syndrome (SS) can present with similar clinical features, particularly during the first 12 months of symptoms. Isolated Raynaud phenomenon, inflammatory polyarthritis, anemia, interstitial lung disease, or pleuropericarditis may occur without an obvious diagnosis. Screening serology findings, such as rheumatoid factor (RF) or antinuclear antibody (ANA), may be positive or negative under these clinical circumstances.

However, well-established connective-tissue diseases have defined, discrete diagnostic criteria. Patients who present with symptoms, positive serology results, or physical findings consistent with an established connective-tissue disease but not fulfilling classification criteria for one of these established connective-tissue diseases are diagnosed with undifferentiated connective-tissue disease (UCTD). UCTD is a relatively new entity, suggested by LeRoy et al in 1980. The definition of UCTD is still under debate, although it is becoming more clear. Mosca et al recently reviewed UCTD literature and proposed that preliminary classification criteria include signs and symptoms suggestive of a connective-tissue disease, positive ANA results, and a disease that lasts at least 3 years.

Pathophysiology

The pathophysiology of most connective-tissue diseases is unclear, and UCTD is no different in this respect. The presence of autoantibodies commonly precedes disease onset, suggesting that they are not secondary to tissue damage or disease expression. Therefore, autoantibodies may be etiopathogenic or may only be clinical markers of the disease process. Like most connective-tissue diseases, the theory and research have been concentrated on genetically susceptible hosts, T- and B-cell abnormalities, and environmental triggers, such as ultraviolet light or infection. Recent studies into specific antibodies associated with UCTD have demonstrated significant correspondence with

anti-HSP60 and anti-HSP65 antibodies, as well as anti-Sp1 antibodies; however, further research is needed to evaluate the implications of these associations further.

Frequency

Very little information exists on the frequency and/or epidemiology of UCTD. However, studies in the United States and Europe have attempted to examine the prevalence of UCTD by comparing patients over many years from the onset of well-established connective-tissue diseases to patients with UCTD. Although these studies are difficult to compare because of patient enrollment variability, the diagnosis of UCTD clearly is relatively common even after monitoring patients for as long as 10 years.

Mortality and morbidity

The vast majority of patients diagnosed with UTCD at onset who do not progress to a definite connective-tissue disease within 12 months of the onset of symptoms remain undifferentiated after 10 years. Progression to definite connective-tissue disease decreases exponentially over time with over 70% of patients who evolve, doing so within 24 months from diagnosis.

In general, overall survival rates in patients with UCTD are better than patients with rheumatoid arthritis or systemic lupus erythematosus. Patients who do progress from UCTD to a definite connective-tissue disease also have a better prognosis than those diagnosed with a definite connective-tissue disease from the onset especially when compared to systemic lupus erythematosus.

Mortality and morbidity are directly related to the extent of disabling organ involvement such as progressive interstitial lung disease, pulmonary hypertension, or vascular complications. Thrombosis related to the presence of antiphospholipid antibodies can occur but is rare.

Race, sex and age particularities

Most of the studies on UCTD have been performed in Europe, and the majority of patients have been white. However, this may not be representative of UCTD patients around the world. A female predominance exists in UCTD similar to that observed in the common connective-tissue diseases such as rheumatoid arthritis and systemic lupus

erythematosus. The onset of UCTD is similar to most connective-tissue diseases, peaking in the middle years of life. UCTD has been described in children.

History of UCTD

Patients may present with systemic symptoms, such as fatigue, fever, or weight loss, preceding any organ involvement. The most common symptoms include arthralgias, unexplained or undifferentiated polyarthritis, Raynaud syndrome, mucocutaneous manifestations, and sicca symptoms. It is unusual for a patient with undifferentiated connective-tissue disease (UCTD) to have major organ involvement. However, patients may manifest many signs or symptoms observed with other connective-tissue diseases as described in the potential features listed below.

- Skin - Malar rash, digital skin ulcers, purpura, alopecia, skin tightening, urticaria, or photosensitivity
- Eyes - Dry eyes, conjunctivitis, or ocular inflammation
- Salivary glands - Dry mouth or salivary gland enlargement
- Reticuloendothelial - Lymphadenopathy or splenomegaly
- Lungs - Dyspnea, orthopnea, cough, wheezing, or pleuritic chest pain
- Heart - Angina, atypical chest pain, dyspnea, orthopnea, dependent edema, or pericarditis
- Vascular - Raynaud phenomenon (exaggerated vascular response to cold temperatures leading to episodic color changes in the skin of the digits), history of arterial or venous thrombosis, history of frequent miscarriages, or vasculitis
- Gastrointestinal - Anorexia, dysphagia, dyspepsia, abdominal pain, vomiting, nausea, hematemesis, melena, jaundice, or diarrhea
- Genitalia - Urethral discharge or dysuria
- Muscles - Muscle weakness, muscle pain, or history of myositis
- Joints - Arthralgia or arthritis
- Nervous system - History of seizures, neuropathy or altered mental status

Physical findings

Physical findings can be limited or may involve many organs. The potential physical manifestations of UCTD are best described by organ systems.

- Skin - Telangiectasia, purpura, petechiae, digital ulcers or scars, sclerodactyly, acroscleroderma, calcinosis, malar rash, discoid rash, erythema nodosum, erythematous knuckle pads, periungual erythema, alopecia, heliotrope eyelids, subcutaneous nodules
- Eye - Conjunctivitis, scleral-episcleral disease, uveitis, iritis, or keratoconjunctiva sicca
- Salivary glands - Xerostomia or salivary gland enlargement
- Reticuloendothelial - Lymphadenopathy or splenomegaly
- Lungs - Rales, wheezing, pleural effusion, or pleural rub

- Heart - Enlarged heart, murmur, pericardial rub, dependent edema, arrhythmia, or abnormal P_2 sound
- Vascular - Acrocyanosis, absent pulses, arterial and/or venous thrombosis
- Gastrointestinal - Hepatomegaly, gastroesophageal disease, esophageal dysmotility, or malabsorption syndromes
- Genitalia - Ulcerations, rashes, or discharge
- Muscles - Muscle tenderness, muscle atrophy, or proximal muscle weakness
- Joints - Joint tenderness, swelling, effusion, synovitis, or deformity
- Nervous system - Cranial nerve palsy, peripheral motor neuropathy, sensory neuropathy, entrapment neuropathy, psychosis, or personality change

Differential diagnosis.

Definite connective-tissue disease should be included in the differential diagnoses for any patient who presents with features of undifferentiated connective-tissue disease (UCTD). Brief descriptions of the characteristics of the diseases considered in the differential diagnosis of UCTD are provided below. Recent studies have demonstrated that certain manifestations at the time of diagnosis of UCTD are predictive of potential progression to definite connective-tissue disease, as illustrated in Table 11.

Table 11

Predictors of Progression to Definite Connective-Tissue Disease Diagnosis

Definite Connective-Tissue Disease Association	Presenting Signs or Symptoms	Presenting Laboratory Data
Systemic lupus erythematosus	Fever, photosensitivity, serositis, alopecia	ANA, dsDNA*, anti-Smith antibodies, anti-cardiolipin antibodies, leukopenia
Systemic sclerosis	Sclerodactyly, Raynaud phenomenon	ANA with nucleolar pattern
Sjögren syndrome	Xerostomia, xerophthalmia	Anti-SSA antibodies, Anti-SSB antibodies
Rheumatoid arthritis	Symmetrical polyarthritis	RF, elevated ESR† (>70)
Mixed connective-tissue disease	Esophageal reflux, Raynaud	ANA, anti-RNP‡ antibodies
Polymyositis/dermatomyositis	Proximal muscle weakness	+/- ANA

Note: * - Indicates anti–double-stranded DNA antibody, † - Indicates erythrocyte sedimentation rate, ‡ - Indicates ribonucleoprotein.

Systemic lupus erythematosus

Systemic lupus erythematosus is a classic autoimmune disease characterized by antinuclear antibodies and multiorgan involvement. The peak incidence of systemic lupus erythematosus is in people aged 15-40 years, with a female-to-male ratio of at least 5:1. A patient with systemic lupus erythematosus usually has 4 or more of the 11 classification criteria for diagnosis. The criteria include malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurologic disorder, hematologic disorder, immunologic disorder, and positive ANA.

Systemic sclerosis

Systemic sclerosis is an uncommon connective-tissue disease involving both the skin and internal organs. This most often is diagnosed in people aged 35-64 years, with a female-to-male ratio of 3:1. A patient will be classified as having systemic sclerosis if one major or 2 or more minor criteria are present. The major criterion is scleroderma proximal to the metacarpophalangeal or metatarsophalangeal joints. Minor criteria include sclerodactyly, digital pitting scars, or bibasilar pulmonary fibrosis. Virtually all patients with systemic sclerosis have Raynaud phenomenon.

Polymyositis/dermatomyositis

The diagnosis of polymyositis/dermatomyositis is uncommon, with an incidence range from 2-10 cases per million. A bimodal age distribution exists, with peaks at ages 10-15 years and at ages 45-60 years. The overall female-to-male ratio is 3:1. The 5 possible criteria for diagnosis are symmetrical weakness, elevation of muscle enzymes, electromyographic evidence, muscle biopsy evidence, and dermatologic features. A definite diagnosis of polymyositis must include 4 criteria without a rash. The diagnosis of dermatomyositis is made when 3 criteria are present plus the rash.

Mixed connective-tissue disease

Mixed connective-tissue disease is characterized by clinical manifestations that are observed in systemic lupus erythematosus, systemic sclerosis, and/or polymyositis. The incidence of mixed connective-tissue disease is considered less frequent than systemic lupus erythematosus but occurs more frequently than systemic sclerosis or polymyositis. It is much more common in women, with a ratio of 15:1, and occurs at a mean age of 37 years. The most common features are arthritis, sclerodactyly, Raynaud phenomenon,

esophageal dysmotility, and myositis. In addition to a positive ANA, patients with mixed connective-tissue disease have high titer antibodies to RNP.

Sjögren syndrome

Sjögren syndrome results from lymphocytic infiltration of exocrine glands. The frequency of Sjцgren syndrome is similar to systemic lupus erythematosus in that it occurs in 1 per 1000 people. Primary Sjцgren syndrome is diagnosed predominantly in women, with a female-to-male ratio of 9:1 and an age range of 30-50 years. The classic clinical presentation for Sjögren syndrome is the combination of dry eyes (keratoconjunctiva sicca) and dry mouth (xerostomia). The criteria for diagnosis of primary Sjögren syndrome include symptoms and objective signs of ocular dryness, symptoms and objective signs of dry mouth, and serologic evidence of a systemic autoimmunity by the presence of RF, ANA, or antibodies to SSA (Ro) or SSB (La). Primary Sjögren syndrome may involve multiple organs other than the eyes and mouth. Secondary Sjögren syndrome occurs when the symptoms and signs of Sjögren syndrome are present with another connective-tissue disease and most frequently with rheumatoid arthritis.

Rheumatoid arthritis

Rheumatoid arthritis is a chronic inflammatory systemic disease primarily characterized by diarthrodial joint involvement. The prevalence of rheumatoid arthritis increases with age and has a peak incidence in persons aged 40-60 years, with a female-to-male ratio of 3:1. A patient has rheumatoid arthritis if he or she satisfies at least 4 of 7 classification criteria. The criteria include morning stiffness for at least 1 hour, arthritis of 3 or more joint areas, arthritis of the hands, symmetric arthritis, rheumatoid nodules, serum RF, and radiographic changes. RF is found in the serum of approximately 85% of patients with rheumatoid arthritis.

Overlap syndrome

An individual patient may satisfy diagnostic criteria for 2 or more connective-tissue diseases. This is referred to as an overlap syndrome. Examples include an overlap of systemic lupus erythematosus and rheumatoid arthritis, mixed connective-tissue disease and polymyositis, and systemic sclerosis and mixed connective-tissue disease.

Lab Studies

- Laboratory test screening is helpful to identify markers that may suggest systemic disease, autoimmune disease, or specific organ involvement. Routine screening tests for undifferentiated connective-tissue disease (UCTD) should include CBC count, erythrocyte sedimentation rate (ESR), urinalysis, chemistry panel, RF, ANA, and VDRL. Other studies to consider, if clinically indicated, would be creatine kinase (CK), C3, C4, Jo-1 antibody, anti-SSA antibody, anti-SSB antibody, Smith antibody, RNP, antitopoisomerase antibody, sclerosis (Scl)-70 antibody, and anticardiolipin antibody.

Imaging Studies

Findings on chest x-ray (CXR) in patients with cardiopulmonary signs and symptoms can be normal or can show evidence of mediastinal lymphadenopathy, interstitial lung disease, pleural effusion, pulmonary infiltrate, pericardial effusion, or cardiac chamber enlargement.

Computed tomography (CT) scan, especially high-resolution CT scan, can define anatomical intrapulmonary abnormalities more clearly.

Other Tests

Pulmonary function tests, including total lung volumes and carbon monoxide diffusion capacity, will assist in identifying patients with interstitial lung disease or reactive airway disease.

Electrocardiogram may be useful in patients with cardiopulmonary signs and symptoms reflecting ST–T-wave abnormalities, axis deviation, or findings consistent with atrial or ventricular enlargement.

Echocardiogram can best clarify chamber sizes and function, estimate physiologic pressures, and identify and quantitate the size of a pericardial effusion.

The Schirmer test is useful to screen for dry eyes secondary to decreased tearing in association with primary or secondary Sjögren syndrome. This test also can have an abnormal result in patients taking medications that have anticholinergic side effects.

Rose Bengal stain of the cornea can detect keratitis associated with Sjögren syndrome.

Nailfold capillary microscopy may demonstrate dilated tortuous capillary loops and areas of avascularity ("dropout") in patients with secondary Raynaud syndrome associated with an underlying connective-tissue disease, particularly systemic sclerosis, polymyositis/dermatomyositis, and mixed connective-tissue disease.

Medical Care

A patient with possible undifferentiated connective-tissue disease (UCTD) can be evaluated primarily as an outpatient. A holistic approach to therapy should be offered to the patient once a comprehensive evaluation is completed.

Surgical Care

Surgery for patients with UCTD is not routinely necessary and should be initiated only when indicated for diagnosis or treatment.

Consultations

- Rheumatology consultation
- Patient education consultation
- Other consultations that may be clinically indicated include dermatology, ophthalmology, pulmonary, cardiology, neurology, physical medicine, physical therapy, or occupational therapy.

Diet

No special diet is recommended for patients with UCTD.

Activity

In general, activities are not restricted unless specific functional limitations associated with UCTD are present (eg, interstitial lung disease). Patients with photosensitivity should minimize prolonged exposure to the sunlight and use protective clothing and sun block lotions/creams to protect against ultraviolet light, which may flare UCTD. Patients with severe Raynaud syndrome should minimize unnecessary exposure to severe cold to avoid digital vasospasm. Layered clothing, hats, and gloves help to maintain a warm core body temperature and limit extremity symptoms. Tobacco use should be avoided.

Further Inpatient Care

Inpatient care may only be necessary for complex diagnostic or therapeutic reasons.

Further Outpatient Care

Patients typically are monitored for possible progression of undifferentiated connective-tissue disease (UCTD) organ involvement, evolution to a specific connective-tissue disease, and for safety and efficacy of treatment. The frequency of outpatient visits is dependent on the severity of disease.

In/Out Patient Meds

Medications will be prescribed, adjusted, and monitored as indicated for symptoms and safe medical therapy.

Transfer

Transfer of care ultimately will depend on any complications of UCTD that might require subspecialty medical or surgical care.

Deterrence and prevention

Deterrence and prevention is directly related to the organ(s) involved. However, appropriate preventive medicine screening and immunizations should be considered annually.

Complications

The complications of UCTD are related directly to organ involvement, susceptibility to infections, drug intolerance, or drug interactions.

Prognosis

The overall prognosis for UCTD is better than that of other connective-tissue diseases. UCTD may remit permanently, progress to an established connective-tissue disease, or remain a stable chronic disease with a wide manifestation of symptoms that involve many organ systems. In 2004, Mosca et al best summarized the literature regarding the rate of evolution of UCTD to differentiated connective-tissue disease and the factors predictive of this evolution. A comparison of various studies suggested that patients with UCTD monitored in a primary clinical setting appear to have a better prognosis than those followed at a tertiary care center.

In general, less than 40 percent of patients with UCTD develop systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, mixed connective-tissue disease, Sjögren syndrome, or polymyositis/dermatomyositis over a 2- to 5-year period. Organ involvement and disease-specific autoantibodies were most predictive of UCTD evolv-

ing to a differentiated connective-tissue disease. Therefore, most patients with UCTD still have the same diagnosis after 10 years of clinical monitoring. A positive ANA is common, ranging from 60-100%, and has a stable profile over time. The incidence of isolated disease-specific autoantibodies is low. Certain serologies and presenting symptom complexes are associated with higher rates of evolution to a definite connective-tissue disease. The extent of organ involvement primarily influences the prognosis in patients with UCTD.

References.

1. Al-Allaf A.W., Belch J. Raynaud's phenomenon. In: Hochberg et al, eds. Practical Rheumatology. 3rd ed. Philadelphia, Pa: Mosby; 2004: 467-472.
2. Alarcon G.S. Unclassified or undifferentiated connective tissue disease. Baillieres Best Pract Res Clin Rheumatol. 2000; 14(1): 125-137.
3. American Rheumatism Association. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum. 1980; 23(5):581-590.
4. Arnett F.C., Edworthy S.M., Bloch D.A. et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988; 31(3):315-324.
5. Asmussen K., Andersen V., Bendixen G. et al. A new model for classification of disease manifestations in primary Sjogren"s syndrome: evaluation in a retrospective long-term study. J. Intern. Med. 1996; 239(6): 475-482
6. Belch J.J., Newman P., Drury J.K. et al. Intermittent epoprostenol (prostacyclin) infusion in patients with Raynaud"s syndrome. A double-blind controlled trial. Lancet. 1983; 1(8320): 313-315.
7. Bodolay E., Csiki Z., Szekanecz Z. et al. Five-year follow-up of 665 Hungarian patients with undifferentiated connective tissue disease (UCTD). Clin Exp Rheumatol. 2003; 21(3):313-20.
8. Bonaci-Nikolic B., Nikolic M.M., Andrejevic S. et al. Antineutrophil cytoplasmic antibody (ANCA)-associated autoimmune diseases induced by antithyroid drugs: comparison with idiopathic ANCA vasculitides. Arthritis Res. Ther. 2005; 7(5): R1072-1081.
9. Boyer D., Vargas S.O., Slattery D. et al. Churg-Strauss syndrome in children: a clinical and pathologic review. Pediatrics. 2006; 118(3): 9e914-20.
10. Braun J., Baraliakos X., Golder W., et al. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis, before and after successful therapy with infliximab: evaluation of a new scoring system. Arthritis Rheum. 2003; 48(4): 1126-1136.
11. Braun J., Bollow M., Remlinger G. et al. Prevalence of spondylarthropathies in HLA-B27 positive and negative blood donors. Arthritis Rheum. 1998; 41(1): 58-67.
12. Braun J., Davis J, Dougados M. et al. First update of the international ASAS consensus statement for the use of anti-TNF agents in patients with ankylosing spondylitis. Ann Rheum Dis. Mar 2006; 65(3):316-20.
13. Braun J., Landewe R., Hermann K.G. et al. Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a

multicenter, randomized, double-blind, placebo-controlled magnetic resonance imaging study. Arthritis Rheum. 2006; 54(5): 1646-1652.
14. Burgos-Vargas R., Petty R.E. Juvenile ankylosing spondylitis. Rheum Dis Clin North Am. 1992; 18(1): 123-142.
15. Burns J.C., Glode M.P. Kawasaki syndrome. Lancet. 2004; 364: 533-344.
16. Callen J.P. Cutaneous vasculitis: Relationship to systemic disease and therapy. Curr Probl Dermatol. 1993; 5: 45-80.
17. Calvo-Alen J., Alarcon G.S., Burgard S.L. et al. Systemic lupus erythematosus: predictors of its occurrence among a cohort of patients with early undifferentiated connective tissue disease: multivariate analyses and identification of risk factors. J. Rheumatol. 1996; 23(3):469-475.
18. Carlson J.A., Cavaliere L.F., Grant-Kels J.M. Cutaneous vasculitis: diagnosis and management. Clin Dermatol. 2006; 24(5): 414-429.
19. Chen J., Liu C. Is sulfasalazine effective in ankylosing spondylitis? A systematic review of randomized controlled trials. J Rheumatol. Apr 2006; 33(4): 722-731.
20. Chen J., Liu C., Lin J. Methotrexate for ankylosing spondylitis. Cochrane Database Syst Rev. 2006;CD004524.
21. Clegg D.O., Reda D.J., Weisman M.H., et al. Comparison of sulfasalazine and placebo in the treatment of ankylosing spondylitis. A Department of Veterans Affairs Cooperative Study. Arthritis Rheum. 1996; 39(12): 2004-2012.
22. Collantes-Estevez E., Cisnal del Mazo A., Munoz-Gomariz E. Assessment of 2 systems of spondyloarthropathy diagnostic and classification criteria (Amor and ESSG) by a Spanish multicenter study. European Spondyloarthropathy Study Group. J Rheumatol. 1995; 22(2): 246-51.
23. Davis J.C., Van Der Heijde D., Braun J., et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum. 2003; 48(11): 3230-6.
24. De Angelis R., Cerioni A., Del Medico P., Blasetti P. Raynaud's phenomenon in undifferentiated connective tissue disease (UCTD). Clin Rheumatol. 2005; 24(2): 145-51.
25. Duhaut P., Bosshard S., Dumontet C. Giant cell arteritis and polymyalgia rheumatica: role of viral infections. Clin. Exp. Rheumatol. 2000; 18(4 Suppl 20): S22-23.
26. Feldtkeller E., Khan M.A., van der Heijde D., et al. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. Rheumatol Int. 2003; 23(2): 61-66.
27. Furtado R.N., Pucinelli M.L., Cristo V.V. et al. Scleroderma-like nailfold capillaroscopic abnormalities are associated with anti-U1-RNP antibodies and Raynaud"s phenomenon in SLE patients. Lupus. 2002; 11(1): 35-41.
28. Giannakopoulos B., Passam F., Rahgozar S., Krilis S.A. Current concepts on the pathogenesis of the antiphospholipid syndrome. Blood. 2007; 109(2):422-430.

29.Girardi G., Redecha P., Salmon JE. Heparin prevents antiphospholipid antibody-induced fetal loss by inhibiting complement activation. Nat Med. 2004; 10(11):1222-1226.
30.Gorman J.D., Sack K.E., Davis J.C. Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. N Engl J Med. 2002; 346(18): 1349-1356.
31.Grader-Beck T., Wigley F.M. Raynaud's phenomenon in mixed connective tissue disease. Rheum Dis Clin North Am. 2005; 31(3): 465-481.
32.Gran J.T., Husby G. The epidemiology of ankylosing spondylitis. Semin Arthritis Rheum. 1993; 22(5): 319-34.
33.Hammer R.E., Maika S.D., Richardson J.A., et al. Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human beta 2m: an animal model of HLA-B27-associated human disorders. Cell. 1990;63(5):1099-112.
34.Hochberg M.C., Altman R.D., Brandt K.D., Clark B.M., Dieppe P.A., Griffin M.R. et al. Guidelines for the medical management of osteoarthritis. Part 1. Osteoarthritis of the hip. Arthritis Rheum. 1995;38:1535-40.
35.Hochberg M.C., Altman R.D., Brandt K.D., Clark B.M., Dieppe P.A., Griffin M.R. et al. Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. Arthritis Rheum. 1995; 38: 1541-1546.
36.Hoffman R.W. Mixed connective tissue disease, overlap syndromes and Sjogren's syndrome. In: Lahita RG, ed. Systemic Lupus Erythematosus. 4th ed. San Diego, Calif: Academic Press; 2004.
37.Hoffman R.W. T cells in the pathogenesis of systemic lupus erythematosus. Clin Immunol. 2004;113(1):4-13.
38.Hoffman R.W. Undifferentiated and mixed connective tissue disease. In: Wallace D., Hahn B., eds. Dubois Systemic Lupus Erythematosus. Lippincott, P: In press.
39.Holderbaum D., Haqqi T.M., Moskowitz R.W. Genetics and osteo arthritis: exposing the iceberg. Arthritis Rheum. 1999; 42: 397-405.
40.Jaakkola E., Herzberg I., Laiho K., et al. Finnish HLA studies confirm the increased risk conferred by HLA-B27 homozygosity in ankylosing spondylitis. Ann. Rheum. Dis. 2006;65(6):775-80.
41.Jenks K, Treharne GJ, Garcia J, Stebbings S. The ankylosing spondylitis quality of life questionnaire: validation in a New Zealand cohort. Int J Rheum Dis. 2010; 13(4): 361-6.
42.Jennette J.C., Falk R.J., Milling D.M. Pathogenesis of vasculitis. Semin Neurol 1994; 14(4): 291-299.
43.Khare S.D., Luthra H.S., David C.S. Animal models of human leukocyte antigen B27-linked arthritides. Am. Rheum Dis Clin North Am. 1998; 24(4): 883-894.
44.Lawrence R.C., Helmick C.G., Arnett F.C., Deyo R.A., Felson D.T., Giannini E.H. et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum. 1998; 41: 778-99.

45. Lockshin M.D. Update on antiphospholipid syndrome. Bull NYU Hosp Jt Dis. 2006; 64(1-2):57-59.
46. McGonagle D., Gibbon W., Emery P. Classification of inflammatory arthritis by enthesitis. Lancet. 1998; 352(9134): 1137-1140.
47. McGonagle D., Stockwin L., Isaacs J., Emery P. An enthesitis based model for the pathogenesis of spondyloarthropathy. additive effects of microbial adjuvant and biomechanical factors at disease sites. J. Rheumatol. 2001; 28(10): 2155-2159.
48. Medsger T.A. Systemic sclerosis. In: Arthritis and Allied Conditions. Philadelphia, Pa:. Lippincott Williams & Wilkins;1993:1438-1439.
49. Miyakis S., Lockshin M.D., Atsumi T., Branch D.W., Brey R.L., Cervera R. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J. Thromb. Haemost. 2006; 4(2):295-306.
50. Mow V.C., Setton L.A., Fuilak F., Ratcliffe A. Mechanical factors in articular cartilage and their role in osteoarthritis. In: Kuettner KE, RECOMMENDATIONS FOR HIP AND KNEE OA MANAGEMENT Goldberg VM, editors. Osteoarthritic disorders. Rosemont (IL): American Academy of Orthopaedic Surgeons; 1995. p. 147-172.
51. Poole A.R. Imbalances of anabolism and catabolism of cartilage matrix components in osteoarthritis. In: Kuettner KE, Goldberg VM, editors. Osteoarthritic disorders. Rosemont (IL): American Academy of Orthopaedic Surgeons; 1995. p. 247-260.
52. Ramos-Casals M., Brito-Zeron P., Nardi N. et al. Successful treatment of severe Raynaud's phenomenon with bosentan in four patients with systemic sclerosis. Rheumatology (Oxford). Nov 2004;43(11):1454-1456.
53. Reveille J.D., Arnett F.C. Spondyloarthritis: update on pathogenesis and management. Am J Med. 2005;118(6):592-603.
54. Rezaian M.M., Brent L.H. Undifferentiated spondyloarthropathy: Seven-year follow-up study of 357 patients. Arthritis Rheum. 2001; 44: S93.
55. Rudwaleit M., Metter A., Listing J., et al. Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. Arthritis Rheum. 2006; 54(2): 569-578.
56. Sakane T., Takeno M., Suzuki N., Inaba G. Behçet's disease. N. Engl. J. Med. 1999; 341(17): 1284-1291.
57. Sampaio-Barros P.D., Bertolo M.B., Kraemer M.H. et al. Undifferentiated spondyloarthropathies: a 2-year follow-up study. Clin. Rheumatol. 2001; 20(3): 201-206.
58. Schlosstein L., Terasaki P.I., Bluestone R., Pearson C.M. High association of an HLA antigen, W27, with ankylosing spondylitis. N. Engl. J. Med. 1973; 288(14):704-706.
59. Sieper J., Braun J. Pathogenesis of spondylarthropathies. Persistent bacterial antigen, autoimmunity, or both?. Arthritis Rheum. 1995; 38(11): 1547-1554.

60. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017. doi: 10.1136/annrheumdis-2016-210715. [Epub ahead of print]
61. Tse SM, Burgos-Vargas R, Laxer RM. Anti-tumor necrosis factor alpha blockade in the treatment of juvenile spondylarthropathy. Arthritis Rheum. 2005; 52(7): 2103-2108.
62. van der Heijde D., Dijkmans B., Geusens P. et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum. 2005;52(2): 582-591
63. van der Heijde D., Dijkmans B., Geusens P., et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum. 2005; 52(2): 582-591.
64. van der Heijde D., Kivitz A., Schiff M.H., et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2006; 54(7): 2136-2146.
65. van der Linden S., van der Heijde D. Ankylosing spondylitis. Clinical features. Rheum. Dis. Clin. North Am. 1998; 24(4): 663-676.
66. Wanders A., Heijde D., Landewe R. et al. Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. Arthritis Rheum. 2005; 52(6): 1756-1765.
67. Watts R.A., Jolliffe V.A., Carruthers D.M. et al. Effect of classification on the incidence of polyarteritis nodosa and microscopic polyangiitis. Arthritis Rheum. 1996; 39(7): 1208-1212
68. Wordsworth P. Genes in the spondyloarthropathies. Rheum. Dis. Clin. North Am. 1998; 24(4): 845-863.
69. Zeidler H., Mau W., Khan M.A. Undifferentiated spondyloarthropathies. Rheum. Dis. Clin. North Am. 1992; 18(1): 187-202.
70. Zochling J., van der Heijde D., Burgos-Vargas R., et al. ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis. 2006; 65(4): 442-452.
71. Zochling J.Measures of symptoms and disease status in ankylosing spondylitis: Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), and Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S). Arthritis Care Res (Hoboken). 2011; 63 Suppl 11:S47-58.

Additional materials

Anti-inflammatory, Immunomodulators and Immunosuppressive agents

Drug name	Generic name	Description	Adult Dose	Contraindications	Interactions	Precautions
Ibuprofen	Ibuprin, Motrin	For relief of mild to moderate pain; inhibits inflammatory reactions and pain by decreasing activity of cyclooxygenase, which results in decrease of prostaglandin synthesis.	600-800 mg PO tid/qid	Documented hypersensitivity; history of peptic ulcer disease (unless prophylaxis is adequate); renal insufficiency, anticoagulation, and coagulopathy; caution should be used in patients with cardiovascular disease	Coadministration with ACE inhibitors, angiotensin-II receptor blockers, and potassium-sparing diuretics may result in hyperkalemia; coadministration with warfarin may increase PT due to displacement of warfarin from plasma proteins and may aggravate bleeding tendency due to antiplatelet effect of NSAIDs; may decrease the effect of diuretics	Most common toxicities include gastrointestinal manifestations such as nausea, abdominal pain, peptic ulcer disease, and renal insufficiency; may cause increased blood pressure in patients with hypertension due to blunting of effects of antihypertensive medications; patients with congestive heart failure may have exacerbations due to fluid and sodium retention; patients with diabetes mellitus should have close monitoring of renal function
Naproxen	Naprosyn, Naprelan, Aleve, Anaprox		500 mg PO bid/tid			
Diclophenac	Voltaren		75-150 mg PO bid/tid			
Sulfasalazine	Azulfidine, EN-tabs	Shown to reduce inflammatory symptoms of rheumatic diseases in controlled studies; most common toxicities include nausea, diarrhea, and hypersensitivity reactions (rash).	2000-3000 mg/d PO divided bid/tid	Documented hypersensitivity; porphyria (may precipitate acute exacerbations)	Absorption may be reduced by coadministration of oral iron	Most common toxicities include nausea, diarrhea, and hypersensitivity; caution in renal or hepatic impairment, blood dyscrasias, or urinary obstruction; rarely, patients may develop blood dyscrasias, especially leukopenia, which may progress to agranulocytosis or hepatotoxicity
Etanercept	Enbrel	Consists of a fusion protein of the extracellular portion of the p75 TNF-□ receptor and Fc portion of IgG. Inhibits TNF-□, reducing inflammation and symptoms of ankylosing spondylitis. Given as a subcutaneous injection. Also approved for rheumatoid	25 mg SC 2 times/wk or 50 mg SC qwk	Active bacterial or mycobacterial infection; decompensated CHF; demyelinating disease; recent live vaccination	None reported	Adverse events include injection-site reactions, occasional hematologic abnormalities, and elevated LFTs (check laboratory tests at least every 3 mo); respiratory and other types of infections may be more common, so hold medication until infection cleared); may exacerbate CHF (do not give to a patient with decompensated CHF); occasionally induces autoantibody production; drug-

		arthritis, psoriatic arthritis, psoriasis, and juvenile idiopathic arthritis.				induced SLE, demyelinating diseases, and lymphoma may rarely occur (association not clear); TNF-□ antagonists are associated with rare cases of mycobacterial and other opportunistic infections (check PPD before starting etanercept; isoniazid prophylaxis recommended if PPD results are positive)
Infliximab	Remicade	Chimeric IgG1□ mab directed against TNF-□. Variable region of heavy and light chains are murine in origin, constant regions are human. Inhibits TNF-□, reducing inflammation and symptoms of ankylosing spondylitis. Given as an intravenous infusion. Also approved for rheumatoid arthritis, ankylosing spondylitis and Crohn disease.	5 mg/kg IV at weeks 0, 2, and 6, then q6wk depending on clinical response; dose may be increased to 10 mg/kg/dose if needed	Severe infusion reactions such as hypotension and dyspnea; active bacterial or mycobacterial infection; decompensated CHF; demyelinating disease; recent live vaccination		
Adalimumab	Humira	Humanized IgG1 mab directed against TNF-□. Inhibits TNF-□, reducing inflammation.	40 mg SC every other week, may be increased to every weekend prn	Active bacterial or mycobacterial infection; decompensated CHF; demyelinating disease; recent live vaccination	Methotrexate reduces adalimumab clearance	
Mycophenolate	CellCept	Inhibits inosine monophosphate dehydrogenase (IMPDH) and suppresses de novo purine synthesis by lymphocytes, thereby inhibiting their proliferation. Inhibits antibody production. Two formulations are available and are not interchangeable. The original formulation, my-	Mycophenolate mofetil: Renal transplantation: 1g PO/IV q12h Hepatic transplantation: PO: 1.5g PO q12h IV: 1 g IV q12h infused over at least 2 h Mycophenolic ac-	Documented hypersensitivity	In combination with either acyclovir or ganciclovir, may result in higher levels for both interacting drugs because of competition for renal tubular excretion; aluminum/ magnesium present in some antacids and cholestyramine-containing products may decrease absorption, reducing levels (do not administer	Increases risk for infection (monitor blood count); severe renal impairment (CrCl <25 mL/min) may have increased adverse effects due to increase free MPA; caution in active peptic ulcer disease; incidence of malignancies and lymphoma consistent with that reported for other immunosuppressants (0.9%); commonly causes constipation, nausea, diarrhea, urinary tract infection, and nasopharyngitis; rare reports include

		cophenolate mofetil (MMF, CellCept) is a prodrug that, once hydrolyzed in vivo, releases the active moiety mycophenolic acid. A newer formulation, mycophenolic acid (MPA, Myfortic) is an enteric-coated product that delivers the active moiety.	id: Renal transplantation: 720 mg PO bid; administer on empty stomach 1 h before or 2 h pc		together); probenecid may increase levels of mycophenolate; salicylates and azathioprine may increase toxicity; may decrease levonorgestrel AUC; may decrease live-virus vaccine immune response; when administered in combination with theophylline, may increase free fraction levels of theophylline	interstitial lung disorders, colitis, pancreatitis, intestinal perforation, GI hemorrhage, gastric ulcers, duodenal ulcers, and ileus; do not chew, crush, or cut Myfortic tab
Rituximab	Rituxan	Antibody genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. Antibody is an IgG1-kappa immunoglobulin that contains murine light- and heavy-chain variable region sequences and human constant region sequences.	375 mg/m^2 IV qwk for 4 doses (days 1, 8, 15, and 22)	Documented hypersensitivity	None reported	Hypotension, bronchospasm, and angioedema may occur; discontinue treatment if life-threatening cardiac arrhythmias occur
Methotrexate	Rheumatrex, Folex PFS	Unknown mechanism of action in treatment of inflammatory reactions; may affect immune function. Ameliorates symptoms of inflammation (eg, pain, swelling, stiffness). Adjust dose gradually to attain sa-	10-25 mg PO/SC qwk	Documented hypersensitivity; alcoholism; hepatic insufficiency; documented immunodeficiency syndromes; preexisting blood dyscrasias (eg, bone marrow hypoplasia, leukopenia, thrombocytope-	Oral aminoglycosides may decrease absorption and blood levels of concurrent oral methotrexate; charcoal lowers levels; coadministration with etretinate may increase hepatotoxicity; indomethacin and phenylbutazone can increase plasma	Monitor CBC counts monthly and liver and renal function every 1-3 mo during therapy (monitor more frequently during initial dosing, dose adjustments, or when risk of elevated levels, eg, dehydration); has toxic effects on hematologic, renal, GI, pulmonary, and neurologic systems; discontinue if significant drop in blood counts oc-

		tisfactory response.		nia, significant anemia); renal insufficiency	levels; may decrease phenytoin serum levels; probenecid, salicylates, procarbazine, and sulfonamides (including TMP-SMZ) may increase effects and toxicity; may increase plasma levels of thiopurines	curs; aspirin, NSAIDs, or low-dose steroids may be administered concomitantly (possibility of increased toxicity with NSAIDs including salicylates has not been tested); oral folic acid therapy (1 mg/d) reduces adverse effects (especially GI) without reducing effectiveness
Hydroxychloroquine	Plaquenil	Most common antimalarial used in rheumatic diseases, mostly because of excellent safety profile.	6-7 mg/kg/d; usually 200-400 mg/d PO qd or divided doses	Documented hypersensitivity; retinal and visual-field changes attributable to 4-aminoquinolones	Hepatotoxic or dermotoxic drugs may increase toxicity; serum levels increase with cimetidine; choline magnesium trisalicylate may decrease absorption	Perform periodic ophthalmologic examinations (q6-12mo); hepatic disease, G-6-PD deficiency, psoriasis, and porphyria
Cyclophosphamide	Cytoxan, Neosar	Chemically related to nitrogen mustards. As an alkylating agent, mechanism of action of active metabolites may involve cross-linking of DNA, which may interfere with growth of normal and neoplastic cells.	0.5-1 g/m^2 IVPB single dose 2-3 mg/kg/d PO single morning dose	Documented hypersensitivity; infection; severely depressed bone marrow function; severe cytopenias	Allopurinol may increase risk of bleeding or infection and enhance myelosuppressive effects; may potentiate doxorubicin-induced cardiotoxicity; may reduce digoxin serum levels and antimicrobial effects of quinolones; chloramphenicol may increase half-life while decreasing metabolite concentrations; may increase effect of anticoagulants; coadministration with high doses of phenobarbital may increase rate of metabolism and leukopenic activity; thiazide diuretics may prolong cyclophosphamide-induced leukopenia and neuromuscular	Leukopenia and thrombocytopenia; monitor CBC and platelet counts and perform urinalysis q1-2wk with any change in dosing; perform urinalysis with cytology q6-12mo after cessation of drug (especially with PO regimen)

					blockade by inhibiting cholinesterase activity	
Intravenous immune globulins, 5%	Gammagard, Gamimune	Following features may be relevant to efficacy: neutralization of circulating myelin antibodies through antiidiotypic antibodies, down-regulation of proinflammatory cytokines (including IFN-gamma), blockade of Fc receptors on macrophages, suppression of helper/inducer T and B cells and augmentation of suppressor T cells, blockade of the complement cascade, promotion of remyelination, and 10% increase in CSF IgG.	400 mg/kg/d IV for 5 d; alternatively, 1000 mg/kg/d for 1-2 consecutive days	Documented hypersensitivity; IgA deficiency; anti-IgE/IgG antibodies	Live viral vaccines	Caution in IgA-deficient patients, may have severe reactions; check serum IgA levels prior to use; may increase serum viscosity and thromboembolic events; adverse effects may include migraine attacks, 10% increased risk of aseptic meningitis, and increased risk of urticaria or pruritus or petechiae 2-5 d postinfusion (may last as long as 1 mo); increased risk of renal tubular necrosis in patients who are older, have diabetes, are volume depleted, or have preexisting kidney disease; can lead to changes in laboratory values (eg, elevated antiviral or antibacterial antibody titers for 1 mo, 6-fold increased ESR for 2-3 wk, apparent hyponatremia)
Tacrolimus	Prograf	Immunomodulator produced by the bacteria *Streptomyces tsukubaensis.* Mechanisms of action similar to cyclosporine. Primarily used in transplants	0.15 mg/kg/d PO	Documented hypersensitivity (including hypersensitivity reactions to tacrolimus or HCO-60 [polyoxyl 60 hydrogenated castor oil])	Caution with drugs associated with renal dysfunction, including aminoglycoside, amphotericin B, cisplatin, and others (can enhance nephrotoxicity); concentrations may be increased in presence of diltiazem, nicardipine, nifedipine, verapamil, clotrimazole, fluconazole, itraconazole, ketoconazole, clarithromycin, erythromycin, troleandomycin, cisapride, metoclopramide, bromocrip-	Insulin-dependent diabetes reported in 20% of patients using tacrolimus for transplants, which is reversible in 15% after 1 year and in 50% after 2 years; increased risk for African American and Hispanic patients; nephrotoxicity, neurotoxicity, hyperglycemia, hyperkalemia, tremor, headache, and increased risk of lymphomas and other malignancies (especially skin tumors) may occur; anaphylaxis, hypertension, myocardial hypertrophy, GI abnormalities, arthralgias, cramps, asthma, and bronchitis have been

					tine, cimetidine, cyclosporine, danazol, methylprednisolone, and protease inhibitors; concentrations may decrease when administered with carbamazepine, phenobarbital, phenytoin, rifabutin, and rifampin	reported with its use
Levamisole	Ergamisol	An immunomodulator approved for the treatment of colon cancer. Restores immune function and stimulates T-cell activation and proliferation and monocyte function. Stimulates neutrophil chemotaxis, adhesion, and mobility.	150 mg PO twice/wk	Documented hypersensitivity	May produce Antabuse reactions if administered with alcohol; may lead to increased blood levels of phenytoin; may also increase prothrombin times in patients on warfarin	Malaise, fatigue, flulike symptoms, pruritus, nausea, vomiting, stomatitis, and diarrhea may occur; skin rashes, hyperbilirubinemia, and increased infections have been reported
Dapsone	Avlosulfon	May be useful for erythema nodosum and genital ulcers. Not approved for this use but approved for the treatment of dermatitis herpetiformis and leprosy.	50-100 mg/d PO	Documented hypersensitivity; known G-6-PD deficiency	May inhibit anti-inflammatory effects of clofazimine; hematologic reactions may increase with folic acid antagonists (eg, pyrimethamine), monitor for agranulocytosis during the second and third months of therapy; probenecid increases dapsone toxicity; trimethoprim with dapsone may increase toxicity of both drugs; because of increase in renal clearance, dapsone levels may significantly decrease when administered concurrent-	Agranulocytosis, aplastic anemia, and other blood dyscrasias may occur; check CBC counts at frequent intervals; conduct routine screening for G-6-PD because patients are at increased risk for dose-related hemolysis; do not administer folic acid antagonists with dapsone; cutaneous reactions, fever, sore throat, jaundice, hepatitis, pallor, hemolysis, methemoglobinuria, and purpura may occur; peripheral neuropathy is associated with dapsone use; skin rashes include erythema multiforme, toxic epidermal necrolysis, urticaria, erythema nodosum, and scarlatiniform reactions; car-

					ly with rifampin	cinogenic in male rats and female mice
Colchicine	Colchicine	Inhibits cellular microtubule formation and may cause a transient leukopenia, followed by leukocytosis. Use in autoimmune disease primarily is empiric, and mechanism of action in decreasing inflammation is not clear, nor is it truly an immunomodulating agent.	0.6 mg PO bid/tid	Documented hypersensitivity; severe renal or hepatic disorders; blood dyscrasias	Sympathomimetic agent toxicity and effect of CNS depressants are significantly increased with colchicine	May affect spermatogenesis; teratogenic in animals and plants; caution in renal or hepatic failure; dose-related adverse effects include neuritis, nausea and vomiting, diarrhea, bone marrow suppression, urticaria, skin rashes, myopathy, and alopecia; at high doses, vascular damage, diarrhea, and renal damage may occur; difficult excretion in patients with severe renal insufficiency; attenuate doses or overdose levels with toxicity may occur
Chlorambucil	Leukeran	Potent alkylating agent that inhibits various cellular functions. Alkylation of DNA results in cross-linking, impaired DNA synthesis, and cell death. Onset of action is slower than cyclophosphamide.	0.1 mg/kg/d PO	Documented hypersensitivity; previous resistance to this medication; severe bone marrow depression	None reported	Carcinogenic and teratogenic; caution in patients taking other chemotherapeutic agents or patients with bone marrow suppression; GI symptoms and damage may occur; leukopenia, thrombocytopenia, lymphopenia, and neutropenia; drug fevers and hypersensitivity reactions may occur; may cause hepatotoxicity and seizures; may have cross-reactions with other alkylating agents
Azathioprine	Imuran	Purine analog that inhibits DNA synthesis. The 50-mg tabs are metabolized to 6-mercaptopurine in the liver and RBCs.	2-3 mg/kg/d PO in single or divided doses; 1 mg/kg/d initial dose; increase depending on clinical and hematologic response and toxicity	Documented hypersensitivity; active infection; severe cytopenias (relative); hepatic dysfunction; severe liver disease	Toxicity increases with allopurinol; concurrent use with ACE inhibitors may induce severe leukopenia; may increase levels of methotrexate metabolites and decrease effects of anticoagulants, neuromuscular blockers, and cyclosporine	Nausea and vomiting, leukopenia, thrombocytopenia, anemia, infection, pancreatitis, and abnormal liver function test results may occur. Reports of increased squamous cell carcinomas of the skin.
Dexamethasone	Decadron	Has many pharmaco-	0.5 mg/d	Documented hyper-	Effects decrease with	Increases risk of multiple compli-

		logic benefits but significant adverse effects. Stabilizes cell and lysosomal membranes, increases surfactant synthesis, increases serum vitamin A concentration, and inhibits prostaglandin and proinflammatory cytokines (eg, TNF-alpha, IL-6, IL-2, and IFN-gamma). The inhibition of chemotactic factors and factors that increase capillary permeability inhibits recruitment of inflammatory cells into affected areas. Suppresses lymphocyte proliferation through direct cytolysis and inhibits mitosis. Breaks down granulocyte aggregates, and improves pulmonary microcirculation. Adverse effects include hyperglycemia, hypertension, weight loss, GI bleeding or perforation synthesis, cerebral palsy, adrenal suppression, and death. Most of the adverse effects of corticosteroids are dose-dependent or duration-dependent.	PO/IV/IM; titrate up or down depending on clinical response	sensitivity; active bacterial or fungal infection	coadministration of barbiturates, phenytoin, and rifampin; dexamethasone decreases effect of salicylates and vaccines used for immunization	cations, including severe infections; monitor adrenal insufficiency when tapering drug; abrupt discontinuation of glucocorticoids may cause adrenal crisis; hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, myasthenia gravis, growth suppression, and infections are possible complications of glucocorticoid use

		Readily absorbed via the GI tract and metabolized in the liver. Inactive metabolites are excreted via the kidneys. Lacks salt-retaining property of hydrocortisone. Patients can be switched from an IV to PO regimen in a 1:1 ratio.				
Prednisone	Deltasone, Sterapred, Orasone	Decreases release of inflammatory mediators, neutrophil migration, monocyte and T-cell function.	Up to 60 mg/d PO, depending on clinical manifestations	No absolute contraindications exist; caution in diabetes mellitus, hypertension, aseptic necrosis, cataracts, or active infection	Coadministration with estrogens may decrease prednisone clearance; concurrent use with digoxin may cause digitalis toxicity secondary to hypokalemia; phenobarbital, phenytoin, and rifampin may increase metabolism of glucocorticoids (consider increasing maintenance dose); monitor for hypokalemia with coadministration of diuretics	Abrupt discontinuation of glucocorticoids may cause adrenal crisis; hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer disease (in combination with NSAIDs), hypokalemia, hypertension, osteoporosis, euphoria, psychosis, growth suppression, and infections may occur with glucocorticoid use
Methylprednisolone	Solu-Medrol	Decreases inflammation by suppressing migration of polymorphonuclear leukocytes and reversing increased capillary permeability. Administered intravenously in severe cases.	1 mg/kg/d IV, depending on clinical manifestations	Documented hypersensitivity; viral, fungal, or tubercular skin infections	Coadministration with digoxin may increase digitalis toxicity secondary to hypokalemia; estrogens may increase levels of methylprednisolone; phenobarbital, phenytoin, and rifampin may decrease levels of methylprednisolone (adjust dose); monitor patients for hypokalemia when taking medication concurrently with diuretics;	Hyperglycemia, edema, osteonecrosis, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, growth suppression, myopathy, and infections are possible complications of glucocorticoid use. Depo-Medrol contains benzyl alcohol, which is potentially toxic when administered locally to neural tissue; administration of Depo-Medrol by other than indicated routes, including the epidural route, has been associated with reports of serious

					grapefruit juice increases prednisolone concentrations; methylprednisolone and cyclosporine mutually inhibit one another, resulting in increased plasma levels of each drug	medical events, including arachnoiditis, meningitis, paraparesis/paraplegia, sensory disturbances, bowel/bladder dysfunction, seizures, visual impairment including blindness, ocular and periocular inflammation, and residue or slough at injection site

Tests and squeezes

1. Indicate a sources of pain in osteoarthritis
   - All mentioned above
   - Joint effusion and stretching of the joint capsule
   - Increased vascular pressure in subchondral bone
   - Torn menisci
   - Inflammation of periarticularbursae
2. Indicate the most common causes of osteoarthritis
   - All mentioned above
   - Metabolic disorders
   - Infection
   - Repetitive occupational trauma
   - Genetic factors
3. Determine result of synovial fluid analysis that is usually available for patients with osteoarthritis
   - white cell count less than 2000 per mm^3 with a mononuclear predominance
   - white cell count more than 2000 per mm^3
   - white cell count more than 4000 per mm^3
   - white cell count more than 2000 per mm^3 with a neutrophiles predominance
   - white cell count more than 2000 per mm^3 with a lymphocytes predominance
4. Determinedirection of pharmacologic therapy that should be provide in patients with osteoarthritis
   - acetaminophen for mild or moderate pain
   - analgesic tramadol for all patients
   - opiates are recommended for relief pain
   - acetaminophen with codeine for mild or moderate pain
   - NSAIDs for all clinical situation are recommended
5. Determineearly X-ray findings for osteoarthritis:

- asymmetric joint space narrowing
- subchondral sclerosis
- subchondral cyst formation
- presence of osteophytes
- ankilosis

6. Determine factors that contributes poor prognostic for rheumatoid arthritispatients
    - All mentioned above.
    - persistent synovitis
    - early erosive disease
    - positive serum rheumatoid factor
    - family history of rheumatoid arthritis,
7. Indicate uncorrected criteria for the American College of Rheumatology classification of rheumatoid arthritis
    - Distal arthritis of hand joints
    - Morning stiffness
    - Arthritis of 3 or more joint areas
    - Symmetric arthritis with simultaneous involvement of the same joint areas on both sides of the body
    - Rheumatoid nodules
    - Serum RF
8. Indicate uncorrected feature of joint involvement in the patients with rheumatoid arthritis
    - Bushar' nodes
    - symmetric distribution
    - inflammation with swelling, tenderness, warmth
    - decreased range of motion
    - Atrophy of the interosseous muscles of the hands
9. Determine the most commonly observed musculoskeletal manifestations in the patients with rheumatoid arthritis
    - All mentioned above
    - tenosynovitis

- tendon rupture
- immobilization-related changes
- carpal tunnel syndrome

10. Indicate signs that is the common for first stage of rheumatoid arthritis' patients
    - evidence of osteoporosis
    - slight subchondral bone destruction
    - Adjacent muscle atrophy
    - Extra-articular soft tissue lesions
    - Joint mobility is limited
11. Indicate signs that is the common for second stage of rheumatoid arthritis' patients
    - All mentioned above
    - evidence of osteoporosis
    - slight subchondral bone destruction
    - Adjacent muscle atrophy
    - Joint mobility is limited
12. Indicate extra sign that is the common for third stage of rheumatoid arthritis' patients
    - Fibrous or bony ankylosis
    - Joint deformity without fibrous or bony ankylosis
    - Extensive muscle atrophy
    - Extra-articular soft tissue lesions
    - evidence of osteoporosis
13. Indicate uncorrected sign that is the common for fourth stage of rheumatoid arthritis' patients
    - Fibrous or bony ankylosis
    - Lack of muscle atrophy
    - Extra-articular soft tissue lesions
    - evidence of cartilage and bone destruction
    - evidence of periarticular osteoporosis

14. Indicate the most common criteria for class III functional status of patients with rheumatoid arthritis
    - Able to perform usual self-care activities but limited in vocational and avocational activities
    - Able to perform usual self-care and vocational activities but limited in avocational activities
    - Limited in ability to perform usual self-care, vocational, and avocational activities
    - Completely able to perform usual activities of daily living
    - Lack of appropriated criteria
15. What disease are characterized an appearance of distal symmetric arthritis
    - osteoarthritis
    - rheumatoid arthritis
    - Infectious arthritis
    - polyarticular gout
    - ankylosing spondylitis
16. Indicate uncorrected criteria for third X-ray stage of rheumatoid arthritis
    - Fibrous or bony ankylosis
    - Extra-articular soft tissue lesions
    - evidence of cartilage and bone destruction
    - evidence ofperiarticular osteoporosis
    - evidence of articular fissure increase
17. Indicate uncorrected criteria for an inflammatory synovial fluid
    - mononuclear cell predominance
    - WBC count >2000/μL
    - countsgenerally from 5,000-50,000/μL.
    - neutrophil predominance (60-80%)
    - compared to serum glucose levels
18. Indicate the most common histological findings for rheumatoid arthritis
    - lymphoplasmacytic infiltration of the synovium with neovascularization
    - rheumatoid nodules

- mononuclear cell predominance in the synovium
- rheumatoid factor in the synovium
- Evidence of small vessel vasculitis

19. Indicate uncorrected DMARDs for initial treatmentof rheumatoid arthritis patients
    - anakinra
    - sulfasalazine
    - methotrexate,
    - azathioprine,
    - cyclosporin A
20. Indicate corrected biologic agentthat is recommended for initial treatment of the rheumatoid arthritis patients
    - Methotrexate
    - etanercept
    - Adalimumab
    - Infliximab
    - Anakinra
21. Indicate correct daily dose of prednisone that are typically used for treatment of the rheumatoid arthritis' patients
    - up to 10 mg per day
    - up to 15 mg per day
    - up to 20 mg per day
    - up to 30 mg per day
    - up to 40 mg per day
22. Indicate analgesic medications can be employed to reduce pain in rheumatoid arthritis patients
    - diclofenak
    - Acetaminophen/paracetamol,
    - tramadol,
    - codeine,
    - opiates

23.Indicate uncorrected features among the most common complications of rheumatoid arthritis' patients

- Lung disease
- Anemia,
- Scleritis,
- Infections,
- GI bleeding,

24.Indicate more appropriate immune-suppression treatment regime for ANCA-associated vasculitis

- combination of cyclophosphamide (intravenous or oral) and glucocorticoids
- cyclophosphamide (intravenous or oral)
- glucocorticoids(intravenous or oral)
- chimer antibody to ANCA
- lack appropriate data

25.Indicate correct remission-maintenance therapyfor vasculitis

- combination of low dose glucocorticoid therapy and, either azathioprine, leflunomide or methotrexate
- combination of low dose glucocorticoid therapy and methotrexate
- combination of low dose glucocorticoid therapy andazathioprine
- combination of low dose glucocorticoid therapy and cyclosporine A
- combination of low dose glucocorticoid therapy and leflunomide

26. What items are correct for DMARDs in rheumatoid arthritis

- Treatment with DMARDs should begin as soon as possible after diagnosis
- DMARDs don't take several weeks to start working
- DMARDs should not be continued indefinitely
- DMARDs cannot improve long-term prognosis
- DMARDs should be withdraw as soon as possible after achieving positive response

27.What items are correct for highly selective Cox2 agents implementation in patients with arthritis

- they reduce the incidence of ulcer complications in routine clinical practice
- it does not be necessary for GI protective agents to be co-prescribed in patients at high risk of ulcer complications

- they have not on NSAID- associated renal and cardiovascular events
- they reduce stroke incidence
- they are more effective than old NSAID

28. Indicate uncorrected diagnostic criteria of polyarteritisnodosa
    - obesity
    - Livedoreticularis
    - Testicularpainortenderness
    - Mononeuropathyorpolyneuropathy
    - Myalgias, weaknessorlegtenderness
29. Indicate the correct items that elucidate role of anti-TNF therapy in the treatment of patients with earlyrheumatoid arthritis
    - all items are correct
    - as 'bridge therapy' to induce remission while waiting for DMARDs to take effect
    - in combination with DMARD therapy when there has been insufficient beneficial effect
    - the optimal dosage and method of administration of anti-TNF therapy and the issue of immunogenicity
    - efficacy of anti-TNF agents in preventing joint damage and maintaining function over the longer term
    - long term data on whether anti-TNF therapy will increase susceptibility to infection or tumours
30. Indicate uncorrected criteria for complete remission inrheumatoid arthritis
    - morning stiffness >15 minutes
    - no fatigue
    - no joint pain
    - no joint tenderness or pain on motion
    - no soft tissue swelling in joint/tendon sheaths
31. Indicatethe most common cause of reactive arthritis
    - Chlamydiatrachomatis
    - Yersinia,
    - Shigella,

- Campylobacter
- Salmonella

32.Indicate uncorrected diagnostic criteria for the Henoch-SchönleinPurpura

- Palpable purpura related to thrombocytopenia
- Patient 20 years or younger at onset of first symptoms
- Bowel angina
- Diffuse abdominal pain, worse after meals, or the diagnosis of bowel ischemia, usually including bloody diarrhoea
- Wall granulocytes on biopsy

33.Indicate uncorrected diagnostic criteria for the Hypersensitivity Vasculitis

- Flat and raised lesions of the skin around mouth.
- Ageatdiseaseonset>16 years
- Palpablepurpura
- Maculopapularrash
- Histologic changes showing granulocytes in a perivascular or extravascular location

34.Indicate uncorrected diagnostic criteria for theTakayasuVasculitis

- Age at disease onset >16 years
- Claudicationofextremities
- Decreasedbrachialarterypulse
- Difference of >10 mm Hg in systolic blood pressure between arms
- Bruit audible on auscultation over 1 or both subclavian arteries or abdominal aorta

35.Indicate uncorrected diagnostic criteria for the Wegener’s Granulomatosis

- Age at disease onset >40 years
- Nasalororalinflammation
- Chest radiograph showing the presence of nodules, fixed infiltrates, or cavities
- Microhematuria (>5 red blood cells per high power field) or red cell casts in urine sediment
- Granulomatousinflammationonbiopsy

36.Indicate uncorrected diagnostic criteria of Systemic Lupus Erythematosus

- Erosive Arthritis
- Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
- Discoidrash
- Photosensitivity
- PleuritisorPericarditis

37. Indicate uncorrected Hematologic Disorder of Systemic Lupus Erythematosus
    - All items are correct
    - Hemolytic anemia with reticulocytosis
    - Leukopenia < 4,000/mm^3 on ≥ 2 occasions
    - Lyphopenia< 1,500/ mm^3 on ≥ 2 occasions
    - Thrombocytopenia <100,000/ mm^3 in the absence of offending drugs
    - Nonhemolytic anemia with Leukopenia < 4,000/mm^3on ≥ 2 occasions
38. Indicate appropriate immunologic disorder of Systemic Lupus Erythematosus
    - All items are correct
    - anti DNA antibodies
    - presence of antibody to Sm nuclear antigen
    - an abnormal serum level of IgG or IgM anticardiolipin antibodies
    - a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
39. Indicate unncorrected specific antibodies to streptococcal antigens of rheumatic fever
    - anti-DNA antibodies.
    - Anti streptolysin O,
    - antideoxyribonuclease B (anti-DNAase B),
    - antistreptokinase,
    - antihyaluronidase,
40. Indicate recommended approach can be divided into primary and secondary prevention of rheumatic fever
    - All items are correct

- Eradicate *Streptococcus* from the pharynx, which generally entails administering a single intramuscular injection of benzathinebenzylpenicillin.
- in high-risk situations, administration every 3 weeks benzathinebenzylpenicillin at 1.2 million units intramuscularly
- Oral prophylaxis withfphenoxymethylpenicillin (penicillin V) or sulfadiazine.
- prophylaxis should be continued for at least 10 years after the last episode of rheumatic fever

41.Indicate major therapeutic strategy to be prevent and treat the amyloid

- useofcolchicines
- use diet
- use oral corticoids
- use ative immunosuppression with metotrexate
- no treat

42. Indicate uncorrected signs of systemic manifestations of dermatomyositis

- all items are correct
- Arthralgia / arthritis,
- dyspnea,
- dysphagia,
- arrhythmia,

43.Indicate inappropriate immunologic disorder ofdermatomyositis

- Anti - DNA
- A positive ANA
- Anti–Mi-2 antibodies
- Anti–Jo-1 (antihistidyl transfer RNA synthetase)
- Anti -antisignalrecognitionprotein

44.Indicate disease that does not associated with prevalence of *HLA-B27* in the general population

- dermatomyositis
- ankylosingspondylitis

- rheumatoid arthritis
- reactive arthritis
- psoriatic arthritis

45. Indicate the most common clinically finding in patients with ankylosing spondylitis
    - All items are correct
    - Peripheralenthesitisandarthropathy
    - Inflammatorybackpain
    - Peripheralmusculoskeletal disorders
    - Symmetric and non symmetricspondylitis
46. Indicate the most common cardiovascular involvement in patients with ankylosing spondylitis
    - All items are correct
    - Aortitisoftheascendingaorta
    - Mitralvalveinsufficiency
    - Fibrosisoftheconductionsystem
    - Aorta regurgitation
47. Indicate uncorrected exclusion criteria for ankylosing spondylitis
    - Enthesitis
    - DiagnosisofspecificSpA
    - Keratodermablennorrhagicum
    - Psoriasis
    - Positiverheumatoidfactor
48. Indicate appropriate sign that does not associate with Felty syndrome:
    - Obesity
    - Splenomegaly
    - Hepatomegaly
    - Lymphadenopathy
    - Sjögrensyndrome

49. Indicate uncorrected item for clinical characteristics of gout
    - The attacks usually ispolyarticular.
    - Acute flares of gout also can occur in situations that lead to decreased levels of serum uric acid
    - Tophi are collections of uric acid crystals in the soft tissues
    - erythema over the joint is present
    - During an acute gout attack, patients can have a fever
50. Determine correcteditem forSjögren's syndrome features:
    - Development of an autoimmune inflammation of endocrine glands with extensive beta-lymphocytic infiltration of salivary, lachrymal glands and circulation in blood of auto antibodies to epithelium cells of these glands.
    - The systemic inflammation of the connecting tissue developed after the undergone acute streptococcal infection.
    - Inflammatory lesion of various departments of intestine with primary affection of a small and large intestine.
    - An initial degeneration of an articular cartilage with the subsequent deformation of articular surfaces.
    - Inflammatory lesion of vertebral column joints with ankylosing of intervertebral joints
51. Indicate uncorrected structural changes for acute glomerulonephritis
    - The structural changes should be focal only
    - Cellular proliferation
    - Leukocyte proliferation
    - Glomerular basement membrane thickening
    - Hyalinization or sclerosis
52. Indicate uncorrected functional changes for acute glomerulonephritis
    - anuria
    - proteinuria
    - hematuria
    - reduction in GFR
    - active urine sediment with RBCs and RBC casts

53. Indicate uncorrected physical signs for acute glomerulonephritis
    - purpura
    - Signs of fluid overload
    - Periorbital and/or pedal edema
    - Edema and hypertension due to fluid overload
    - Elevated jugular venous pressure
54. Indicate uncorrected causes for acute glomerulonephritis
    - Streptococcal infection
    - Systemic lupus erythematosus,
    - Henoch-Schonleinpurpura,
    - Goodpasture syndrome,
    - Wegener granulomatosis
55. Indicate uncorrected causes for chronic glomerulonephritis
    - Poststreptococcal glomerulonephritis
    - Focal segmental glomerulosclerosis
    - Membranous nephropathy
    - Membranoproliferative glomerulonephritis
    - IgA nephropathy
56. Indicate uncorrected histological findings of chronic glomerulonephritis
    - Granulomatous vasculities
    - Membranoproliferative glomerulonephritis
    - Mesangioprolifarative glomerulonephritis
    - Minimal changes disease

- Focal hyalinization

57. Indicate uncorrected cause for Anti-GBM antibodyproduction
    - Goodpasture syndrome
    - Henoch-Schonleinpurpura
    - Wegener granulomatosis
    - Mixed cryoglobulinemia
    - Lupus nephritis