

ZAPORIZHYA STATE MEDICAL UNIVERSITY

THE DEPARTMENT OF INTERNAL DISEASES 3

Casebook in HEMATOLOGY

**(tutorial for practical exercises for 6-year students of
medical faculty)**

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Практикум “Сборник клинических задач по внутренней медицине (часть V: гематология)” (на английском языке) предназначен для самостоятельной подготовки к практическим занятиям по дисциплине внутренние болезни англоговорящим студентам 6-го курса лечебного факультета. В практикум включены клинические задачи, вопросы и ответы к ним, дискуссии по синдромной диагностике в гематологической практике.

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Path I: ANEMIA

CASE 1

A healthy 52-year-old man presents to the doctor's office complaining of increasing fatigue for the past 4 to 5 months. He exercises every day, but lately he has noticed becoming short of breath while jogging. He denies orthopnea, paroxysmal nocturnal dyspnea (PND), or swelling in his ankles. The patient reports occasional joint pain, for which he uses over-the-counter ibuprofen. He denies bowel changes, melena, or bright red blood per rectum, but he reports vague left-side abdominal pain for a few months off and on, not related to food intake. The patient denies fever, chills, nausea, or vomiting. He has lost a few pounds intentionally with diet and exercise.

On examination, he weighs 205 lb, and he is afebrile. There is slight pallor of the conjunctiva, skin, and palms. No lymphadenopathy is noted. Chest is clear to auscultation bilaterally. Examination of the cardiovascular system reveals a regular rate and rhythm, with no rub or gallop. There is a systolic ejection murmur. His abdomen is soft, nontender, and without hepatosplenomegaly. Bowel sounds are present. He has no extremity edema, cyanosis, or clubbing. His peripheral pulses are palpable and symmetric. Hemoglobin level is 8.2 g/dL.

- > What is the most likely diagnosis?
- > What is the next diagnostic step?

CASE 2

A 43-year-old man presents with a 2-month history of fatigue, malaise, and dyspnea on exertion. He does not take any medications. CBC from 2 years ago was normal. On physical exam, there is conjunctival pallor. Hb is 5 g/dL, and HCT is 15%. Reticulocyte

count is 20/mL, and RI is 0.1%. WBC and platelet counts are normal. There are very few normocytic RBCs on peripheral smear. CXR is normal except for an anterior mediastinal mass. EKG is normal.

- > What type of anemia does this patient have?

CASE 3

A 27-year-old woman in her 18th week of gestation has Hb of 11.5 g/dL. She is asymptomatic. There is no pallor or tachycardia. Reticulocyte count is 150,000, and RI is 1%. Iron studies are normal. Peripheral blood smear demonstrates normocytic RBCs.

- > What is the next step in management?

CASE 4

A 65-year-old man presents with a 3-month history of back pain, fatigue, and an unintentional 10-lb weight loss. The pain increases with movement. On physical exam, there is pallor and vertebral tenderness. Abnormal findings on CBC are Hb 9.7 mg/dL, HCT 29%, RI 0.5%, and MCV 90 dL. Figure 4–1 is the patient's peripheral smear.

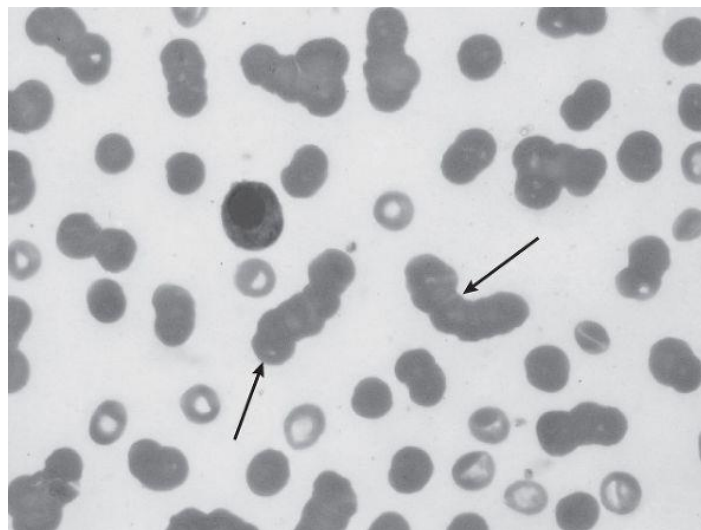


Figure 4–1. Blood smear showing rouleaux.

- > What is the most likely diagnosis?

CASE 5

A 76-year-old woman presents with fatigue and short-term memory loss. She does not drink alcohol or smoke cigarettes. On physical exam, her tongue is shiny (atrophic

glossitis). She walks with a broad-based clumsy gait (ataxia). There is decreased vibration and position sensation in both feet. Hb is 9 mg/dL, and HCT is 28%. Reticulocyte count is 40,000/mL, and RI is 0.4%. MCV is 114 dL. Figure 10-7 is her peripheral smear.

- > What is the most likely diagnosis?

CASE 6

A 60-year-old alcoholic man presents with fatigue and difficulty concentrating. His daughter mentions that he has not been eating well. On physical exam, the conjunctiva and nail beds are pale. Neurological exam is normal. Laboratory studies demonstrate macrocytic megaloblastic anemia.

- > What is the most likely cause of macrocytic anemia in this patient?

CASE 7

A 57-year-old alcoholic man presents with fatigue and difficulty walking. He has an ataxic gait and mild hand tremor. There is no spasticity. Deep tendon reflexes are normal. Proprioception and vibration are intact. Laboratory studies reveal macrocytic anemia with MCV of 105 dL and no hypersegmented PMNs.

- > What is the most likely diagnosis?

CASE 8

A 25-year-old African American man is admitted to your service with the diagnosis of a sickle cell pain episode. He was admitted to the hospital six times last year with the same diagnosis, and he was last discharged 2 months ago. Again he presented to the emergency room complaining of abdominal and bilateral lower extremity pain, his usual sites of pain. When you examine him, you note he is febrile to 101°F, respiratory rate 25 breaths per minute, normal blood pressure, and slight tachycardia of 100 bpm. Lung examination reveals bronchial breath sounds and egophony in the right lung base. His oxygen saturation on 2 L/min nasal cannula is 92%. Besides the usual abdominal and leg pain, he is now complaining of chest pain, which is worse on inspiration. Although he is tender on palpation of his extremities, the remainder of his examination is normal. His

laboratory examinations reveal elevated white blood cell and reticulocyte counts, and a hemoglobin and hematocrit that are slightly lower than baseline. Sickle and target cells are seen on the peripheral smear.

- > What is the most likely diagnosis?
- > What is your next step?

CASE 9

A 50-year-old African-American man presents to the clinic with a 2-day history of fever, cough, and pleuritic chest pain. CXR shows a left upper lobe infiltrate. He is diagnosed with community-acquired pneumonia and is given azithromycin. One day later, he returns with abdominal pain and dark urine. Both sclera are icteric. LFTs detect increased indirect bilirubin. Hb is 10.2 mg/dL, HCT is 31%, reticulocyte count is 6%, RI is 3%, and serum haptoglobin is 25 mg/dL. Figure 9-1 is the patient's blood smear.

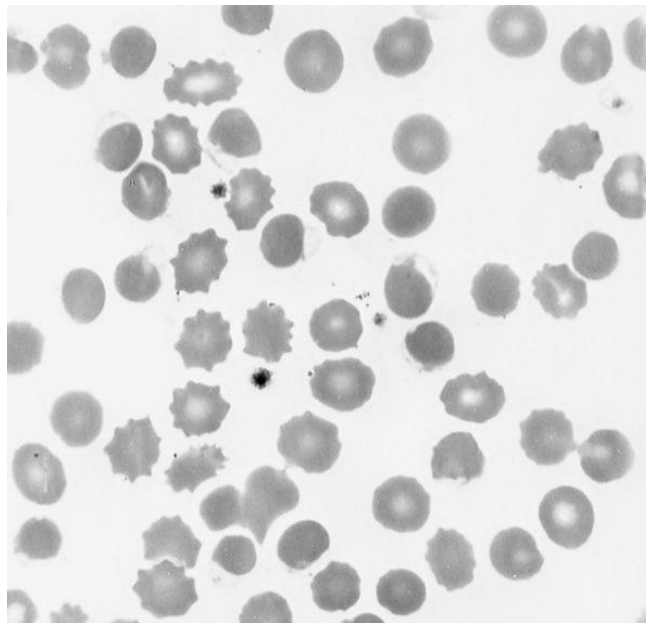


Figure 9–1. Blood smear showing bite cells and Heinz bodies.

- > What are the causes of hemolytic anemia?

CASE 10

An 18-year-old man presents with chronic fatigue. Vital signs are normal. Laboratory studies indicate the patient has a hemolytic anemia. In addition, mean

corpuscular Hb concentration (MCHC) is increased. The patient's peripheral blood smear shows sphere-shaped RBCs with no central pallor.

- > What is the diagnosis?

CASE 11

A 34-year-old woman with a history of systemic lupus erythematosus (SLE) presents with fatigue. On physical exam, she appears jaundiced. Laboratory studies reveal hemolytic anemia with spherocytosis on the peripheral smear. Osmotic fragility test is negative. Direct Coomb's test demonstrates RBC agglutination at room temperature (37°C) in response to IgG antibodies.

- > What is the diagnosis?

CASE 12

A 22-year-old man complains of fever, sore throat, and fatigue over the last 3 days. Physical exam is significant for splenomegaly, cervical adenopathy, and jaundice. The fingertips and toes are dark purple. Pertinent laboratory findings are positive monospot test and hemolytic anemia.

- > What diagnosis should you suspect?

CASE 13

A 32-year-old man presents with episodes of dark urine when he wakes up in the morning. The urine gets clearer over the day. He also reports erectile dysfunction and brief episodes of epigastric pain and dysphagia. On physical exam, there is jaundice and pallor. Laboratory studies indicate that he has a hemolytic anemia. On urinalysis, the sediment is clear and the supernatant is red. Urine dipstick is heme-positive with clear plasma. There are no characteristic findings on peripheral blood smear. Coomb's test is negative.

- > What diagnosis should you suspect?

CASE 14

A 24-year-old man presents with a 3-day history of persistent fever, chills, fatigue, and myalgias. He recently returned from a monsoon wedding in India. Physical exam is significant for pallor, jaundice, and splenomegaly. Temperature is 102°F. Laboratory studies reveal the patient has a hemolytic anemia. Figure 10-10 is the patient's Giemsa-stained peripheral smear.

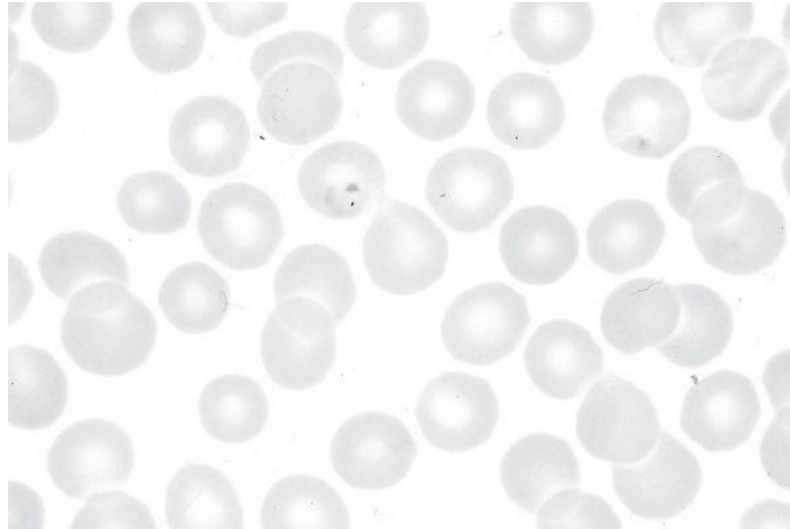


Figure 12–1. Giemsa-stained blood smear showing malaria.

> What is the diagnosis?

CASE 15

A 60-year-old man presents with episodes of colicky abdominal pain and arthralgias. He also reports fatigue and difficulty concentrating. He has a history of frequently drinking “moonshine” (illegally distilled alcohol). Oral and conjunctival mucosa is pale. There is a blue line at the gum–tooth border. Abdominal obstructive series is negative. Hb is 9.5 mg/dL and HCT is 29%. Figure 15-1 is the patient's peripheral blood smear.

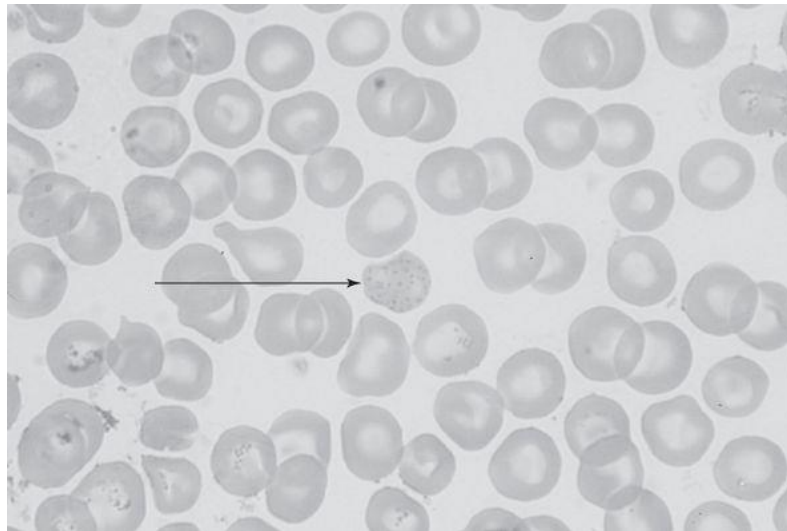


Figure 15–1 Blood smear with basophilic stippling (due to lead poisoning).

› What disorders can cause this pattern?

Path II: LEUKEMIA AND LEUKEMOID REACTION

CASE 16

A 63-year-old white man is seen in the emergency room with complaints of fever, fatigue, and malaise. He reports having intermittent epistaxis during the last week, mouth sores for the last 3 days, and a nonpruritic rash over his lower extremities, which was noted 24 hours before. He has experienced midchest pain for the last day, only on swallowing. He denies chemical, drug, or radiation exposure.

Physical examination reveals a temperature of 38.6B°C (101.48B°F). He has mild tachycardia, at 108 beats per minute. Head, eyes, ears, nose, and throat findings consist of a few petechiae over the soft palate. Multiple white plaques are seen on the oral mucosa, and there is hypertrophy of the gingivae. During examination of the skin, petechiae are found over the distal lower extremities. Other examination findings are normal. Specifically, no lymphadenopathy or hepatosplenomegaly are found. Other sites of possible infection, including the chest and perirectal area, are clear. The chest radiographic study is likewise normal.

Laboratory findings are as follows: white blood cell count, 17,200/mm³ with 2% polymorphonuclear leukocytes, 1% band forms, 16% lymphocytes, 4% monocytes, 5% metamyelocytes, 4% basophils, and 68% blastocytes; hemoglobin, 11.1 g/dL;

hematocrit, 32.6%; and platelets, 14,000/mm³. His electrolyte, blood urea nitrogen (BUN), creatinine, and aminotransferase levels are normal. His uric acid level is mildly increased at 9.2 mg/dL (normal, 3.5 to 8.0 mg/dL), as are his LDH level at 373 IU/L (normal, 30 to 220 IU/L). Examination of a peripheral blood smear reveals occasional nucleated red blood cells, few platelets, and many large cells containing finely reticulated nuclei, several nucleoli, cytoplasmic granules, and occasional Auer rods. Large cells with folded nuclei and large, prominent nucleoli are also seen.

- > What is the most likely diagnosis in this patient?
- > How is the absolute neutrophil count (ANC) calculated, and what is it in this patient?
- > Of what importance is the ANC?
- > Do the evaluation findings point to any specific infections?
- > What would you expect this patient's bone marrow to show?
- > Should a lumbar puncture be performed in this patient?

CASE 17

A 54-year-old man presents to the emergency room complaining of 24 hours of fevers with shaking chills. He is currently being treated for acute lymphoblastic leukemia (ALL). His most recent chemotherapy with hyperfractionated CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) was 7 days ago. He denies any cough or dyspnea, headache, abdominal pain, or diarrhea. He has had no sick contacts or recent travel. On physical examination, he is febrile to 103°F, tachycardic with heart rate 122 bpm, blood pressure 118/65 mm Hg, and respiratory rate 22 breaths per minute. He is ill appearing; his skin is warm and moist but without any rashes. He has no oral lesions, his chest is clear to auscultation, his heart rhythm is tachycardic but regular with a soft systolic murmur at the left sternal border, and his abdominal examination is benign. The perirectal area is normal, digital rectal examination is deferred, but his stool is negative for occult blood. He has a tunneled vascular catheter at the right internal jugular vein with erythema overlying the subcutaneous tract, but no purulent discharge at the catheter exit site. Laboratory studies reveal a total white blood cell count of 1100 cells/mm³, with a differential of 10% neutrophils, 16% band forms,

70% lymphocytes, and 4% monocytes (absolute neutrophil count 286). Chest radiograph and urinalysis are normal.

- > What is the most likely diagnosis?

CASE 18

A 63-year-old African American woman is brought to the emergency room for upper arm pain and swelling following a fall at home. The family has noted that for approximately the past 2 months, the patient has become progressively fatigued and absent-minded, and she has developed loss of appetite and weight loss. She has been getting up to urinate several times per night and complains of thirst; however, a test for diabetes in her doctor's office was negative. This morning, she lost her balance because she felt "lightheaded" and fell, landing on her left arm. Physical examination is notable for an elderly, thin woman in mild distress as a result of pain. She is afebrile; her blood pressure is 110/70 mm Hg and heart rate 80 bpm. Her thyroid gland is normal to palpation. Her mucus membranes are somewhat dry and sticky. Heart and lung examinations are normal, and carotid auscultation reveals no bruits. Examination of her extremities is significant only for deformity of the left mid-humerus with swelling. The left radial pulse is 2+ and symmetric. The radiologist calls you to confirm the fracture of the mid-left humerus but also states that there is the suggestion of some lytic lesions of the proximal humerus and recommends a skull film. Serum creatinine level is 2.1 mg/dL, with normal electrolyte and glucose concentrations, but serum calcium level is 13 mg/dL and hemoglobin level is 9.2 g/dL.

- > What is the most likely diagnosis?
- > What is the most likely underlying etiology in this patient?

CASE 19

A 37-year-old white man is seen because of lack of energy, night sweats, and poor appetite with a sensation of fullness after eating even very small amounts of food.

Physical examination reveals signs of anemia, splenomegaly, and the existence of petechiae. A complete blood count is performed and yields the following findings: hematocrit, 25%; platelets, 300,000/mm³, and white blood cells, 72,000/mm³. A bone

marrow biopsy is performed and the specimen is found to exhibit a granulocytic erythroid ratio of 10:1 with 100% cellularity and 1% blastocytes.

> What is the differential diagnosis in this patient, based on the physical examination findings?

> On the basis of the hematologic findings, what hematopoietic abnormalities would you expect in this patient with suspected CML?

> What do the bone marrow findings indicate in this patient?

> What would be the most specific test for establishing the diagnosis of CML in this patient?

> If the patient is started on single-agent chemotherapy, what would be the likely effect?

CASE 20

A 65-year-old man presents with a 2-month history of fatigue and dyspnea on exertion. He also reports frequent nosebleeds in the last 2 months. On physical exam, there is conjunctival pallor and petechiae. WBC count is 20,000/ μL , Hb is 8 mg/dL, and platelets are 40,000/ μL .

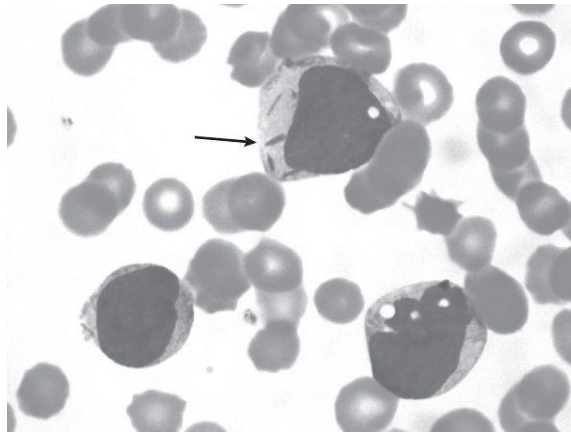


Figure 20–1. Blood smear showing blast cells with Auer rods.

> What is the differential diagnosis?

> What is the most likely diagnosis?

CASE 21

During routine testing of a 55-year-old man, WBC count is found to be 80,000/ μ L. Hb is 12.2 mg/dL and platelets are 300,000/ μ L. Figure 21–1 is the patient's peripheral smear.

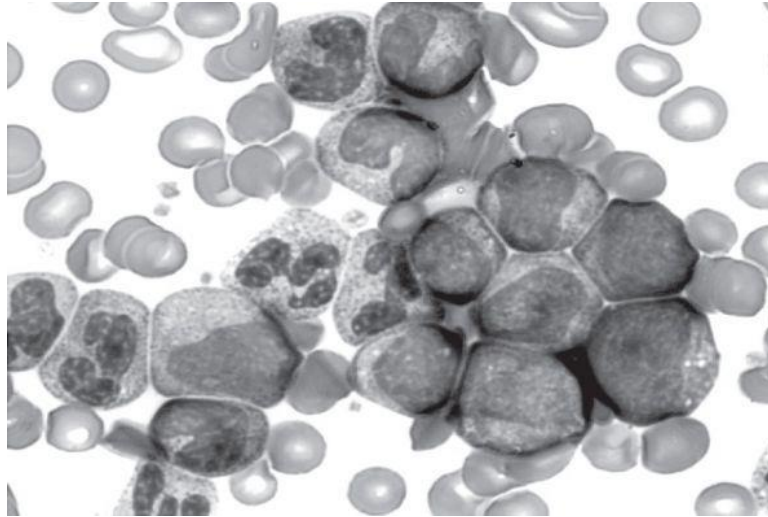


Figure 21–1. Blood smear: granulocytes in different stages of maturation.

- > What is the differential diagnosis?
- > What diagnostic studies can help confirm the diagnosis?
- > How is CML treated?

Path III: POLYCYTHEMIA

CASE 22

A 55-year-old man who is a smoker and has hypertension sees his internist because of malaise and nasal stuffiness with full sensation in his frontal sinuses. On further questioning, the patient also describes having itchy, red feet that worsen in the shower. The patient has no shortness of breath with activity and does not snore or experience daytime drowsiness.

Physical examination reveals a plethoric patient who is in no acute distress. His lungs are clear to auscultation. His liver span is 18 cm and his spleen tip is palpable.

The following laboratory values are reported: hematocrit, 65%; white blood cell count, $5,500/\text{mm}^3$; platelets, $210,000/\text{mm}^3$; and differential: 50% segmented neutrophils, 30% lymphocytes, 3% basophils, and 10% monocytes.

Arterial blood gas determinations performed on room air reveal a partial pressure of oxygen of 65 mm Hg, a partial pressure of carbon dioxide of 38 mm Hg, and an oxygen saturation of 93%.

- > What is the diagnosis in this patient?
- > Why is it important to know whether the patient snores or experiences daytime drowsiness?
- > What is the cause of this patient's nasal stuffiness?
- > What should be the initial treatment in this patient?
- > What is this patient's prognosis?

CASE 23

A 50-year-old man presents with a 4-week history of fatigue, headache, blurry vision, and pruritus. He also reports episodes of burning and erythema in his hands and feet (erythromelalgia). He does not take any medications. He does not smoke cigarettes or drink alcohol. There is splenomegaly on physical exam. Vital signs and oxygen saturation are normal. Body mass index is 23. LFTs and serum chemistries are normal. Abnormal findings on CBC are Hb 20 g/dL, HCT 60%, and platelets $500,000/\mu\text{L}$.

- > What are the most common causes of polycythemia?
- > What diagnosis do the history and physical exam findings suggest?

Path IV: PURPURA

CASE 24

A 26-year-old woman presents to the emergency room on a Saturday afternoon with complaints of bleeding from her nose and mouth since the previous night. She also noticed small, reddish spots on her lower extremities when she got out of the bed in the morning. She denies fever, chills, nausea, vomiting, abdominal pain, or joint pain. The patient reports she had developed an upper respiratory infection 2 weeks prior to the

emergency room visit, but the infection has now resolved. She denies significant medical problems. Her menses have been normal, and her last menstrual period was approximately 2 weeks ago. She denies excessive bleeding in the past, even after delivering her baby. Prior to this episode, she never had epistaxis, easy bruisability, or bleeding into her joints. There is no family history of abnormal bleeding. The patient does not take any medications.

On examination she is alert, oriented, and somewhat anxious. Her blood pressure is 110/70 mm Hg, her heart rate is 90 bpm, and she is afebrile. No pallor or jaundice is noted. There is bright red oozing from the nose and the gingiva. Skin examination reveals multiple 1mm flat reddish spots on her lower extremities. The rest of the examination is normal. There is no lymphadenopathy or hepatosplenomegaly. Her complete blood cell count (CBC) is normal except for a platelet count of 18,000/mm³. Prothrombin time (PT) and partial thromboplastin time (PTT) are normal.

- > What is your most likely diagnosis?
- > What is the best initial treatment?

CASE 26

A 22-year-old man requires extraction of his wisdom teeth. He recently emigrated from Sudan. He was separated from his family at the age of 5. During the procedure, he bleeds excessively and is referred for medical evaluation. On physical exam, there are two large ecchymoses. Review of systems is positive for joint pain. CBC is normal, PT is normal, but PTT is elevated.

- > What is the next step in diagnosis?
- > What is the next diagnostic step?

Path V: LYMPHADENOPATHY

CASE 27

A 42-year-old woman is referred to you by her family physician for the evaluation of bilateral neck adenopathy. She has noticed this swelling intermittently for approximately 6 months. She has occasionally noticed axillary node swelling but denies any other adenopathy. She has noticed that she tires more easily and seems to pick up

every little virus. She admits to experiencing occasional early satiety, but denies any increase in abdominal girth or changes in bowel habits. She denies any fever, chills, night sweats, weight loss, or change in appetite.

Her family history is remarkable for a mother with breast cancer (the patient's last mammogram 1 year ago was normal). She does not smoke or drink.

Physical examination findings are remarkable for bilateral neck and axillary adenopathy. She has no oral or pharyngeal lesions and no breast masses. Her spleen is mildly enlarged but her liver size is normal. She has no other physical abnormalities.

Laboratory findings are remarkable for a mild normochromic, normocytic anemia (hemoglobin, 13.0 g/dL; hematocrit, 39%); the platelet count is 250,000/mm³ and the white blood cell count is 5,200/mm³ with a normal differential. A chemistry panel is remarkable for a slightly elevated LDH level, but the AST, ALT, bilirubin, and alkaline phosphatase values are normal. Her chest radiographic study is normal.

A staging evaluation is done and reveals the following findings. Tissue analysis reveals malignant lymphoma consisting of follicular small cleaved (nodular poorly differentiated) cells that are CD20 positive. Bone marrow biopsy reveals normal cellularity with lymphoid follicles (normal for age), a slight increase in the number of erythroid precursors, normal megakaryocytes, and a decrease in the iron content. Cytogenetic examination identifies a balanced translocation, t(14;18). CT scan of the abdomen depicts moderate splenomegaly and mild retroperitoneal adenopathy. Serum immunoelectrophoresis reveals mild hypogammaglobulinemia with a monoclonal immunoglobulin M (IgM) spike.

> On the basis of the physical examination and laboratory findings, what is the differential diagnosis in this patient?

CASE 28

A 38-year-old man presents to his general practitioner (GP) complaining of a painless lump on the right side of his neck. This has been present for about 2 months and seems to be enlarging. He has had no recent throat infections. He has been feeling generally unwell and has lost about 5 kg in weight. The patient has also developed drenching night sweats. Simultaneously he has noticed severe generalized itching. He has

had no significant past medical history. He is an accountant, and married with three children. He neither smokes nor drinks alcohol and is not taking any regular medication.

His temperature is 37.8°C. There is a smooth, firm 3 X 4cm palpable mass in the right supraclavicular fossa. There are also lymph nodes 1-2 cm in diameter, palpable in both axillae and inguinal areas. His oropharynx appears normal. There are multiple excoriations of his skin. His pulse rate is 100/min regular and blood pressure 112/66 mmHg. Examination of his cardiovascular and respiratory systems is normal. On abdominal examination, there is a mass palpable 3 cm below the left costal margin. The mass is dull to percussion and it is impossible to palpate its upper edge. Neurological examination is normal.

		Normal
Haemoglobin	11.6 g/dL	13.3-17.7 g/dL
White cell count	12.2 X 10 ⁹ /L	3.9-10.6 X 10 ⁹ /L
Platelets	321 X 10 ⁹ /L	150-440 X 10 ⁹ /L
Erythrocyte sedimentation rate	74 mm/h	<10 mm/h
Sodium	138 mmol/L	135-145 mmol/L
Potassium	4.2 mmol/L	3.5-5.0 mmol/L
Urea	5.2 mmol/L	2.5-6.7 mmol/L
Creatinine	114 µmol/L	70-120 µmol/L
Calcium	2.44 mmol/L	2.12-2.65 mmol/L
Phosphate	1.1 mmol/L	0.8-1.45 mmol/L
Total protein	65 g/L	60-80 g/L
Albumin	41 g/L	35-50 g/L
Bilirubin	16 mmol/L	3-17 mmol/L
Alanine transaminase	22 IU/L	5-35 IU/L
Alkaline phosphatase	228IU/L	30-300 IU/L

Urinalysis: no protein; no blood

- > What is the likely diagnosis?
- > How would you investigate and manage this patient?

ANSWERS AND DISCUSSION TO

ANSWERS TO CASE 1:

What is the most likely diagnosis and next diagnostic step?

A healthy 52-year-old man complains of a 4- to 5-month history of increasing exercise intolerance, but he denies orthopnea, PND, edema, or other signs of heart failure. The patient uses a nonsteroidal anti-inflammatory drug (NSAID) regularly. He has not had any overt gastrointestinal (GI) blood loss. On examination, he weighs 205 lb, and he has slight pallor of the conjunctiva, skin, and palms. He is anemic, with a hemoglobin level of 8.2 g/dL.

- > Most likely diagnosis: Iron-deficiency anemia as a result of chronic blood loss.
- > Next diagnostic step: Analyze the complete blood count (CBC), particularly the mean corpuscular volume (MCV), to determine if the anemia is microcytic, normocytic, or macrocytic; assess the leukocyte count and platelet count.

ANALYSIS

Considerations

This 52-year-old man presents to the doctor's office with complaints of fatigue and dyspnea on exertion for the few months prior to the office visit. His physical examination is significant only for pallor. The serum hemoglobin level confirms anemia. The next step would be to characterize the anemia as microcytic, which would be consistent with iron deficiency, and confirmed with further testing for total iron-binding capacity (TIBC) and ferritin. The most likely source of blood loss in male patients is the GI tract; therefore, finding iron-deficiency anemia should suggest the presence of a possible GI source of bleeding, with colon cancer the most serious possibility. This patient is using ibuprofen, which may predispose to erosive gastritis. Once iron-deficiency anemia is confirmed, a thorough evaluation of the GI tract, including upper and lower endoscopy, is needed.

APPROACH TO

DEFINITIONS

ANEMIA: Decreased red blood cell (RBC) mass, leading to less oxygen-carrying

capacity. Hemoglobin levels less than 13 g/dL in men and less than 12 g/dL in women are generally used.

IRON STUDIES: Ferritin is a marker of iron stores, but it also is an acute-phase reactant, which is decreased in iron deficiency but increased with chronic disease. The TIBC is an indirect measure of transferrin saturation levels and is increased in iron deficiency.

MEAN CORPUSCULAR VOLUME (MCV): Average RBC volume. This offers a method of categorizing anemias as microcytic (MCV <80 fL), normocytic (MCV 80-100 fL), and macrocytic (MCV >100 fL).

RETICULOCYTE: New RBC that usually is 1 to 1.5 days old.

RETICULOCYTE COUNT: Fraction of RBCs consisting of reticulocytes that indirectly indicates the bone marrow activity of the erythrocyte line. It usually is expressed as a percentage and normally is 1%. Corrected reticulocyte count accounts for anemia.

CLINICAL APPROACH

Iron Deficiency

Although anemia may be caused by disorders of bone marrow production, red cell maturation, or increased destruction, iron deficiency is the most common cause of anemia in the United States, affecting all ages and both genders. Iron is essential to the synthesis of hemoglobin. The normal daily intake of elemental iron is approximately 15 mg, of which only 1 to 2 mg is absorbed. The daily iron losses are about the same, but menstruation adds approximately 30 mg of iron lost each month. The primary etiology for iron-deficiency anemia is blood loss (Table 1-1). In men, the most frequent cause is chronic GI tract occult bleeding. In women, menstrual loss may be the main mechanism, but other sites must be considered. Supplemental iron is needed during pregnancy because of iron transfer from the mother to the developing fetus. Iron deficiency may also be a result of increased iron requirements, diminished iron absorption, or both. Iron deficiency can develop during the first 2 years of life if dietary iron is inadequate for the demands of rapid growth. Adolescent girls may become iron deficient from inadequate diet plus the added loss from menstruation. The growth spurt in adolescent boys may

also produce a significant increase in demand for iron. Other possible causes of anemia are decreased iron absorption after gastrectomy and upper-bowel malabsorption syndrome, but such mechanisms are rare when compared to blood loss.

Table 1-1 Common causes of iron-deficiency anemia

Blood loss	Malabsorption
<p>Gastrointestinal blood loss</p> <ul style="list-style-type: none"> . Esophageal varices . Peptic ulcer disease . Gastritis, eg, NSAID induced . Small-bowel polyp or carcinoma . Colonic angiodysplasia . Colon cancer . Inflammatory bowel disease, eg, ulcerative colitis . Hookworm infestation <p>Uterine blood loss</p> <ul style="list-style-type: none"> . Menstruation/menorrhagia . Uterine fibroids <p>Other blood loss</p> <ul style="list-style-type: none"> . Chronic hemodialysis . Surgical blood loss . Repeated blood donation or phlebotomy . Paroxysmal nocturnal hemoglobinuria 	<ul style="list-style-type: none"> . Gastrectomy . Celiac disease . Inflammatory bowel disease, eg, Crohn disease <p>Inadequate dietary intake/ increased physiologic demands</p> <ul style="list-style-type: none"> . Infancy/adolescence . Pregnancy . Vegetarian diet

When iron loss exceeds intake, iron deposits are progressively depleted. Hemoglobin and serum iron levels may remain normal in the initial stages, but the serum ferritin level (iron stores) will start to fall. As serum iron levels fall, the percent of transferrin saturation falls and the TIBC will increase, leading to a progressive decrease in iron available for RBC formation. At this point, anemia will develop initially with normal-appearing RBCs. As the iron deficiency becomes more severe, microcytosis and hypochromia will develop. Later in the disease process, iron deficiency will affect other tissues, resulting in a variety of symptoms and signs.

Typical symptoms of anemia include fatigue, shortness of breath, dizziness, headache, palpitations, and impaired concentration. Additionally, patients with chronic severe iron deficiency may develop cravings for dirt, paint (pica), or ice (pagophagia). Glossitis, cheilosis, or koilonychia may develop and, in rare advanced cases, dysphagia, associated with a postcricoid esophageal web (Plummer-Vinson syndrome). When the

anemia develops over a long period, the typical symptoms of fatigue and shortness of breath may not be evident. Many patients with iron-deficiency anemia may be asymptomatic. The lack of symptoms reflects the very slow development of iron deficiency and the ability of the body to adapt to lower iron reserves and anemia.

Evaluation of Anemia

Once anemia is discovered, a CBC with differential, platelets, and RBC indices are helpful in narrowing the differential diagnosis. The first step is to look at the MCV to classify the common causes of anemia (Table 1-2). Iron deficiency usually leads to a microcytic anemia. The red blood cell distribution width (RDW) is a calculated index that quantitates the variation in the size of RBCs. RDW is a quantitative measure of anisocytosis that helps to distinguish uncomplicated iron deficiencies from uncomplicated thalassemia. An increased RDW associated with microcytic anemia is suggestive of iron-deficiency anemia, because the bone marrow produces erythrocytes of various sizes. A normal RDW in the presence of microcytic anemia may be more suggestive of chronic disease, thalassemia, or even iron deficiency associated with anemia of a chronic disease. A detailed history, physical examination, and further laboratory data may be necessary to achieve a final diagnosis.

The reticulocyte count is another important parameter to help in the differential diagnosis of anemia. A new RBC remains a reticulocyte for 1 to 1.5 days, after which the RBC circulates for approximately 120 days. The blood normally contains about 1 reticulocyte per 100 RBCs. The reticulocyte count, usually reported as a percentage of reticulocytes per 100 RBCs, may be falsely elevated in the presence of anemia. Therefore, a corrected reticulocyte percentage is calculated by multiplying the reported reticulocyte count by the patient's hematocrit divided by 45 (normal hematocrit). The reticulocyte may also be converted to an absolute number by multiplying the reported reticulocyte count by the RBC count and dividing by 100. The absolute reticulocyte count is normally 50,000 to 70,000 reticulocytes/mm³. If the reticulocyte count is low, causes of hypoproliferative bone marrow disorders should be suspected. A high reticulocyte count may reflect acute blood losses, hemolysis, or a response to therapy for anemia.

Table 1-2 Classification of anemia by MCV

Microcytic (low MCV)	Lead poisoning Normocytic (normal MCV)	Macrocytic anemia (high MCV)
<ul style="list-style-type: none">• Iron deficiency• Thalassemia• Sideroblastic anemia	<ul style="list-style-type: none">• Acute blood loss• Hemolysis• Anemia of chronic disease• Anemia of renal failure• Myelodysplastic syndromes	<ul style="list-style-type: none">• Folate deficiency• Vitamin B12 deficiency• Drug toxicity, eg, zidovudine• Alcoholism/chronic liver disease

Iron studies are very helpful to confirm a diagnosis of iron deficiency anemia and to help in the differential diagnosis with other types of anemia, such as anemia of chronic disease and sideroblastic anemia (Table 1-3). Serum ferritin concentration is a reliable indication of iron deficiency. Serum ferritin values are increased with chronic inflammatory disease, malignancy, or liver injury; therefore, serum ferritin concentration may be above normal when iron deficiency exists with chronic diseases, such as rheumatoid arthritis, Hodgkin disease, or hepatitis, among many other disorders. Measurement of serum iron concentration, serum TIBC, and calculation of percent saturation of transferrin has been widely used for diagnosis of iron deficiency. True iron deficiency is strongly suspected on the basis of low serum iron level and normal or high binding capacity, which will result in a low calculated saturation. In anemia of chronic disease, serum iron concentration is low, but usually the TIBC is also reduced; therefore, percent transferrin saturation typically is normal in anemia of chronic disease. Chronic disease typically causes elevation in serum ferritin concentration. When chronic disease and iron-deficiency anemia coexist, serum ferritin concentration may be normal. Sideroblastic anemia is commonly microcytic and hypochromic. The iron studies in sideroblastic anemia include increases in serum iron and serum ferritin concentration and saturation of transferrin. An important clue to the presence of sideroblastic anemia is the presence of stippled RBCs in the peripheral blood smear. Iron stain in the bone marrow reveals pathognomonic feature of engorged mitochondria in the developing RBCs called ringed sideroblasts.

Table 1-3 Different anemias with characteristics and laborator

Tests	Iron Deficiency	Inflammation	Thalassemia	Sideroblastic Anemia
Smear	Microcytic/hypochromic	Normal microcytic/hypochromic	Microcytic/hypochromic with targeting	Variable
Serum iron g/dL	<30	<50	Normal to high	Normal to high
TIBC g/dL	>360	<300	Normal	Normal
Percent saturation	<10	10-20	30-80	30-80
Ferritin g/L	<15	30-200	50-300	50-300
Hemoglobin electrophoresis	Normal	Normal	Abnormal	Normal

Abbreviations: *SI*, serum iron; *TIBC*, total iron-binding capacity.

Evaluating the peripheral blood smear for specific abnormalities in RBC morphology may be very useful for determining the etiology of anemia. In iron-deficiency anemia, the peripheral blood smear shows RBCs smaller than normal (microcytes) and hypochromia.

Although the treatment of iron deficiency is straightforward, finding the underlying etiology is paramount. Treatment of iron-deficiency anemia consists of iron replacement therapy, typically with oral ferrous sulfate 325 mg two or three times daily. Correction of anemia usually occurs within 6 weeks, but therapy should continue for at least 6 months to replenish the iron stores. A number of patients may develop GI side effects, such as constipation, nausea, and abdominal cramping. Taking the iron with meals may help with tolerance but can reduce absorption. Parenteral iron therapy is indicated in rare instances, such as in patients with a poor absorption state or with excessive intolerance to oral therapy. Caution must be taken with parenteral iron because anaphylaxis may occur.

Comprehension Questions

1.1 A 25-year-old man with a history of a duodenal ulcer is noted to have a hemoglobin level of 10 g/dL. Which of the following most likely will be seen on laboratory investigation?

- A. Reticulocyte count of 4%
- B. Elevated total iron-binding capacity

- C. Normal serum ferritin
- D. Mean corpuscular volume of 105 fL

1.2 A 22-year-old woman is pregnant and at 14-week gestation. Her hemoglobin level is 9 g/dL. She asks why she could have iron deficiency when she is no longer menstruating. Which of the following is the best explanation? A 35-year-old man has undertaken a self-imposed diet for 3 months. He previously had been healthy but now complains of fatigue. His hemoglobin level is 10 g/dL, and his MCV is 105 fL. Which of the following is the most likely etiology of his anemia?

- A. Iron deficiency
- B. Folate deficiency
- C. Vitamin B12 deficiency
- D. Thalassemia
- E. Sideroblastic anemia

1.3 A 35-year-old man has undertaken a self-imposed diet for 3 months. He previously had been healthy but now complains of fatigue. His hemoglobin level is 10 g/dL, and his MCV is 105 fL. Which of the following is the most likely etiology of his anemia?

- A. Iron deficiency
- B. Folate deficiency
- C. Vitamin B12 deficiency
- D. Thalassemia
- E. Sideroblastic anemia

For the following questions (1.4 to 1.6) choose the laboratory parameter (A-E) that matches the clinical picture.

	RDW	MCV	Ferritin	TIBC
A.	Decrease	Elevated	Decreased	Elevated
B.	Increased	Decreased	Decreased	Elevated
C.	Normal	Normal	Elevated	Normal

D.	Normal	Decreased	Increased	Normal
E.	Increased	Elevated	Increased	Decreased

1.4 A 20-year-old woman with heavy menses

1.5 A 34-year-old man of Mediterranean descent with a family history of anemia

1.6 A 50-year-old man with severe rheumatoid arthritis

ANSWERS

1.1 B. Chronic gastrointestinal blood loss leads to low ferritin levels reflecting diminished iron stores, elevated TIBC, and low iron saturation. There is a microcytic anemia (low MCV) with a low reticulocyte count.

1.2 B. Iron deficiency occurs in pregnancy as a result of the expanded blood volume and active transport of iron to the fetus.

1.3 B. Macrocytic anemia is usually a result of folate or vitamin B12 deficiency. Because vitamin B12 stores last for nearly 10 years, a diet of several months would more likely cause folate deficiency. Folate is found in green leafy vegetables.

1.4 B. This laboratory finding is diagnostic of iron-deficiency anemia (microcytic, low ferritin, high TIBC, high RDW).

1.5 D. Thalassemia usually leads to a microcytic anemia with uniform red cell size (normal RDW) and excess iron stores.

1.6 C. Chronic disease generally leads to a normocytic anemia with elevated ferritin level (acute-phase reactant).

Clinical Pearls

- Anemia is a clinical finding, not a diagnosis, and requires some investigation to determine the underlying etiology.

- Iron-deficiency anemia in men or postmenopausal women is primarily a result of gastrointestinal blood losses; therefore, finding iron-deficiency anemia in this patient population warrants a thorough gastrointestinal workup.

- Iron-deficiency anemia in women of reproductive age is most often caused by menstrual blood loss.

- Fecal occult blood testing is negative in approximately 50% of patients with gastrointestinal cancer. Therefore, a negative fecal occult blood test in the presence of iron-deficiency anemia should not discourage you from pursuing a thorough gastrointestinal workup.

- The mean corpuscular volume, red blood cell distribution width, and reticulocyte index are important parameters in the evaluation of anemia.

ANSWERS TO CASE 2:

What type of anemia does this patient have?

Profound normocytic anemia in a patient with normal WBC and platelet production suggests pure red cell aplasia (PRCA). This rare condition can be acute and self-limiting or chronic. The diagnosis can be confirmed with bone marrow biopsy (patients with PRCA have few RBC precursors but normal WBC and platelet precursors).

DISCUSSION

What is the most likely cause of PRCA?

The presence of an anterior mediastinal mass suggests the patient has a thymoma (rare neoplasm of the thymus). Confirm the diagnosis with CT-guided needle biopsy.

- Acute, self-limiting causes:
 - Viral infection (parvovirus B19, viral hepatitis): PRCA is more likely if the patient has underlying thalassemia or hemolytic anemia (e.g., sickle cell anemia (SCA))
 - Drugs:
 - Immune mediated injury (EPO)
 - Direct toxic effects (anti-epileptic drugs, INH, procainamide)
- Chronic causes (mnemonic: “Diamond TAIL”)
 - Diamond-Blackfan syndrome: lifelong PRCA that presents in the neonatal period; autosomal dominant inheritance.
 - Thymoma
 - Autoimmune disorders (particularly SLE)
 - Idiopathic

- Lymphoproliferative disorders (leukemia, lymphoma, MDS)

What would have been the most likely cause of PRCA if CXR were normal but the patient had a history of chronic renal failure (CRF) on hemodialysis and took lisinopril, atorvastatin,, insulin, and EPO?

Patients with CRF often require EPO to treat CRF-induced anemia (normocytic anemia with Burr cells on peripheral smear). Ironically, EPO can sometimes induce PRCA. Confirm the diagnosis by measuring anti-EPO antibodies. Treatment is to administer PRBC transfusions and discontinue EPO.

How would management differ if PRCA were caused by an autoimmune disorder?

First-line treatment of PRCA caused by autoimmune disorders is prednisone. Second-line treatment is cyclophosphamide.

ANSWERS TO CASE 3:

What is the next step in management?

By the second trimester of pregnancy, RBC volume increases by approximately 30%. However, patients have mild anemia (mean Hb 11.5 g/dL) because plasma volume increases by approximately 50%. Dilutional anemia of pregnancy is a normal physiological condition that does not require any treatment. Consider treatment only if the patient develops symptoms of anemia or laboratory findings of a pathological anemia (e.g., iron deficiency).

ANSWERS TO CASE 4:

What is the most likely diagnosis?

The patient with back pain has risk factors for malignancy (age >50 years and weight loss). The peripheral smear demonstrates rouleaux (RBCs stacked like coins), which occurs when a patient has increased serum protein. The most likely diagnosis is multiple myeloma (MM). MM is the neoplastic proliferation of a single plasma cell line to produce large amounts of monoclonal antibodies (M proteins), usually IgA or IgM. The disease is most common among elderly patients.

DISCUSSION

What are the clinical manifestations of MM?

Common clinical manifestations of MM with the mnemonic “I, CRAB”:

- Infections: Increased production of defective antibodies (immunoglobulins) and decreased production of normal immunoglobulins leads to decreased humoral immunity.
- Calcium: Malignant plasma cells release osteoclast-activating factor, which breaks down bone and leads to hypercalcemia.
- Renal failure: MM can cause chronic or acute renal failure. Most common causes are hypercalcemia and excretion of immunoglobulin light chains in the urine. In some patients, renal failure is caused by amyloidosis.
- Anemia: MM can cause replacement of bone marrow by malignant plasma cells, which leads to normocytic anemia. MM also causes normocytic ACD. Rouleaux is the characteristic finding on peripheral smear.
- Bones: Osteoclast-activating factor breaks down bone, which leads to bone pain (particularly in the chest and vertebrae) and pathological fractures. Classic x-ray finding is “punched out” lytic bony lesions.
- Hyperviscosity syndrome: Increased serum protein causes increased serum viscosity, which leads to easy bleeding, blurry vision, fatigue, hypoxia, and nonspecific neurological symptoms. Most common causes are Waldenström's macroglobulinemia and MM.

What are the next diagnostic steps?

Initial tests in the diagnostic workup besides CBC are serum chemistry, skeletal survey, serum protein electrophoresis (SPEP), and urine protein electrophoresis (UPEP). If diagnostic tests are suggestive, perform bone marrow biopsy to confirm the diagnosis. The Myeloma Working Group suggests three simplified criteria:

- End-organ damage attributable to MM (I, CRAB)
- SPEP or UPEP: increased M proteins (e.g., Bence Jones protein on UPEP)

Bone marrow biopsy: >10% clonal plasma cells
Skeletal survey: X-rays of the skull, axial skeleton, and proximal long bones are more sensitive than a bone scan.

Erythrocyte sedimentation rate, lactic acid dehydrogenase (LDH), C-reactive protein, and β 2-microglobulin levels are not helpful diagnostically (nonspecific); however, they help assess prognosis when the diagnosis is established.

How is MM treated?

MM is associated with a poor prognosis. Treatment is either chemotherapy or autologous stem cell transplant.

What would have been the most likely diagnosis if the patient had 2.7 g/dL of M proteins on SPEP or UPEP but was otherwise asymptomatic with normal CBC, serum chemistry, skeletal survey, and bone marrow biopsy?

The patient meets diagnostic criteria for monoclonal gammopathy of uncertain significance (MGUS):

- No signs of end-organ damage due to MM
- SPEP/UPEP: M-protein spike <3 g/dL

Bone marrow biopsy: $<10\%$ plasma cells. Obtain bone marrow biopsy in all patients with M-proteins >1.5 g/dL.

How is MGUS managed?

Repeat SPEP and UPEP after 6 months. If the level of M-proteins remains stable (\leftrightarrow), then monitor SPEP and UPEP annually because patients with MGUS have increased risk of MM.

Waldenström's macroglobulinemia: This rare, low-grade (indolent), non-Hodgkin's lymphoma (NHL), which causes an IgM M-protein spike, presents with lymphadenopathy, easy bleeding, hepatomegaly, splenomegaly, and hyperviscosity.

Causes of nonhemolytic normocytic anemia are ACD, PRCA, MM, chronic liver or kidney disease, dilutional anemia, endocrine disorders, and hemoglobinopathies.

ANSWERS TO CASE 5:

What is the most likely diagnosis?

In addition to macrocytes, the peripheral smear contains ovalocytes and hypersegmented neutrophils, which indicates that she has a megaloblastic anemia (Fig. 10-8). Atrophic glossitis and neurological signs indicate that the patient has vitamin B12

deficiency. Concurrent folate deficiency is also possible, so the next step is to measure serum levels of folic acid and vitamin B12.

DISCUSSION

What are common neurological signs of vitamin B12 deficiency?

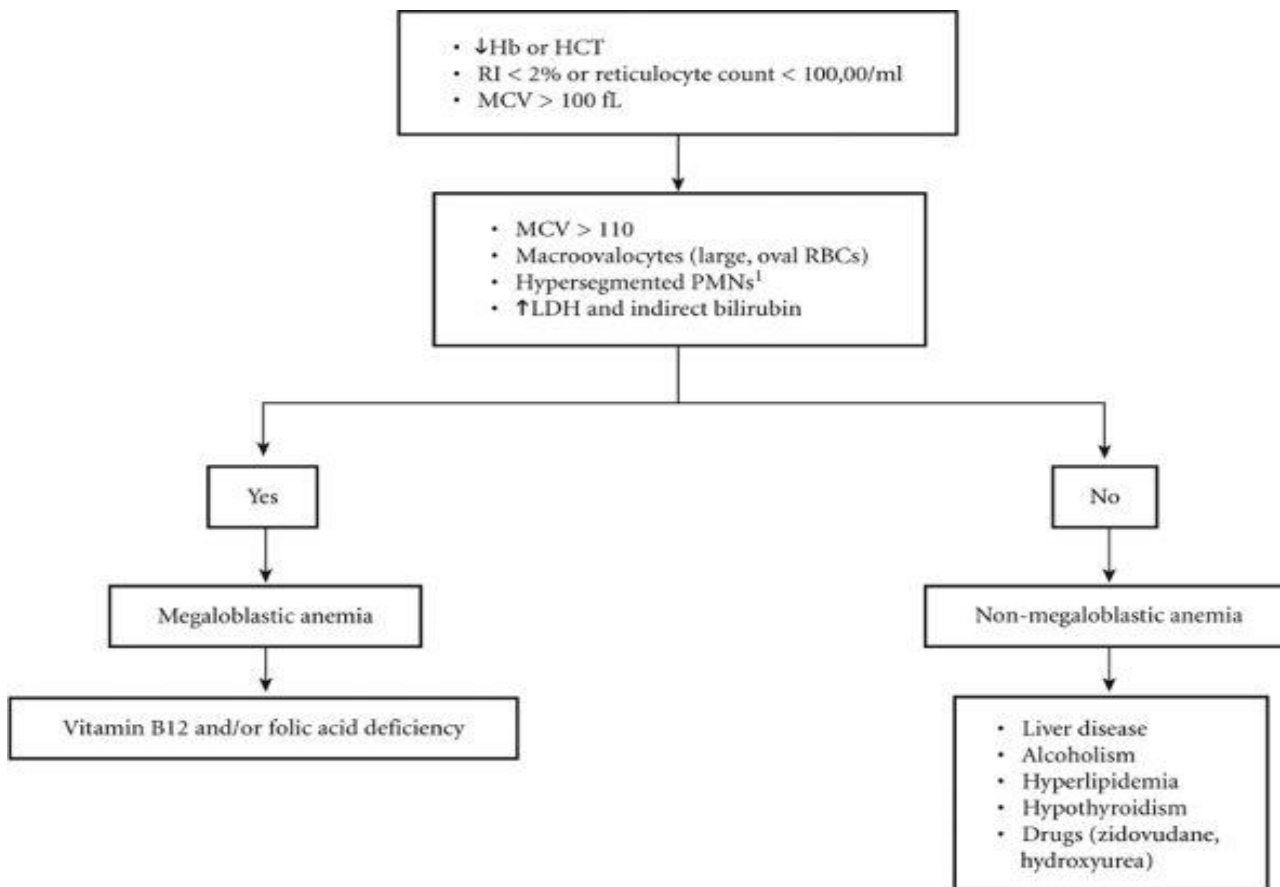
- Autonomic dysfunction: impotence and urinary or fecal incontinence
- Myelopathy: ataxia, spasticity, and loss of deep tendon reflexes
- Peripheral neuropathy: paresthesia, weakness, decreased vibration and position sense due to dorsal column degeneration
- Psychiatric: dementia, depression, psychosis, and short-term memory loss. (Check for vitamin B12 deficiency in any patient with unexplained dementia).

How should you interpret these values?

Serum vitamin B12 <200 pg/mL is diagnostic of vitamin B12 deficiency. Serum folate levels >4 mg/dL rule out folic acid deficiency. Serum vitamin B12 >300 pg/mL: no vitamin B12 deficiency. Serum vitamin B12 200 to 300 pg/mL: normal or subclinical deficiency.

How is vitamin B12 absorbed into the bloodstream?

Gastric acid cleaves vitamin B12 from other dietary proteins. Gastric parietal cells release intrinsic factor (IF), which binds to vitamin B12 in the stomach and duodenum. The IF-B12 complex facilitates absorption at the terminal ileum. This mechanism is responsible for 99% of vitamin B12 absorption.



¹≥ 5 % of PMNs with 5 lobes or ≥ 1 PMN with 6 lobes

What are the next steps in management?

First, administer oral or intramuscular vitamin B12 to prevent further neurological degeneration. Then, search for an underlying cause for vitamin B12 deficiency :

- Vegan diet: Dietary sources of vitamin B12 are meat, eggs, and dairy products, so vegans who do not take vitamin B12 supplements develop deficiency.
- Intestinal malabsorption: chronic pancreatitis, Crohn's disease, bowel resection, etc.
- Tea and toast diet: Consumption of a nutritionally poor diet is common among alcoholics and the elderly.
- Autoimmune gastritis (pernicious anemia): autoantibodies against parietal cells.
- Medications (chronic use); remember the medications with the mnemonic “PAM”:
 - PPIs: Decreased gastric acid leads to decreased cobalamin release from food.
 - Antibiotics: Non-gut flora overgrowth causes malabsorption.
 - Metformin.

- Intestinal tapeworm: *Diphyllobothrium latum* (fish tapeworm) was a notable cause in the past, but is less common today.
- Surgery: Gastrectomy leads to decreased gastric acid production. Also, any abdominal surgery can cause strictures or blind loops that result in bacterial overgrowth.

This patient with no obvious cause should have serum levels of anti-parietal cell and anti-IF antibodies measured. Positive antibodies are diagnostic of pernicious anemia (common in the elderly and patients with other autoimmune disorders). Treatment of pernicious anemia is lifelong vitamin B12 replacement (oral or intramuscular).

Schilling test: an older, uncommonly used test used to diagnose pernicious anemia.

Large oral doses are as effective as intramuscular doses of vitamin B12 in pernicious anemia because 1% of vitamin B12 is absorbed by an alternative mechanism.

ANSWERS TO CASE 6:

What is the most likely cause of macrocytic anemia in this patient?

Absence of neurological signs suggests that this patient's anemia is caused by folate rather than vitamin B12 deficiency. However, concurrent subclinical vitamin B12 deficiency is also possible.

DISCUSSION

What risk factors does this patient have for macrocytic anemia?

Chronic alcohol intake can cause nonmegaloblastic macrocytic anemia. Alcoholism also causes liver disease, which is associated with nonmegaloblastic anemia. Finally, malnutrition is common among alcoholic patients, which can lead to megaloblastic anemia because of folate and/or vitamin B12 (cobalamin) deficiency.

What is the next step in management?

Obtain both vitamin B12 and folic acid levels. It is important to rule out concurrent vitamin B12 deficiency because treatment of folic acid deficiency will correct the anemia even if the patient has vitamin B12 deficiency, but it will not stop progression of

neurological signs and symptoms. Serum vitamin B12 is 250 pg/mL, and serum folate is 2 ng/mL.

What is the next step in management?

The laboratory tests confirm folic acid deficiency. However, this patient with serum cobalamin between 200 and 300 pg/mL may or may not have subclinical vitamin B12 deficiency. The next step is to obtain homocysteine and methylmalonic acid (MMA). If further testing confirms isolated folic acid deficiency, treat with oral folic acid.

What are other important causes of folic acid deficiency?

In addition to malnutrition and malabsorption, folic acid deficiency can also result from pregnancy, hemolytic anemia, and drugs (trimethoprim-sulfamethoxazole, methotrexate, and phenytoin).

ANSWERS TO CASE 7:

What is the most likely diagnosis?

Ataxia and tremor are signs of cerebellar degeneration as a result of chronic alcohol abuse. Chronic alcohol ingestion can cause macrocytic anemia with a mean MCV of 105 dL. Unlike vitamin B12 deficiency, alcoholic cerebellar degeneration does not cause myelopathy, peripheral neuropathy, or megaloblastic anemia.

DISCUSSION

What are the next steps in management?

The next step is to measure serum vitamin B12 and folic acid levels to rule out concurrent deficiencies. Treatment of alcohol-induced macrocytic anemia is abstinence.

What would have been the most likely diagnosis if the patient with macrocytic nonmegaloblastic anemia had no history of alcohol use and presented with fatigue, difficulty concentrating, slow relaxation phase of deep tendon reflexes, and normal vitamin B12 and folic acid levels?

Fatigue, difficulty concentrating, and slow relaxation of deep tendon reflexes are features of hypothyroidism. The next step in this case is to obtain serum thyroid-stimulating hormone.

Sideroblastic anemia, cold agglutinin disease, MDS, and aplastic anemia occasionally cause macrocytic nonmegaloblastic anemia. Rarely, when there are a large number of reticulocytes, the red cells may be measured as macrocytic.

ANSWERS TO CASE 8:

What is the most likely diagnosis and your next step?

A 25-year-old African American man with a history of numerous pain crises is admitted for abdominal and bilateral lower extremity pain. He is febrile to 101°F, respiratory rate 25 breaths per minute, and slight tachycardia of 100 bpm. Lung examination reveals bronchial breath sounds and egophony in the right lung base. His oxygen saturation on 2 L/min nasal cannula is 92%. He is now complaining of chest pain, which is worse on inspiration. He has a leukocytosis, an elevated reticulocyte count, and a hemoglobin and hematocrit that are slightly lower than baseline. Sickle and target cells are seen on the peripheral smear.

- > Most likely diagnosis: Acute chest syndrome.
- > Next step: Chest radiograph and empiric antibiotic therapy.
- > Potential complications: Respiratory failure, possible death.

CLINICAL APPROACH

Pathophysiology

The molecular structure of a normal hemoglobin molecule consists of two alpha-globin chains and two beta-globin chains. Sickle cell anemia is an autosomal recessive disorder resulting from a substitution of valine for glutamine in the sixth amino acid position of the beta-globin chain. This substitution results in an alteration of the quaternary structure of the hemoglobin molecule. Individuals in whom only half of their beta chains are affected are heterozygous, a state referred to as *sickle cell trait*. When both beta chains are affected, the patient is homozygous and has sickle cell anemia. In patients with sickle cell disease, the altered quaternary structure of the hemoglobin molecule causes polymerization of the molecules under conditions of deoxygenation. These rigid polymers distort the red blood cell into a sickle shape, which is characteristic of the disease. Sickling is promoted by hypoxia, acidosis, dehydration, or variations in body

temperature.

Epidemiology

Sickle cell anemia is the most common autosomal recessive disorder and the most common cause of hemolytic anemia in African Americans. Approximately 8% of African Americans carry the gene (ie, sickle cell trait), with one in 625 affected by the disease.

Complications of Sickle Cell Disease

Acute painful episodes, also known as *pain crisis*, are a consequence of microvascular occlusion of bones by sickled cells. The most common sites are the long bones of the arms, legs, vertebral column, and sternum. Acute painful episodes are precipitated by infection, cold exposure, dehydration, venous stasis, or acidosis. They usually last 2 to 7 days.

Infections are another complication. Patients with sickle cell disease are at greater risk for infections, especially with encapsulated bacterial organisms. Autoinfarction of the spleen occurs during early childhood secondary to microvascular obstruction by sickled red blood cells. The spleen gradually regresses in size and by age 4 years is no longer palpable. As a consequence of infarction and fibrosis, the immunologic capacity of the spleen is diminished. Patients with sickle cell disease are at greater risk for pneumonia, sepsis, and meningitis by encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. For the same reason, patients with sickle cell disease are at greater risk for osteomyelitis with *Salmonella* spp.

Acute chest syndrome is a vasoocclusive crisis within the lungs and is associated with infection or pulmonary infarction. Patients with acute chest syndrome will present with hypoxia, dyspnea, fever, chest pain, and progressive pulmonary infiltrates on radiography. These episodes may be precipitated by pneumonia causing sickling in the infected lung segments, or, in the absence of infection, intrapulmonary sickling can occur as a primary event. It is virtually impossible to clinically distinguish whether or not infection is present; thus, empiric antibiotic therapy is used.

Aplastic crisis occurs secondary to viral suppression of red blood cell precursors, most often by parvovirus B19. It occurs because of the very short half-life of sickled red blood cells and consequent need for brisk erythropoiesis. If red blood cell production is

inhibited, even for a short time, profound anemia may result. The process is acute and usually reversible, with spontaneous recovery.

Other complications of sickle cell disease include hemorrhagic or ischemic stroke as a result of thrombosis, pigmented gallstones, papillary necrosis of the kidney, priapism, and congestive heart failure.

Treatment

The mainstay of treatment of pain crisis is hydration and pain control with nonsteroidal anti-inflammatory agents and narcotics. It is important to also provide adequate oxygenation to reduce sickling. One must search diligently for any underlying infection, and antibiotics are often used empirically when infection is suspected. Acute chest syndrome is treated with oxygen, analgesia, and antibiotics. Sometimes exchange transfusions are necessary. In general, blood transfusions may be required for aplastic crisis, for severe hypoxia in acute chest syndrome, or to decrease viscosity and cerebral thrombosis in patients with stroke. Transfusion does not shorten the duration of pain crisis. To protect against encapsulated organisms, all patients with sickle cell disease should receive penicillin prophylaxis and a vaccination against pneumococcus. Hydroxyurea is often used to reduce the occurrence of painful crisis by stimulating hemoglobin F production and thus decreasing hemoglobin S concentration, and should be considered in patients who have repeated episodes of acute chest syndrome, or frequent severe pain crises. The antineoplastic agent 5-deoxyazacytidine (decitabine) may also elevate levels of hemoglobin F without excessive side effects.

Comprehension Questions

3.1 Which of the following therapies would most likely decrease the number of sickle cell crises?

- A. Hydroxyurea
- B. Folate supplementation
- C. Prophylactic penicillin
- D. Pneumococcal vaccination

For the following questions (3.2 to 3.4) choose the finding (A-E) that best matches with the syndrome to which it is commonly associated in persons with sickle cell anemia.

- A. *Salmonella* spp

- B. *Streptococcus pneumoniae*
- C. Parvovirus B19
- D. Fat embolus
- E. Hematuria

3.2 Aplastic crisis

3.3 Osteomyelitis

3.4 Pneumonia

ANSWERS

3.1 A. Hydroxyurea and decitabine may decrease the incidence of sickle cell crises by increasing levels of hemoglobin F.

3.2 C. Parvovirus B19 is associated with aplastic crisis, especially in individuals with sickle cell disease.

3.3 A. Patients with sickle cell disease are at risk for *Salmonella* osteomyelitis.

3.4 B. *Streptococcus pneumoniae* is the most common causative agent for pneumonia.

Clinical Pearls

- Treatment of an acute painful episode in sickle cell disease includes hydration, narcotic analgesia, adequate oxygenation, and search for underlying infection.

- Acute chest syndrome is characterized by chest pain, cough, dyspnea, fever, and radiographic pulmonary infiltrate; it can be caused by pneumonia, vasoocclusion, or pulmonary embolism.

- Blood transfusion may be required for aplastic crisis, for severe hypoxemia in acute chest syndrome, or to decrease viscosity and cerebral thrombosis in patients with stroke.

- Hydroxyurea and decitabine increase hemoglobin F production (decreasing hemoglobin S concentration) and thus reduce the frequency of pain crises and other complications.

ANSWERS TO CASE 9:

What is the most likely cause of hemolytic anemia in this patient?

Glucose 6 phosphate dehydrogenase (G6PD) deficiency is the most likely diagnosis in this patient with bite cells and Heinz bodies on peripheral smear (see Table 10-3). This X-linked disorder occurs in 10% of African-American men. G6PD deficiency is typically asymptomatic unless the patient undergoes oxidative stress (infection, diabetic ketoacidosis, and certain sulfa drugs like trimethoprim-sulfamethoxazole).

Favism: Fava bean ingestion can cause severe hemolysis in this subtype of G6PD deficiency, which occurs mainly in Mediterranean men.

DISCUSSION

What are the causes of hemolytic anemia?

Reticulocyte count is typically >4% to 5% in hemolytic anemia. There are several ways to categorize hemolytic anemia. One way is to categorize them on the basis of whether the defect is intrinsic or extrinsic:

- **Intrinsic:** Intracorpuscular defect (i.e., defective enzyme, membrane protein, or Hb) leads to formation of RBCs that are easily prone to intravascular destruction. With the exception of paroxysmal nocturnal hemoglobinuria (PNH), intrinsic hemolytic anemias are all hereditary.
- **Extrinsic:** Acquired causes such as autoantibodies, trauma, infections, or splenic entrapment cause intravascular and extravascular RBC destruction.

Other ways to categorize hemolytic anemia are:

- Inherited versus acquired
- Intravascular versus extravascular
- **Intravascular hemolysis:** Hemolysis in the bloodstream can cause urinary hemosiderin (pink) and schistocytes on peripheral smear.

Extravascular hemolysis: The spleen or liver “pluck” out the RBCs. Splenomegaly and spherocytes are commonly seen.

All types of hemolysis can cause jaundice, increased indirect bilirubin, increased

LDH, ↓ haptoglobin.

What is the next step in management?

The acute hemolytic anemia is usually self-limited and resolves with supportive care. In the long term, the key recommendation is to avoid precipitants.

How can you confirm the diagnosis?

G6PD assays that demonstrate reduced NADPH formation can confirm the diagnosis. The test is often falsely negative during acute hemolysis because the defective RBCs have been lysed. Consider testing this patient 2 to 3 months after the acute episode.

ANSWERS TO CASE 10:

What is the diagnosis?

The patient has hereditary spherocytosis (HS). In this autosomal dominant condition, abnormalities in RBC membrane proteins lead to decreased RBC surface area but not RBC volume. As a result, RBCs assume a spherical shape. Spherical RBCs become trapped in the spleen and are destroyed by splenic macrophages. The preferred treatment for anemic patients with HS is splenectomy. Gallstones: This common complication of HS due to chronic hyperbilirubinemia can be prevented by splenectomy.

DISCUSSION

What is the next step in management?

The peripheral smear contains numerous spherocytes. Both hereditary spherocytosis (HS) and warm autoimmune hemolytic anemia (AIHA) can cause increased MCHC and spherocytosis. Obtain osmotic fragility and Coomb's test to distinguish between these two disorders. Osmotic fragility test is positive, and Coomb's test is negative.

- Positive Coomb's test: RBCs agglutinate when antibodies or complement is added to blood sample.
- Positive osmotic fragility test: RBCs rupture easily when exposed to dilute saline.

ANSWERS TO CASE 11:

What is the diagnosis?

The patient has warm autoimmune hemolytic anemia (AIHA). Important causes of warm AIHA can be remembered with the mnemonic “DIAL”: Drugs, (e.g., penicillin), Idiopathic, Autoimmune disorders (particularly SLE), and Lymphoproliferative disorders (particularly chronic lymphocytic leukemia).

DISCUSSION

What is the next step in management?

First-line therapy for warm AIHA is PRBCs (if the patient is unstable) and urgent systemic corticosteroids. Also treat the underlying cause. If hemolytic anemia persists, consider splenectomy.

ANSWERS TO CASE 12:

What diagnosis should you suspect?

Hemolytic anemia and dark purple discoloration of the distal extremities in a patient with infectious mononucleosis should raise suspicion for cold autoimmune hemolytic anemia (AIHA) (cold agglutinin disease). Other important causes of cold AIHA are mycoplasma pneumonia infection and lymphoproliferative disorders. Many cases are idiopathic.

DISCUSSION

What is the next step in management?

First-line therapy for warm AIHA is PRBCs (if the patient is unstable) and urgent systemic corticosteroids. Also treat the underlying cause. If hemolytic anemia persists, consider splenectomy.

ANSWERS TO CASE 13:

What diagnosis should you suspect?

Episodes of dark urine on waking along with hemolytic anemia should raise suspicion for PNH. Urinalysis demonstrates hemoglobinuria, which increases the likelihood of this rare condition. Confirm the diagnosis using flow cytometry to detect deficiency of GPI-linked proteins. Flow cytometry confirms the diagnosis.

DISCUSSION

1. What are possible complications of PNH?

Remember complications of PNH with the acronym “TERM”:

- Thrombosis: PNH increases risk of venous thrombosis in almost every organ (e.g., cerebral veins, hepatic vein, etc.).
- Esophageal spasm and Erectile dysfunction: One possible mechanism is that free plasma Hb soaks up nitric oxide (smooth muscle relaxant).
- Renal failure: PNH can cause acute renal failure as a result of massive hemoglobinuria or CRF from iron overload as a result of chronic hemolytic anemia.
- MDS and leukemia: GPI-linked protein deficiency arises in hematopoietic stem cells, so patients have increased risk of MDS and leukemia.

2. How is anemia of PNH treated?

First-line therapy is supportive care (iron and folic acid supplements, PRBCs when necessary). Options for patients with severe anemia include systemic corticosteroids, EPO, danazol (androgenic hormone), eculizumab (anti-complement antibody), and stem cell transplantation.

ANSWERS TO CASE 14:

What is the diagnosis?

Suspect plasmodium infection (malaria) when a patient with a history of travel to an endemic area presents with fever and hemolytic anemia. This infection is transmitted by the Anopheles mosquito. Giemsa-stained thin and thick smears showing the parasites inside RBCs confirm the diagnosis.

DISCUSSION

What species of plasmodium is most likely to have infected this patient?

Noncyclical fever and symptomatic hemolytic anemia is most likely caused by Plasmodium falciparum infection. P. vivax, P. ovale, and P. malariae tend to cause cyclical fever (temperature spikes every 49 to 72 hours) and less severe hemolytic

anemia.

How is *P. falciparum* infection treated?

Most cases of *P. falciparum* malaria are resistant to chloroquine. The most commonly prescribed regimen is quinine sulfate plus doxycycline or clindamycin. Alternative options are atovaquone-proguanil and mefloquine.

Primaquine: G6PD deficiency was first discovered when this older antimalarial drug caused hemolytic anemia in African-American soldiers during World War II.

Babesiosis: This uncommon parasite infection is transmitted by the deer tick. Clinical manifestations are similar to malaria. Classic finding on Giemsa-stained peripheral smear is a tetrad of organisms inside RBCs. Treat with quinine + clindamycin or atovaquone + azithromycin.

ANSWERS TO CASE 15:

What disorders can cause this pattern?

The blood smear of this anemic patient demonstrates microcytic hypochromic RBCs with basophilic stippling (dark-blue granular inclusions in RBCs). This pattern can result from lead poisoning, thalassemia, and sideroblastic anemia.

DISCUSSION

What is the most likely diagnosis in this patient?

The patient most likely has lead poisoning. Common causes in the United States are occupational exposure (to paint, wires, car radiators, etc.) and moonshine consumption. Remember the clinical manifestations of severe lead poisoning (serum level >80 $\mu\text{g/dL}$) with the mnemonic “LEAD”:

- Lead lines: bluish colored line at the gum–tooth border (specific but not sensitive)
- Encephalopathy: decreased short-term memory and concentration
- Abdominal pain (colicky), arthralgias, and anemia (with basophilic stippling)
- Drops: Wrist or foot drop

What is the next step in management?

Obtain a serum lead level to confirm the diagnosis. The first-line measure in any patient with increased serum lead content is to remove the offending agent (in this case,

moonshine). Lead chelation with calcium EDTA or succimer is indicated in the following situations:

- Serum lead ≥ 80 $\mu\text{g/dL}$: Use lead chelation in any patient.
- Serum lead 60 to 80 $\mu\text{g/dL}$: Use lead chelation in any symptomatic patient.
- Serum lead 40 to 60 $\mu\text{g/dL}$: Consider lead chelation if symptoms persist for >2 weeks despite removing the offending agent.

ANSWERS TO CASE 16:

What is the most likely diagnosis in this patient?

Considering the results of this patient's complete blood count and peripheral blood smear, he has ANLL. The granular myelocytes and monocytes in the smear and the clinical evidence of extramedullary leukemic infiltration (gingival hypertrophy) point to a diagnosis of M4, or acute myelomonocytic leukemia. Examination of bone marrow specimens using special stains and chromosomal analysis can help confirm this diagnosis.

How is the ANC calculated, and what is it in this patient?

To calculate the ANC, multiply the total white blood cell count by the percentage of polymorphonuclear leukocytes plus the percentage of band forms. In this case, the patient has 17,200 white blood cells, with 2% polymorphonuclear leukocytes and 1% band forms, or: $17,200 (0.02 + 0.01) = 516$ absolute neutrophils.

Of what importance is the ANC?

The ANC furnishes a rough estimate of the patient's ability to fight infection. A patient with an ANC of less than 500 is considered neutropenic and very susceptible to overwhelming infection. This patient, with an ANC of approximately 500, fever, and a presumed diagnosis of acute leukemia, falls into this category. Careful examination, together with cultures of blood, sputum, oral lesions, and other possible sites of infection, should be done quickly, and the patient started on broad-spectrum antibiotics immediately. Any delay in the workup or institution of antibiotics may result in overwhelming and possibly fatal infection. Cultures are often negative in neutropenic patients, although clinically they appear to be septic and respond to antibiotics.

Do the evaluation findings point to any specific infections?

This patient complains of midchest pain on swallowing and physical examination reveals white oral plaques. A presumptive diagnosis of Candida esophagitis can be made on the basis of these findings, and the patient should be started on antifungal agents as well as broad-spectrum antibacterial antibiotics. Neutropenic patients are susceptible to opportunistic infections, and candidiasis is very common in them.

What would you expect this patient's bone marrow to show?

The bone marrow in this patient with ANLL would likely exhibit hypercellularity, with cellular elements often constituting 90% or more of the marrow. The numbers of red blood cell precursors and megakaryocytes will be decreased. The morphology may be normal, or there may be dyserythropoiesis (asynchronous maturing of the nuclear and cytoplasmic elements). The marrow will primarily show a monotonous pattern of cells similar to those seen in the peripheral smear. Flow cytometry should show cell surface markers indicative of immature myeloid cells with monocytoid characteristics. The chromosome analysis may show an abnormality such as monosomy 7 (especially if the patient had myelodysplasia), but will not show the abnormalities associated with, for example, M3 leukemia (Table 7-1). Recent studies suggest complex karyotypes in patients older than 60 years, that is, three or more aberrations have decreased response to therapy and based on comorbid factors these patients should be considered for investigational therapy or supportive care.

Should a lumbar puncture be performed in this patient?

This patient has a presumptive diagnosis of acute myelomonocytic leukemia. Lumbar punctures are routinely done in cases of ALL and ANLL-M4 because these leukemias are associated with meningitis. Nevertheless, any patient with acute leukemia and symptoms of meningitis or cranial nerve palsies should undergo a diagnostic lumbar puncture, regardless of the leukemic type.

However, the platelet count in this patient is only 14,000/mm³, and lumbar punctures should not be performed when the platelet count is less than 50,000/mm³ because of the risk of hemorrhage. Therefore, platelet transfusions must be given before attempting lumbar puncture to bring the count to 50,000/mm³ or more.

DISCUSSION

What is the pathology of acute leukemia?

Acute leukemia is the abnormal clonal expansion of blood cell precursors. The abnormality may occur at different stages of maturation of the cell, and this explains the different types of leukemia. Acute leukemia is usually a rapidly progressive disease, although there are occasional patients whose disease remains stable for weeks or even months. In general, however, it is not the leukemic cells per se that cause the morbidity and mortality in this disorder, but a lack of normal blood cells, resulting in anemia, thrombocytopenia, and leukopenia. This is brought about by the leukemic cells crowding out the normal cells in the bone marrow. Other data suggest that especially myeloid leukemia cells have an inhibitory effect on normal marrow cells. This lack of normal cells may therefore lead to life-threatening hemorrhage and infection.

What are the primary classifications of acute leukemia, and why is this differentiation important?

The primary classifications of acute leukemia are ALL and acute nonlymphocytic leukemia (ANLL, myeloid leukemia). The distinction is important because the therapy differs for each type (see answer to question 6). The overall ratio of ALL to ANLL is 1 : 6. ALL occurs most commonly in children, whereas ANLL more commonly affects adults.

What is the FAB classification of acute leukemia?

The FAB classification (Table 16-1) is based largely on the morphologic and histochemical characteristics displayed by the leukemic cells, as well as on the nature of the cell surface antigens and cytogenetic features. This information may lead to changes in patient management, either by directing the course of therapy or by defining the prognosis better. Table 16-1 also includes molecular changes that may affect therapy, but more often affect response to therapy.

Table 16-1 The French, American and British (FAB) Classification of Acute Leukemia

FAB classification	Description	Comment	Associated Chromosome Abnormalities
<u>ALL</u>			

L1	Small blasts with little cytoplasm, little cell-to-cell variation	Most common morphology in childhood ALL	12 : 21
L2	Larger cells with greater amount of cytoplasm, greater cell-to-cell variation; irregular nuclei with multiple nucleoli	Most common morphology in adult ALL	
L3	Large cells, strongly basophilic cytoplasm; often with vacuoles; nucleoli often multiple	Common in leukemia associated with Burkitt's lymphoma	8 : 14 (i.e., Burkitt's lymphoma)
<u>ANLL</u> M1	Acute myelocytic leukemia: cells very undifferentiated with only occasional granules		
M2 ^b	Acute myelocytic leukemia: cells more differentiated with granules, and often with Auer rods		8:21 ^a
M3	Acute promyelocytic leukemia: hypergranular promyelocytes	Often associated with disseminated intravascular coagulation, responds to differentiation agents	15:17 ^a
M4 ^b	Acute myelomonocytic leukemia: both monocytes and myelocytes predominate	Often occurs with extramedullary infiltration (gingival hypertrophy, leukemia cutis, and meningeal leukemia)	Inversion ^a 16
M5 ^b	Acute monocytic leukemia: monoblasts with relatively agranular cytoplasm	Usually affects children or young adults	
M6	Erythroleukemia: red blood cell precursors predominate, but myeloid blasts may also be seen	Also called Di Guglielmo's syndrome	
M7	Megakaryocytic leukemia: extremely variable morphology; may be diagnosed with monoclonal antibodies to platelets	Rare form of leukemia; very poor prognosis	

^a*These karyotypes are generally considered to be more likely to respond to chemotherapy.*

^b*When M2, M4, and M5 leukemia occur after long-term myelodysplasia 11q 2; 3, monosomy 7 and other abnormal karyotypes suggest decreased response to chemotherapy.*

ALL, acute lymphocytic leukemia; ANLL, acute nonlymphocytic leukemia.

Are there any predisposing factors associated with acute leukemia?

Certain genetic and environmental factors may predispose a person to acute leukemia. Many chromosomal alterations exist in the setting of the leukemias. The incidence of leukemia is increased in patients with congenital disorders associated with aneuploidy, such as Down syndrome, congenital agranulocytosis, celiac disease, Fanconi syndrome, and von Recklinghausen's neurofibromatosis. Environmental factors implicated in the development of acute leukemia, particularly ANLL, include exposure to ionizing radiation and chemicals. Occupations and therapy that involve radiation exposure are known to increase the risk for acquiring acute leukemia. Chemicals, particularly the industrial use of benzene, and several therapeutic drugs (chloramphenicol, phenylbutazone, melphalan, chlorambucil, and others) are causal factors in acute leukemia. The findings from animal studies link certain viruses with acute leukemia; however, it is uncertain which viruses are actually an etiologic factor in human forms of leukemia, except for lymphomas caused by viruses that develop into a form of ALL.

What workup and other preparations should be done before initiating antileukemic therapy?

The pretreatment evaluation should include the patient's medical and work history, especially the nature of any radiation or chemical exposure. A physical examination should include the patient's temperature, plus examination of the optic fundi, lymph node areas, oropharynx and gingivae, perianal area, and cranial nerves. Laboratory studies should consist of a complete blood count with differential (the physician should examine the smear), as well as a blood chemistry profile that includes the measurements of uric acid and lactate dehydrogenase (LDH). Bone marrow aspirates and biopsy specimens should be obtained, and investigations should include cytogenetic studies. A transfusion workup should include human lymphocyte antigen (HLA) typing. Lumbar puncture should be performed in all patients suspected of having ALL or ANLL-M4, and the cerebrospinal fluid specimen should be subjected to the usual studies, plus cytologic analysis. A dental examination should be performed.

In addition, the patient's condition should be stabilized before antileukemic therapy

is initiated. Hemorrhage and infection should be brought under control. Greatly elevated myeloblast counts (e.g., $>50,000/\text{mm}^3$) that occur in the setting of ANLL can lead to pulmonary complications as well as fatal intracerebral leukostasis and hemorrhage. Cranial irradiation, hydroxyurea, and leukapheresis have all been used to decrease the numbers of circulating leukemic cells rapidly, and hence reduce the risk of complications. (Because of the physical properties of the lymphocytic leukemic cell, this is rarely a problem in patients with ALL.)

Renal damage stemming from urate nephropathy may exist at the time of presentation or may occur with therapy, therefore urine alkalinization may prevent the need for dialysis. Patients should receive allopurinol (300 to 600 mg) for at least 24 hours before therapy to reduce the uric acid load, and this treatment should be continued until leukopenia and bone marrow hypocellularity have been achieved.

What are induction, consolidation, maintenance chemotherapy, and meningeal prophylactic therapy, and how do they differ in the treatment of ALL and ANLL?

These are the phases of therapy used for acute leukemia. Induction therapy is usually the initial therapy and is intended to accomplish complete remission (that is, no signs or symptoms of disease, normal blood counts, and no evidence of leukemia, i.e., $<5\%$ blasts in the bone marrow). This therapy is usually administered on an inpatient basis, and is very toxic. Consolidation therapy is given after complete remission is achieved. It is similarly toxic, and consists of either the same drugs as those used in induction therapy or different ones. Its object is to reduce the now clinically undetectable leukemic cell mass as much as possible. Maintenance therapy is usually given on an outpatient basis and is less toxic, although complications of therapy can and do arise. This phase usually lasts for 2 to 3 years. Meningeal prophylactic therapy is given by means of lumbar puncture or through a reservoir placed under the scalp that cannulates the third ventricle. Its goal is to reduce the recurrence rate of leukemia in the central nervous system (CNS), which is considered a sanctuary site.

All four therapy phases are used in ALL. In the treatment of ANLL, there is controversy over the use of maintenance therapy, although a second consolidation phase may be used. Meningeal prophylaxis is not used in the treatment of adult ANLL. However, CNS leukemia is more common in childhood ANLL, and prophylaxis is

sometimes used in this setting. In general, the response to treatment and the prognosis are better in patients with ALL than in those with ANLL.

What are the risks associated with antileukemic therapy, and what results can be expected?

As already noted, acute leukemia is usually a rapidly progressive disease that is fatal without therapy. Because the therapy itself is toxic, the mortality rate during induction therapy for ANLL may reach as high as 20%. Some toxicities are specific to the drug used, and these are not discussed here. Nearly all therapies provoke nausea and vomiting, which can be controlled with medications. More significantly, antileukemic therapy is intended to deplete the bone marrow, with subsequent repopulation by normal cells. During this period of depletion, the patient becomes severely thrombocytopenic and must be supported by platelet transfusions (given prophylactically at various intervals to keep the platelet count above 10,000) and, usually, also by red blood cell transfusions.

Patients also become severely leukopenic, and this makes them very susceptible to infection. The typical signs and symptoms of infection (pus and purulent sputum) are often due to the actions of granulocytes, so infection is often subtle. The oral mucosa and perirectal areas are commonly overlooked sites of infection. Fever in a neutropenic patient must be considered infectious by origin, until proved otherwise. When this happens, examination and cultures should be carried out and broad-spectrum antibiotic therapy started quickly. Antifungal agents are usually added if no improvement is seen after 4 to 7 days of fever. The patient must be monitored carefully and treated for herpes virus infection because disseminated infection can be rapidly fatal.

If the leukemic cell burden is great, antileukemic therapy may precipitate the tumor lysis syndrome, caused by the rapid release of cell degradation products. It is characterized by hyperuricemia (causing urate nephropathy), hyperkalemia, hyperphosphatemia, and hypocalcemia. Advance recognition of patients at risk and subsequent treatment with vigorous hydration, allopurinol, and urine alkalinization 24 to 48 hours before the start of chemotherapy can usually prevent the syndrome. These patients must have their electrolyte, uric acid, phosphorus, calcium, and creatinine status repeatedly checked. Any metabolic abnormalities should be corrected and, if necessary, renal dialysis instituted early. Once the leukemic cell burden is decreased and

degradation products cleared, the syndrome resolves.

Most children with ALL respond to therapy and achieve long-term survival. Although 90% of adults with ALL experience complete remission with initial therapy, the median remission duration ranges from 48 to 60 months, depending on the study. Median survival is 3 to 5 years. However, approximately one third of all patients achieve long-term disease-free survival. Late recurrences are rare.

Patients with ANLL face a worse prognosis. Approximately 75% experience complete remission, but most cases recur within 36 months. Of those who achieve complete remission, 20% to 25% show long-term disease-free survival. Bone marrow or stem cell transplantation with high-dose chemotherapy is often used, but is still under investigation as a therapy after the initial chemotherapy in ALL. The timing of transplantation (first remission, first relapse, or second remission), especially in ALL, is controversial. In ANLL, bone marrow transplantation (bone marrow rescue) with high-dose chemotherapy after a first remission has been associated with higher long-term survival rates. Older age (>40 years), use of unrelated donors, and evidence for residual disease at the time of transplantation reduce the efficacy of this treatment approach.

ANSWERS TO CASE 17:

A 54-year-old man with ALL is receiving immunosuppressive chemotherapy. He now presents with fever. He has no respiratory or abdominal symptoms, a clear chest X-ray, and an absolute neutrophil count of $286/\text{mm}^3$. He has redness and purulence along the tract of the vascular catheter.

> Most likely diagnosis: Neutropenic fever and infected vascular catheter.

> Next therapeutic step: After drawing blood cultures, the patient should undergo broad-spectrum intravenous antibiotic administration, including coverage for gram-positive organisms such as *Staphylococcus* spp. The vascular catheter should be removed, if possible.

ANALYSIS

Objectives

1. Be familiar with the possible sources of infection in a neutropenic patient.

2. Learn the management of a patient with neutropenic fever.
3. Be able to diagnose and treat a catheter-related infection.
4. Understand the techniques to prevent infection in immunosuppressed patients, including granulocyte colony-stimulating factor (G-CSF) and vaccination of household contacts.

Considerations

This patient is being treated for a hematologic malignancy with combination chemotherapy, which has a common side effect of leukopenia and, especially, neutropenia. Generally, the nadir of the white cell count occurs 7 to 14 days after the chemotherapy. This patient certainly has neutropenia, defined as an absolute neutrophil count less than 500 cells/mm³. Infection in this immunosuppressed condition is life-threatening, and immediate antibiotic coverage is paramount. Neutropenic patients are at risk for a variety of bacterial, fungal, or viral infections, but the most common sources of infection are gram-positive bacteria from the skin or oral cavity or gram-negative bacteria from the bowel. Infection of the indwelling catheter, as in this individual, is common. Rapid institution of empiric antibiotic therapy is critical while attempts to find a source of infection are in progress. Because the tract of the catheter is infected, the line usually must be removed.

APPROACH TO NEUTROPENIC FEVER

DEFINITIONS

CVC: Central venous catheter.

FEVER: Single oral temperature measurement more than or equal to 101°F (38.3°C) or a temperature more than or equal to 100.4°F (38.0°C) for 1 hour or more.

MUCOSITIS: Breakdown of skin and mucosal barriers as a result of chemotherapy or radiation. Mucositis can result in bacteremia or fungemia. **NEUTROPENIA:** Neutrophil count less than 500 cells/mm³ or a count less than 1000 cells/mm³ with a predicted decrease to less than 500 cells/mm³.

CLINICAL APPROACH

Fever in a neutropenic patient with cancer should be considered a medical emergency. Approximately 5% to 10% of cancer patients will die of neutropenia-associated infection. Individuals with a hematologic malignancy (leukemias or lymphomas) are at even greater risk for sepsis as a result of lymphocyte or granulocyte dysfunction or because of abnormal immunoglobulin production. Chemotherapy often causes further bone marrow suppression and neutropenia. The incidence of an occult infection in a neutropenic patient increases with the severity and duration of the neutropenia (>7-10 days). Some neutropenic patients (eg, the elderly or those receiving corticosteroids) may not be able to mount a febrile response to infection; thus, any neutropenic patient showing signs of clinical deterioration should be suspected of having sepsis.

The typical signs and symptoms of infection noted in immunocompetent patients are the result of the host's inflammatory response and may be minimal or absent in neutropenic patients. Soft tissue infections may have diminished or absent induration, erythema, or purulence; pneumonia may not show a discernible infiltrate on a chest radiograph; meningitis may not reveal cerebrospinal fluid (CSF) pleocytosis; and urinary tract infection may be present without pyuria.

Empirical antibiotic therapy should be administered promptly to all neutropenic patients at the onset of fever. Historically, gram-negative bacilli, mainly enteric flora, were the most common pathogens in these patients. Because of their frequency and because of the high rate of mortality associated with gram-negative septicemia, empiric coverage for gram-negative bacteria, including *Pseudomonas aeruginosa*, is almost always indicated for neutropenic fever. Currently, as a consequence of frequent use of CVCs, gram-positive bacteria now account for 60% to 70% of microbiologically documented infections. Other clues that the infection is likely to be a gram-positive organism include the presence of obvious soft tissue infection, such as cellulitis or oral mucositis, which causes breaks in the mucosal barriers and allows oral flora to enter the bloodstream. If any of these factors are present, an appropriate agent, such as vancomycin, should be added to the regimen. If patients continue to be febrile despite antibacterial therapy, empiric antifungal therapy with either fluconazole or amphotericin B should be considered. Figure 17-1 shows a useful algorithm for patient management.

Central venous catheters are in widespread use and are a common site of infection in hospitalized patients and in those receiving outpatient infusion therapy. Infection may occur as a consequence of contamination by gram-positive skin flora or by hematogenous seeding, usually by enteric gram-negative organisms or *Candida* spp. Erythema, purulent drainage, and induration are evidence of infection. A variety of CVCs are frequently used, with different rates of infection.

The two main decisions impacting suspected catheter-related infection are (1) whether the catheter is really the source of infection and, if it is, (2) must the catheter be removed or can the infection be cleared with antibiotic therapy? Most nontunneled or implanted catheters should be removed. For the more permanent catheters, the decision to remove the catheter depends on the patient's clinical state, identification of the organism, and the presence of complications such as endocarditis or septic venous thrombosis. Infected catheters may produce several manifestations, such as infections of the subcutaneous tunnel, infection at the exit site, or catheter-related bacteremia and sepsis. Generally, erythema overlying the subcutaneous tract of a tunneled catheter necessitates catheter removal. Leaving the catheter in place may result in severe cellulitis and soft tissue necrosis. If there is only erythema at the exit site, it may be possible to salvage the line using antibiotics, usually vancomycin through the CVC. Coagulase-negative staphylococci, such as *Staphylococcus epidermidis*, is the most common organism causing line infections.

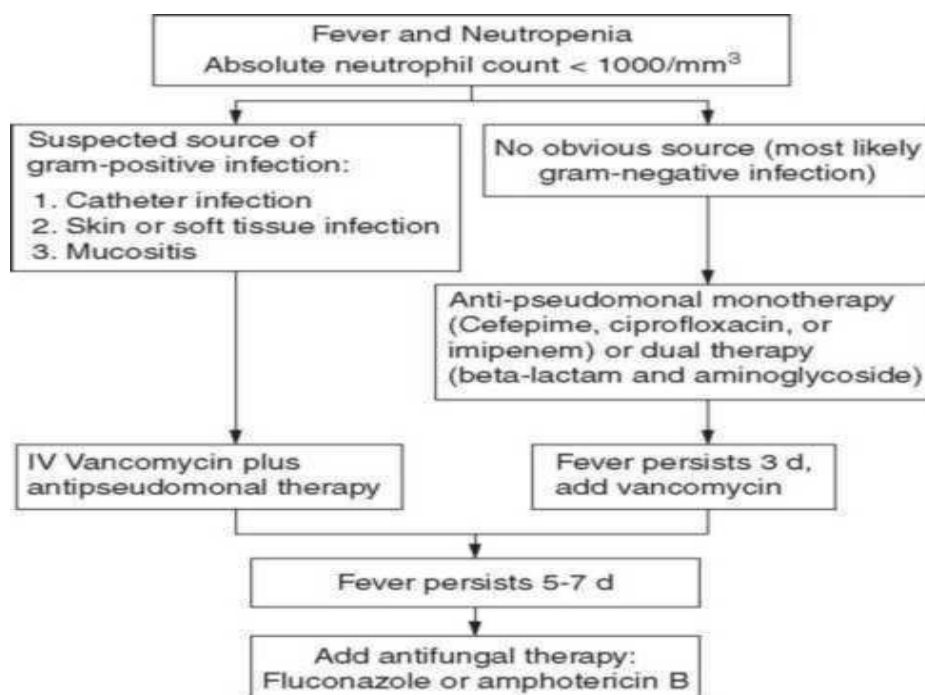


Figure 17-1. Algorithm of a suggested approach to neutropenic fever.

In the absence of obvious tunnel or exit-site infection, authorities recommend obtaining two or more blood cultures to try to diagnose catheter-related bacteremia. Catheter-related infection is suspected when a patient has two or more positive blood cultures obtained from a peripheral vein, clinical manifestation of infection (eg, fever, chills, and/or hypotension), and no apparent source for bloodstream infection except for the catheter. In some institutions, quantitative blood cultures are obtained, that is, counting colony-forming units (CFUs), with the idea that heavier colony counts will be obtained from blood drawn through an infected catheter than from blood obtained from a peripheral vein. If the catheter is removed, the tip of the catheter may be cut off and rolled across a culture plate, again using a quantitative culture method.

Staphylococcus aureus and coagulase-negative *Staphylococcus* are the most common causes of catheter-associated infections. With coagulase-negative *Staphylococcus* bacteremia, response to antibiotic therapy without catheter removal is possible up to 80% of the time; that is, one may seek to “sterilize” the CVC if it is deemed necessary. However, this is usually not advisable in critically ill or hemodynamically unstable patients in whom immediate catheter removal and rapid administration of antibiotics are essential. Bacteremia as a consequence of *S aureus*, gram-negative organisms, or fungemia caused by *Candida* spp respond poorly to antimicrobial therapy alone, and prompt removal of the catheter is recommended.

Because of the serious complications associated with neutropenia, preventive measures are critical in cancer patients who are receiving chemotherapy. They should be immunized against *Pneumococcus* and influenza, but administration of live virus vaccines, such as measles-mumps-rubella or varicellazoster, is contraindicated. G-CSF, which stimulates the bone marrow to produce neutrophils, is frequently used prophylactically in patients receiving chemotherapy to shorten the duration and depth of neutropenia, thereby reducing the risk of infection. It is sometimes used once a neutropenic patient develops a fever, but its use at that point is controversial. Prophylactic use of oral quinolones to prevent gram-negative infection or antifungal agents to prevent *Candida* infection may reduce certain types of infection but may select for resistant organisms and

is not routinely used. In hospitalized patients with neutropenia, use of reverse isolation offers no benefit (the patient is most often infected with his or her own flora) and interferes with patient care.

Comprehension Questions

1 Which of the following infectious agents is the most likely etiology associated with an infected central venous catheter?

- A. *Staphylococcus aureus*
- B. *Pseudomonas aeruginosa*
- C. Coagulase-negative *Staphylococcus*
- D. *Klebsiella pneumoniae*
- E. *Candida albicans*

2 A 32-year-old man with acute myelogenous leukemia is undergoing chemotherapy. He was hospitalized 7 days ago for fever to 102°F with an absolute neutrophil count of 100 cells/mm³, and he has been placed on intravenous imipenem and vancomycin. He continues to have fever to 103°F without an obvious source. Which of the following is the best next step?

- A. Lumbar puncture to assess cerebrospinal fluid.
- B. Continue present therapy.
- C. Stop all antibiotics because he likely has drug fever.
- D. Add an aminoglycoside antibiotic.
- E. Add an antifungal agent.

3 A 68-year-old woman is diagnosed with acute leukemia and is undergoing induction of chemotherapy. Last cycle, she developed neutropenia with an absolute neutrophil count of 350 cells/mm³, which has now resolved. Which of the following is appropriate therapy?

- A. Immunization against varicella
- B. Immunization against mumps
- C. Use of recombinant erythropoietin before the next cycle of chemotherapy

- d. Use of G-CSF after the next cycle of chemotherapy

ANSWERS

1 C. Coagulase-negative staphylococci, such as *Staphylococcus epidermidis*, are the most common etiology of catheter-related infections.

2 E. Antifungal therapy should be added when the fever is persistent despite broad-spectrum antibacterial agents.

3 D. Granulocyte colony-stimulating factor given after chemotherapy can decrease the duration and severity of neutropenia and the subsequent risk of sepsis. Live vaccines, such as varicella and mumps, are contraindicated. Erythropoietin is not indicated because the patient is not anemic.

Clinical Pearls

- Fever in a neutropenic patient should be considered a medical emergency and is associated with a high mortality rate.

- The usual sources of bacterial infection in neutropenic patients are gram-positive skin or oral flora or gram-negative enteric flora, including *Pseudomonas*.

- Antifungal therapy should be started in neutropenic patients who have persistent fever despite broad-spectrum antibiotic therapy and who have no obvious source of infection.

- Vascular catheters with evidence of infection along a subcutaneous tract or purulent discharge at the exit site should be removed; replacement over a guide wire is insufficient.

- If a catheter is deemed necessary but it is infected with coagulase-negative staphylococci, antibiotic treatment may sterilize the catheter, allowing it to remain in place. For *Staphylococcus aureus*, gram-negative rods, or fungal catheter infections, the catheter usually requires removal.

ANSWERS TO CASE 18:

What is the most likely diagnosis and underlying etiology in this patient?

A 63-year-old African American woman is evaluated for a humeral fracture

sustained during a fall because of lightheadedness. She has a 2-month history of fatigue, absent-mindedness, loss of appetite and weight, and nocturia. Her vital signs are normal, and she appears dehydrated. In addition to the fracture seen on X-ray, she also has lytic lesions of the proximal humerus. She has renal insufficiency, anemia, and hypercalcemia.

- > Most likely diagnosis: Hypercalcemia with pathologic fracture of the left humerus.
- > Most likely underlying etiology: Multiple myeloma.
- > Next therapeutic step: Initial therapy of the hypercalcemia with intravenous (IV) fluids could be started in the emergency room.

ANALYSIS

Considerations

The patient presents with acute confusion, fatigue, and lethargy, all symptoms of hypercalcemia, consistent with the calcium level of 13 mg/dL. The first step in therapy should be intravenous saline to restore volume status and facilitate urinary calcium excretion. Given the rapidity of onset of symptoms, weight loss, age, and presence of lytic bone lesions, the first concern should be for malignancy, such as multiple myeloma, or bony metastases from an undiagnosed cancer. Both serum and urine electrophoresis would help to identify the presence of a monoclonal gammopathy. Normal serum parathyroid hormone (PTH) and parathyroid hormone-related protein (PTHrP) levels would exclude other causes of hypercalcemia (diagnostic algorithm is given in Figure 18-1 and causes of hypercalcemia in Table 18-2). Treatment then can be aimed at the underlying cause (Table 18-3).

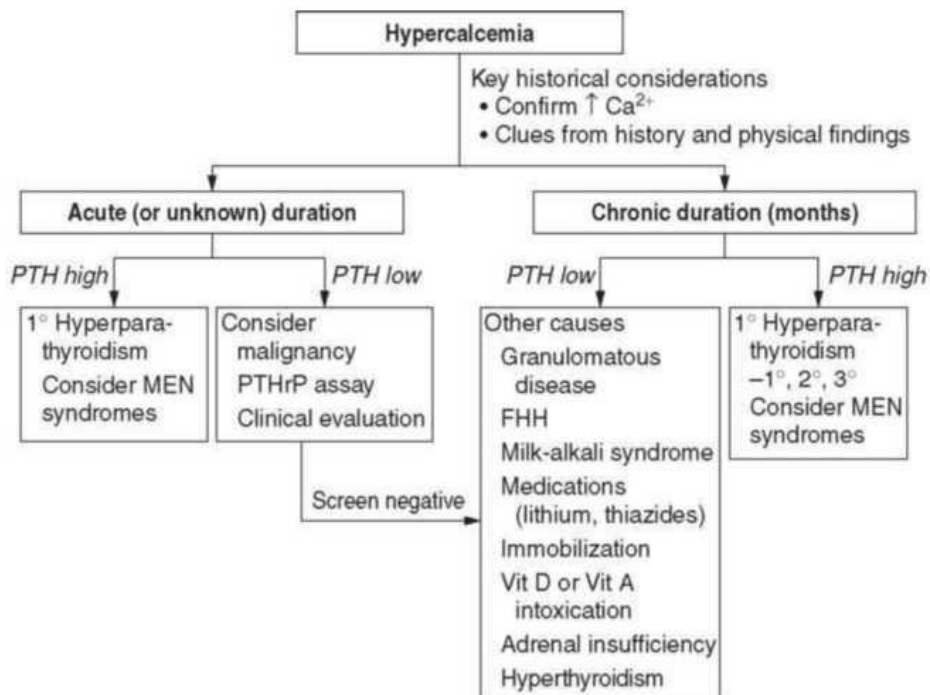


Figure 18-1. Algorithm for evaluation of patients with hypercalcemia. FHH, familial hypocalciuric hypercalcemia; MEN, multiple endocrine neoplasia; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein.

Table 18-2. Causes of hypercalcemia

Disease process	Mechanism	Clinical presentation	Diagnostic criteria	Treatment
Primary hyperparathyroidism	Elevated parathyroid hormone leading to increased turnover of bone	Solitary adenoma or part of multiple endocrine neoplasia (MEN); nephrolithiasis, peptic ulcers, and mental changes (bones, groans, etc.)	Hypercalcemia, hypophosphatemia, elevated PTH	Medical therapy for mild symptoms; surgery for symptoms of hypercalciuria or osteoporosis
Lithium therapy	Stimulation of PTH	Same as with primary hyperparathyroidism	Same as with primary hyperparathyroidism	Discontinue lithium if symptoms
Malignancy-related hypercalcemia	Local destruction of bone (multiple myeloma or leukemia or lymphoma) or humoral release of PTHrP (solid tumors such as breast, renal, or lung cancer)	Symptoms of hypercalcemia and of the particular cancer	Imaging of bones (either plain film or CT), PTHrP levels, bone marrow biopsy	Treatment of the tumor and control of cancer, biphosphonates, calcitonin
Sarcoidosis (and other	Excess 1,25(OH) ₂ D synthesized in	Usually few symptoms	Low PTH levels and elevated	Avoidance of sunlight, decrease

granulomatous disorders)	macrophages and lymphocytes		1,25(OH) ₂ D levels	vitamin D and calcium intake; glucocorticoids if needed
Excessive vitamin D intake	Increased calcium intestinal absorption and, if severe, bone resorption	Symptoms of hypercalcemia	Low PTH levels, markedly elevated levels of 25(OH) ₂ D, and normal 1,25(OH) ₂ D levels	Glucocorticoids and, if needed, intensive hypercalcemia management
Renal insufficiency	Secondary hyperparathyroidism as a result of partial resistance to PTH effects	Bone pain, pruritus, ectopic calcification, osteomalacia	Elevated renal function tests	Limit dietary phosphate intravenous calcitriol

Abbreviations: CT, computed tomography; PTHrP, parathyroid hormone-related protein; PTH, parathyroid hormone.

Table 18 - 3. Treatment of hypercalcemia

Treatment	Onset	Adverse effects
Hydration ± loop diuretic	Acute (effect seen in hours)	Volume overload, electrolyte disturbances
Bisphosphonates	Subacute (1-2 d)	Hypophosphatemia, hypomagnesemia, hypocalcemia, osteonecrosis of jaw
Calcitonin	Acute (hours)	Efficacy short-lived (tachyphylaxis)
Glucocorticoids (effective in cancer-induced hypercalcemia)	Lengthy (days)	Hyperglycemia, osteoporosis, immune suppression
Dialysis (renal insufficiency)	Acute (hours)	Volume shifts, electrolyte disorders, complicated procedure

APPROACH TO

DEFINITIONS

CORRECTED CALCIUM LEVEL: Add 0.8 mg/dL to the serum total calcium for every 1 g/dL of albumin level below 4 g/dL. Example: If the serum calcium level is 9.0 mg/dL and the albumin level is 2.0 g/dL, the corrected calcium level is 10.6 mg/dL.

HYPERCALCEMIA: Elevated serum calcium levels after correction for albumin concentration (normal range approximately 8.8-10.4 mg/dL).

CLINICAL APPROACH

Hypercalcemia

The most common causes of hypercalcemia include malignancies or hyperparathyroidism, accounting for 90% of cases. Other causes include granulomatous disorders such as sarcoid and tuberculosis; less commonly, hypercalcemia may be the presentation of intoxication with vitamin A, vitamin D, or calcium-containing antacids, or may occur as a side effect of therapies with drugs such as lithium or thiazide diuretics. Genetic conditions such as familial hypocalciuric hypercalcemia and hyperparathyroidism as part of a multiple endocrine neoplasia syndrome are less common causes.

The differential diagnosis can be narrowed based on the chronicity of the patient's presentation and the presence or absence of other symptoms and signs. Primary hyperparathyroidism, usually caused by a solitary parathyroid adenoma, is the most likely cause when hypercalcemia is discovered in an otherwise asymptomatic patient on routine laboratory screening. Most patients have no symptoms with mild hypercalcemia less than 12 mg/dL, except perhaps some polyuria and dehydration. With levels more than 13 mg/dL, patients begin developing increasingly severe symptoms, including central nervous system (CNS) symptoms (lethargy, stupor, coma, mental status changes, psychosis), gastrointestinal symptoms (anorexia, nausea, constipation, peptic ulcer disease), kidney problems (polyuria, nephrolithiasis, and prerenal azotemia), and musculoskeletal complaints (arthralgias, myalgias, weakness). The symptoms of hyperparathyroidism can be remembered as stones (kidney), moans (abdominal pain), groans (myalgias), bones (bone pain), and psychiatric overtones (mental status changes). Diagnosis can be established by finding hypercalcemia, hypophosphatemia, with inappropriately elevated PTH levels. Patients may be treated surgically with parathyroidectomy if the hypercalcemia is severe (>15 mg/dL), or if less than 50 years old and significantly decreased bone mineral density.

However, a patient presenting with acute onset of symptomatic hypercalcemia is more likely to have a malignancy. Multiple myeloma, lymphoma, and leukemia all can present with hypercalcemia, as can solid tumors such as breast, lung, and kidney cancers.

Some of these cancers cause elevated calcium levels by stimulating osteoclast activity through direct bone marrow invasion (multiple myeloma, leukemia, and breast cancer). Others produce excess 1,25-vitamin D (lymphomas), whereas others secrete a parathyroid hormone-related protein (PTHrP) that binds the PTH receptor (kidney and lung). Cancer-related hypercalcemia can be differentiated from primary hyperparathyroidism by a suppressed PTH level.

Electrolytes, to assess acid-base status, and renal function are important tests to consider. A normal complete blood count (CBC) and peripheral smear would make leukemia a less likely cause. Levels of PTH and specific assays for PTHrP are generally measured. If multiple myeloma is suspected, serum and urine electrophoresis for monoclonal antibody spikes should be examined. Radiographs showing lytic or blastic lesions may be helpful; finally, a bone marrow biopsy may be considered.

Multiple Myeloma

Multiple myeloma is a neoplastic proliferation of plasma cells that usually produce monoclonal immunoglobulin (Ig)A or IgG antibodies. Patients and an elevated globulin fraction on serum chemistries, which, if separated by electrophoresis, shows a monoclonal proliferation (M-spike). The diagnosis of multiple myeloma requires laboratory and clinical criteria: a monoclonal antibody spike in the serum or light chains in the urine, and more than 10% clonal plasma cells in the bone marrow, and lytic bone lesions.

Patients with lower level monoclonal IgA or IgG antibody production without the signs or symptoms of multiple myeloma have what is termed a *monoclonal gammopathy of undetermined significance* (MGUS). MGUS is much more common than myeloma, affecting up to 1% of the population more than 50 years of age. Long-term studies demonstrate that approximately 16% of these patients will go on to develop multiple myeloma. Patients with MGUS typically require no therapy. Some patients with myeloma with no bone lesions or other endorgan damage have an indolent course (“smoldering myeloma”) and can be observed without treatment for many years. Therapy for symptomatic multiple myeloma includes a high-dose pulsed dexamethasone, often in combination with chemotherapy with vincristine/doxorubicin or thalidomide. Some patients may be

candidates for autologous stem cell transplant.

Comprehension Questions

1 On routine blood work performed for a life insurance application, a 53-year-old woman was found to have a calcium level of 12 mg/dL (normal = 8.8-10.4 mg/dL) and a phosphate level of 2 mg/dL (normal = 3.0-4.5 mg/dL). She is not anemic and has no symptoms. Her medical history is significant for osteoporosis, discovered on a dual-energy X-ray absorptiometry (DEXA) scan performed at the time of her menopause 1 year ago. Which of the following is the most likely cause of her hypercalcemia?

- A. Multiple myeloma
- B. Parathyroid adenoma
- C. Familial hypocalciuric hypercalcemia
- D. Multiple myeloma
- E. Undiagnosed breast cancer

2 A 62-year-old asymptomatic woman is noted to have multiple myeloma and an elevated calcium level, but no bone lesions or end-organ damage. Which of the following therapies is useful for immediate treatment of the hypercalcemia?

- A. Bisphosphonates.
- B. Erythropoietin.
- C. Dexamethasone plus thalidomide.
- D. Interferon- α .
- E. Observe without treatment since she is asymptomatic.

3 A 22-year-old African American woman presents with worsening cough and shortness of breath over 6 weeks, which did not improve with a course of antibiotics or antitussives. Her serum calcium level is found to be 12.5 mg/dL, and a chest X-ray reveals bilateral hilar lymphadenopathy. Which of the following is the most likely diagnosis?

- A. Sarcoidosis
- B. Mycoplasma pneumonia

- c. Acute lymphoblastic leukemia
- d. Squamous cell carcinoma of the lung
- e. Pulmonary embolism

3.4 A 66-year-old man with known metastatic squamous cell carcinoma of the esophagus is brought to the emergency room for increasing lethargy and confusion. He is clinically dehydrated, his serum calcium level is 14 mg/dL, and his creatinine level is 2.5 mg/dL but 1 month ago was 0.9 mg/dL. Which therapy for his hypercalcemia should be instituted first?

- a. Intravenous bisphosphonate
- b. Intravenous furosemide
- c. Glucocorticoids
- d. Intravenous normal saline
- e. Chemotherapy for squamous cell carcinoma

ANSWERS

1 B. An asymptomatic, most likely chronically elevated calcium level is most likely caused by primary hyperparathyroidism caused due to a parathyroid adenoma. The chronicity of this patient's hypercalcemia can be guessed at because she has osteoporosis and is only 1 year postmenopausal.

2 A. Bisphosphonates are helpful in controlling hypercalcemia through inhibition of osteoclastic bone reabsorption. Erythropoietin is useful in treating the anemia associated with multiple myeloma, and dexamethasone, in combination with thalidomide, is useful in treatment of the disease itself.

3 A. Both sarcoidosis and lymphoma can present with cough, dyspnea, and hilar adenopathy on chest X-ray. In approximately 10% of cases, sarcoidosis can cause elevated calcium levels through the production of 1,25-vitamin D that occurs in the macrophages of the granulomas. This can also be seen in granulomas caused by tuberculosis and in lymphoma. Leukemia usually does not present in this manner, although it can cause hypercalcemia. Squamous cell carcinoma of the lung would be unusual in a patient of this age, and the radiographic presentation is atypical.

4 D. Although all of the other therapies listed may be helpful in the treatment of hypercalcemia, given the clinical findings of dehydration and elevated creatinine level with a history of previously normal renal function, volume expansion with normal saline would correct the dehydration and presumed prerenal azotemia, allowing the kidneys to more efficiently excrete calcium. Other therapies can be added if the response to normal saline alone is insufficient.

Clinical Pearls

- Hypercalcemia that is acutely symptomatic is most likely caused by cancer. Asymptomatic hypercalcemia is most likely caused by primary hyperparathyroidism.
- In primary hyperparathyroidism, serum parathyroid hormone and calcium levels are elevated, and phosphate levels are decreased. In malignancy-related hypercalcemia, the calcium level is high and parathyroid hormone levels are suppressed.
- Symptoms of hyperparathyroidism can be remembered as stones, moans, groans, bones, and psychiatric overtones.
- Monoclonal gammopathy of undetermined significance (MGUS) and symptomatic multiple myeloma are on opposite ends of a spectrum of neoplastic disease of plasmacytes.
- The classic triad of multiple myeloma consists of a bone pain due to lytic lesions, anemia, and renal insufficiency.

ANSWERS TO CASE 19:

What is the differential diagnosis in this patient, based on the physical examination findings?

When the diagnosis of CML is considered, other possibilities, such as a solid cancer, lymphomas, and chronic infections must be excluded. These other diseases may cause a leukemoid reaction by increased stimulation of normal myelopoiesis. Usually a leukemoid reaction results in a white blood cell count of less than 100,000/mm³, and less than 10% of cells are myelocytes or more immature forms.

Because normal hematopoiesis is suppressed, the patient could exhibit the signs and symptoms of anemia, such as headache, palpitations, pallor, and cardiac failure. Very

rarely, lymph node enlargement is found in patients with CML. Splenomegaly is almost the rule in patients with CML, and it is the source of poor appetite and upper abdominal pain, such as that seen in this patient. Finally, petechiae, although possible, are not very frequent findings in patients with CML.

On the basis of the hematologic findings, what hematopoietic abnormalities would you expect in this patient with suspected CML?

Normal hematopoiesis is suppressed by the leukemic activity in the bone marrow, leading to a decreased number of red blood cells, as well as decreased hemoglobin level and hematocrit. Typically, the anemia of CML is normochromic normocytic. Hypochromic microcytic anemia is typical of iron deficiency.

Although immature, most of the white blood cells look morphologically normal, and mature neutrophils, band forms, metamyelocytes, and myelocytes constitute most of the white blood cells in this patient. Another characteristic finding is an increased number of basophils. If most of the cells are blasts, this indicates acute leukemia in most cases, although it can also indicate that the patient is in the blastic phase of CML.

What do the bone marrow findings indicate in this patient?

The bone marrow findings are consistent with a diagnosis of CML, and bone marrow biopsy constitutes an important part of the diagnostic evaluation in patients with any kind of leukemia (acute and chronic). Normally, the granulocytic-erythroid ratio ranges from 2 to 4:1, but, in the setting of CML, cells of white lineage predominate and increments of any form of white blood cells, from myeloblasts to mature neutrophils, can be found. An increment in lymphocytes and red blood cell precursors is not characteristic of CML. The normal bone marrow cellularity is 50% fat and 50% or less cells, but, in the leukemias, the accelerated production of abnormal cells causes the fat to be replaced, and the cellularity increases to 100%. Finally, even in normal bone marrow, a very small number of blast cells can be found; in CML, a small percentage of blast cells can be found, but this does not necessarily signify acute leukemia. In blast crisis or acute leukemia, at least 20% of the cells in the bone marrow are blast cells.

What would be the most specific test for establishing the diagnosis of CML in this patient?

The most specific test for establishing the diagnosis of CML is a cytogenetic

investigation for the Ph1 chromosome, or t(9;22), which is found in 90% of cases of CML. Of the remaining 10% at least half will have bcr rearrangements measured by in situ hybridization.

If the patient is started on single-agent chemotherapy, what would be the likely effect?

The chemotherapeutic agent most commonly used in the treatment of CML is hydroxyurea. This therapy can improve the patient's quality of life by rapidly decreasing the number of white blood cells and platelets. It does not prolong survival very much, if at all, in patients with CML. The interferons can induce complete hematologic and cytogenetic remissions, with suppression of the Ph1 chromosome in patients with CML. Most importantly tyrosine kinase inhibitors have high incidence of biologic responses and less toxicity.

Allogeneic bone marrow transplantation has been the only curative treatment for CML but has a high rate of complications. Advanced age and the lack of suitable donors preclude its use in many patients, but it may be the therapy of choice in this 37-year-old man if he does not attain a biologic remission or relapses after this remission is attained.

DISCUSSION

What is the definition of CML?

CML is a hematopoietic stem cell disease characterized by anemia, extreme blood granulocytosis, granulocytic immaturity, basophilia, often thrombocytosis, and splenomegaly.

What is the etiology of CML?

The etiology of CML is unknown, but exposure to ionizing radiation has been found to increase the risk of CML above the expected frequency in certain populations. Some of these major populations are (a) the Japanese exposed to radiation from the Nagasaki and Hiroshima atomic bomb explosions; (b) the British with ankylosing spondylitis treated with spinal irradiation; and (c) women with uterine cervical carcinoma who require radiation therapy. The frequency of CML (as well as acute leukemia) in these populations is significantly greater than that expected for comparable unexposed groups. Chemical leukemogens have not been identified as causative agents of CML.

What is the pathogenic mechanism responsible for CML?

CML results from the acquired (somatic mutation) malignant transformation of a single stem cell whose potency dominates hematopoiesis in the affected person, with the involvement of erythropoiesis, neutrophilopoiesis, eosinophilopoiesis, basophilopoiesis, monocytopoiesis, and thrombopoiesis. Several observations suggest that some lymphocytes may be derived from the primordial malignant cell as well, thereby placing the culprit lesion closer, if not in the pluripotential stem cell. The exact mechanism that causes the transformation to take place has not been fully elucidated, but the Ph1 (Philadelphia) chromosome has been implicated. The hematopoietic cells contain a reciprocal translocation between chromosomes 9 and 22 in more than 90% of patients. This leads to an overtly foreshortened long arm of one of the chromosome 22 pairs. Chromosome 9 contains the c-abl gene at band 34; chromosome 22 has the break point cluster region (bcr) and c-sis genes at band 11. The c-abl gene from chromosome 9 is transported to the chromosome 22 bcr, which is the Ph1 chromosome. As a consequence of these events, a new gene is formed, the bcr-abl gene, which codes for a new protein through the formation of a new messenger RNA. In some cases the chromosomal abnormality is not evident but the bcr-abl gene is identified by in situ hybridization. This new protein is a phosphoprotein with a molecular weight of 210,000 (DaP210 bcr-abl) and possessing tyrosine kinase activity. Its abnormal activity presumably alters the response of the hematopoietic stem cell so that it continues to proliferate rather than being under the control of hematopoietic growth factors.

What is the epidemiology of CML?

CML accounts for approximately 2% of all cases of leukemia and the associated mortality rate is approximately 1.5 per 100,000 population per year. The disease occurs slightly more often in men, but its manifestations and course are similar for both sexes. Approximately 10% of the cases occur in people between 5 and 20 years of age, and CML accounts for approximately 3% of all the childhood leukemias.

What are the clinical characteristics of CML?

The disease is characterized by three phases: (a) a chronic phase, (b) an accelerated phase, and (c) a blast crisis.

The most frequent complaints seen during the chronic phase include easy

fatigability, loss of a sense of well-being, decreased tolerance to exertion, anorexia, abdominal discomfort, early satiety, weight loss, and excessive sweating. The symptoms are vague, nonspecific, and gradual in onset. Physical examination may detect pallor and splenomegaly.

Uncommon presenting signs and symptoms of CML include hypermetabolism that simulates thyrotoxicosis, acute gouty arthritis, priapism, tinnitus, stupor, left upper quadrant and left shoulder pain as a consequence of splenic infarction and perisplenitis, diabetes insipidus, and acute urticaria, which is associated with hyperhistaminemia.

In some patients in this phase, the disease is discovered when blood cell counts are determined during a routine medical examination. The symptoms and signs of the disease and the laboratory findings typically remain stable, and the duration of this phase is variable. Usually it lasts approximately 4 years, but it can last from weeks to many years before transforming to the accelerated phase.

In most cases of CML, the patient's disease eventually changes to a more aggressive, symptomatic, and troublesome form (the accelerated phase) that responds poorly to therapy that formerly controlled the chronic phase. This metamorphosis is often gradual and manifested by refractory splenomegaly; extramedullary tumor masses; changes in the blood, bone marrow, and differential cell counts; and new cytogenetic abnormalities. The onset of fever without infection, weakness, night sweats, weight loss, arthralgias, and bone or left upper quadrant pain may occur before there is laboratory evidence of the accelerated phase. These laboratory abnormalities include a decrease in the hemoglobin content with increasing red blood cell abnormalities, an abrupt increase or fall in the white blood cell count without treatment, and an increase in the number of blast or immature cells. Thrombocytosis or thrombocytopenia and an increase in the number of basophils or eosinophils are also seen.

The blastic phase can be manifested by an extramedullary blast infiltration or by a bone marrow blast crisis.

An extramedullary blast crisis is the first manifestation of the accelerated phase in approximately 10% of patients, and this principally involves the lymph nodes, serosal surfaces, skin and soft tissue, breasts, and the CNS. Bone involvement may lead to severe pain, tenderness, and radiographic changes. The CNS involvement is usually

meningeal and may be preceded by headache, vomiting, stupor, cranial nerve palsies, and papilledema; it is associated with an increase in the number of cells and the protein level, as well as the presence of blast cells in the spinal fluid.

Acute leukemia, the blast phase, develops in most patients with CML, and this can take from days to years to occur after the diagnosis of CML depending on the effectiveness of initial treatment. The signs and symptoms are fever, hemorrhage, bone pain, and lymphadenopathy, as well as the other manifestations already cited. The blastic transformation is usually myeloblastic or myelomonocytic, but can be erythrocytic or lymphoid in nature. Special staining techniques, biochemical assays, or monoclonal antibody determinations are needed to identify the type of transformation once the patient is in the blastic phase. Patients usually die within weeks to months. The median survival in patients in the myeloid blast crisis is approximately 6 to 12 months, and that in patients in the lymphoid blast crisis is 12 months, with survival beyond 2 years unusual. Severe infections, hemorrhage, and organ dysfunction, especially of the liver and kidney, are among the leading causes of death.

What are the laboratory findings encountered in the setting of CML?

The diagnosis of CML can be made on the basis of the hematologic findings, specifically those yielded by the blood count and the blood smear. Common findings are a decrease in the hematocrit; the presence of nucleated red blood cells in the circulation; a leukocyte count that is always elevated, often exceeding $1,000 \Gamma - 10^9/L$; the presence of all stages of granulocyte development in the blood with a generally normal appearance; and a blast cell prevalence ranging from 0.5% to 5%. Myelocytes, metamyelocytes, and band forms account for approximately 40%. The number of basophils is increased, as is the total absolute lymphocyte count (mean, approximately $15 \Gamma - 10^9/L$). In addition, the platelet count is elevated in approximately 50% of patients at the time of diagnosis; platelet counts more than $1,000 \Gamma - 10^9/L$ are not unusual; and neutrophil alkaline phosphatase activity is low or absent in more than 90% of patients. The defects in white cell adhesion, emigration, and phagocytosis are mild and compensated for by high neutrophil concentrations, and therefore do not predispose patients in the chronic phase to infections. Platelet dysfunction can occur but is not associated with spontaneous or exaggerated bleeding, as with other myeloproliferative

disorders.

In terms of the morphologic findings, the bone marrow is markedly hypercellular and hematopoietic tissue takes up 75% to 90% of the marrow volume. Granulopoiesis is dominant, with a granulocytic-erythroid ratio of between 10 and 30:1 (normal, 2 to 4:1). Erythropoiesis is usually decreased, the megakaryocytes are normal or increased in number, and the population of eosinophils and basophils may be increased.

What are the cytogenetic and biochemical abnormalities typically found in patients with CML?

The Ph1 chromosome, designated t(9;22)(q34;q11), is present in more than 90% of patients with CML. During the blast phase, most patients exhibit additional chromosome abnormalities, usually a +8, the gain of a second Ph1 chromosome, or rarely a chromosome loss (-7).

Variant Ph1 chromosome translocations occur in approximately 5% of patients and usually consist of complex rearrangements. Every chromosome is involved except the Y chromosome. There is a small group of patients with CML who do not have the Ph1 chromosome, but virtually all patients have an abnormal chromosome 22 with bcr rearrangements. The characteristic biochemical abnormalities consist of an increase in the uric acid level, an increase in the serum level of cobalamin-binding capacity, a raised cobalamin concentration, an increase in the LDH level, pseudohyperkalemia (an in vitro hyperkalemia secondary to K⁺ release from platelets), pseudohypoglycemia (secondary to leukocyte utilization in vitro), hypercalcemia, hypergammaglobulinemia, and low leukocyte alkaline phosphatase activity.

What is the treatment for CML?

All the biochemical alterations must be corrected. The hyperuricemia must be treated with adequate hydration and allopurinol. However, the specific treatment for the disease depends on the stage and goal of therapy.

For chemotherapy, hydroxyurea is used most often because it has fewer side effects than alkylating agents, which can induce aplastic anemia and acute leukemia in patients with CML. Hydroxyurea treatment has a minimal effect on survival, controls the hematologic alterations (without suppressing the Ph1 chromosome), and improves the patient's quality of life.

Both O±- and Oi-interferons have shown antileukemic activity in the setting of CML; O±-interferon produces a normalization of blood counts in approximately 75% of patients and suppresses the Ph1 chromosome in approximately 15% of treated patients. The Ph1-negative cell also lacks the bcr rearrangements.

Drawbacks to interferon treatment are that maintenance therapy is required and it is not free of side effects. Some studies suggest that the prolonged use of interferon (i.e., >1 year) in responders may make patients less responsive to bone marrow transplantation.

Most recently, tyrosine kinase inhibitors, especially imatinib can lead to a biologic response (normal molecular findings) in more than 50% of patients. These patients may remain in remission for 5 years or more although some patients are starting to show recurrence. Splenic irradiation maybe useful to control splenomegaly and to palliate the symptoms resulting from it. Splenectomy may be useful in carefully selected patients with symptomatic thrombocytopenia, who do not respond to chemotherapy and have a greatly enlarged spleen; however, it is only a palliative measure.

Allogeneic bone marrow transplantations can be useful in the treatment of some patients with CML. This treatment can eradicate the Ph1-carrying clone and has led to an apparent cure of some patients with CML. However, success with agents such as imatinib and the high toxicity resulting from the procedure, particularly in those who lack suitable donors or are of advanced age, limit its use.

Leukapheresis can be useful in two types of patients: pregnant women with a very high white blood cell count and hyperleukocytic patients who need rapid cytoreduction to alleviate the signs and symptoms of leukostasis.

What is the prognosis in patients with CML?

In patients with CML who do not attain a cytogenetic response, the median survival ranges from 45 to 60 months. With improved initial therapy approximately 60% to 80% of patients survive 5 years, and 40% survive 8 years.

ANSWERS TO CASE 20:

What is the differential diagnosis?

Although a number of conditions can cause leukocytosis, concurrent anemia and thrombocytopenia should raise suspicion for neoplastic WBC proliferation. The differential diagnosis for a neoplastic process includes:

- **Lymphoma:** A neoplastic WBC clone originates and proliferates in lymphoid organs (lymph nodes, spleen, and thymus). Lymphoma is broadly classified as Hodgkin's disease (HD) and non-Hodgkin's disease.
- **Leukemia:** Neoplastic WBCs originate in bone marrow and proliferate in peripheral blood. Classified as acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), chronic myelogenous leukemia (CML), and chronic lymphocytic leukemia (CLL).
- **MDS:** As in leukemia, bone marrow produces abnormal clones of one or more blood cells, but the percentage of abnormal bone marrow cells is less than in leukemia. Approximately 30% of MDS progresses to AML (former term for MDS was “pre-leukemia.”)
- **Idiopathic myelofibrosis/agnogenic myeloid metaplasia (MF/AMM):** One of the myeloproliferative disorders in which bone marrow produces excessive amounts of a blood cell type. Initiating event in MF/AMM is clonal proliferation of abnormal myeloid cells in the bone marrow. Clonal cells release growth factors that activate bone marrow fibrosis.

1. What is the most likely diagnosis?

- The peripheral smear contains a number of blast cells, which suggests the patient has an acute leukemia. Some of the blast cells contain needle-like inclusions (Auer rods) (see Figure 20–1), which are specific (but not sensitive) for AML. AML is most common in older persons (mean age is approximately 65 years).

ANSWERS TO CASE 21:

What is the most likely diagnosis?

Suspect CML in this patient with WBCs of the granulocyte series at different stages of maturation on peripheral smear (see Figure 21–1). This condition most frequently occurs

in middle-aged persons. Almost half of patients are asymptomatic at diagnosis. Other common presentations are one or more of the following:

- Fatigue and other constitutional complaints (due to anemia)
- Easy bleeding (due to thrombocytopenia)
- Splenomegaly, hepatomegaly, and recurrent infections (due to abnormal WBCs)

What diagnostic studies can help confirm the diagnosis?

First obtain serum leukocyte alkaline phosphatase (LAP). LAP is decreased in CML but increased in leukemoid reaction. If serum LAP is low or absent, obtain cytogenetics and molecular studies from bone marrow cells. The diagnosis is confirmed if one or more of the following are present:

- Cytogenetics: Philadelphia chromosome (chromosome 9;22 translocation)
- Molecular studies: Fluorescence in situ hybridization or polymerase chain reaction demonstrates Bcr-Abl protein or mRNA.

How is CML treated?

- In general, first-line therapy for older patients is imatinib (Bcr-Abl tyrosine kinase inhibitor). First-line therapy for younger patients is stem cell transplant.

ANSWERS TO CASE 22:

What is the diagnosis in this patient?

This patient most likely has polycythemia vera. The oxygen saturation greater than 90% and the presence of splenomegaly support the diagnosis. The presence of mononuclear and basophilic cells also supports the diagnosis of a myeloproliferative disorder, which would be further supported by a bone marrow biopsy that shows trilinear hyperplasia.

Why is it important to know whether the patient snores or experiences daytime drowsiness?

Snoring and daytime drowsiness are symptoms of sleep apnea, a cause of secondary erythrocytosis. Although phlebotomy can cure the patient's erythrocytosis, it cannot treat the nighttime hypoxia or sleep apnea, and the patient could go on to have right-sided heart failure.

What is the cause of this patient's nasal stuffiness?

Although he may have a sinus infection, the nasal stuffiness is most likely due to increased blood viscosity.

What should be the initial treatment in this patient?

Phlebotomy should be performed as soon as possible to decrease the hematocrit to 45% to 50%. The increased blood viscosity places this patient who has two other risk factors for atherosclerotic disease, namely smoking and hypertension, at risk for a stroke or cardiovascular accident.

What is this patient's prognosis?

Even with careful treatment of his erythrocytosis with phlebotomy and chemotherapy, his life expectancy will probably be more limited because of his smoking and hypertension.

DISCUSSION

What is erythrocytosis?

A patient with a hematocrit greater than 55% that is not due to dehydration is considered to have an erythrocytosis. The chromium 151-labeled red blood cell measurement of the total red blood cell mass is, however, the gold standard for establishing the diagnosis, but if the patient has a hematocrit greater than 60%, no further studies are necessary.

What are the two major types of erythrocytosis?

When the elevated hematocrit is due to increased erythropoietin secretion, this constitutes secondary erythrocytosis. Primary erythrocytosis is caused by increased red blood cell production that does not stem from increased erythropoietin secretion.

What are some causes of secondary erythrocytosis due to appropriate erythropoietin secretion?

Any disorder that causes tissue hypoxia stimulates the renal production of erythropoietin. These disorders include chronic obstructive lung disease, living at high altitudes, hemoglobin (Hb Chesapeake and methemoglobin) that does not release oxygen correctly, or cardiac disease that causes right-to-left shunting. In relative

erythrocytosis, the red blood cell mass is normal, and this occurs in the settings of dehydration or decreased plasma volume.

What are some causes of secondary erythrocytosis due to inappropriate erythropoietin secretion?

Many disease states can be associated with increased erythropoietin production. Diseased kidneys may secrete erythropoietin inappropriately or tumors may secrete hormones that function like erythropoietin. Renal, adrenal, or hepatic tumors, ovarian carcinoma, or benign uterine myomas all secrete erythropoietin-like substances. Other causes of increased erythropoietin secretion are renal artery stenosis, hydronephrosis, renal cysts, or renal transplantation.

What is polycythemia vera?

Polycythemia vera is an absolute erythrocytosis secondary to the clonal expansion of red blood cells, making it a myeloproliferative disorder.

What are the symptoms of polycythemia vera?

Symptoms stem from vascular congestion or obstruction due to increased blood viscosity. Patients complain of headaches, itching and burning feet, or malaise. The retinal veins become engorged and hepatosplenomegaly may be present. The incidence of cardiovascular and cerebrovascular disease is increased in these patients because of the elevated blood viscosity.

How is polycythemia vera diagnosed?

An increased red blood cell mass, an oxygen saturation of 92% or more, and splenomegaly are the cardinal signs of polycythemia vera. If splenomegaly is not present, polycythemia vera is evident if the patient has a platelet count that exceeds 400,000/mm³, a white blood cell count greater than 12,000/mm³, a cobalamin level of 900 pg/mL or greater, or an elevated neutrophil alkaline phosphatase score.

What is the likely length of survival in a patient with polycythemia vera?

Without treatment, half the patients die within 24 months, usually due to vascular disease. Phlebotomy to maintain a hematocrit of 45% can prolong the life span to more than 6 years, and median survival in patients who receive effective chemotherapy is 12.5 years.

What is the rare hepatic complication that can arise in patients with polycythemia vera?

Budd-Chiari syndrome is an occlusion of the hepatic veins sometimes seen in patients with polycythemia vera and other diseases that increase blood viscosity. This causes right upper quadrant pain and elevations in the liver enzyme levels. It is very difficult to treat, and is best prevented by treating the erythrocytosis aggressively.

ANSWERS TO CASE 23:

What are the most common causes of polycythemia?

Polycythemia is defined as increased Hb (>16.5 mg/dL in women and >18.5 mg/dL in men), increased HCT (>48% in women or >52% in men), or increased RBC count (less commonly used). The differential diagnosis includes:

- First-degree polycythemia: The most important first-degree cause of polycythemia is polycythemia vera (PV).
- Second-degree polycythemia: The most important second-degree causes are EPO-secreting tumors and hypoxemia-induced increased EPO secretion.
- Pseudopolycythemia: caused by fluid depletion (polycythemia resolves with fluids), chronic smoking, living at a high altitude, or spurious elevation (Gaisboch's syndrome).

What diagnosis do the history and physical exam findings suggest?

The most likely diagnosis is PV. In this rare, idiopathic, myeloproliferative disorder there is excessive production of RBCs independent of EPO. Many PV patients also have increased platelet and WBC production. Increased RBCs makes the blood thicker than normal (increased viscosity), which causes most clinical manifestations of PV. Remember symptoms of PV using the mnemonic “Carolina Tar Heels Play Excellent Basketball”:

- Constitutional symptoms (e.g., headache, fatigue, decreased concentration, etc.)
- Thrombosis
- Hypertension
- Pruritus (unknown mechanism)
- Erythromelalgia

- Blurry vision
- Bleeding (because increased thrombosis consumes vWF and leads to vWF deficiency)

Remember signs of PV with the acronym “GAPS”:

- Gouty Arthritis (due to breakdown of large numbers of RBCs)
- Plethora (face appears red because of hyperviscosity)
- Splenomegaly ± hepatomegaly (increased RBCs ± platelets get stuck in splenic and hepatic vasculature)

DISCUSSION

What is the next step in management?

Obtain RBC mass, serum EPO, and ambulatory pulse oximetry (Fig. 10-18). Increased EPO indicates second-degree polycythemia, whereas decreased EPO indicates PV.

Does this patient meet diagnostic criteria for PV?

Major PV criteria are:

- Increased RBC mass
- Ambulatory oxygen saturation $\geq 92\%$
- Splenomegaly

Minor PV criteria are:

- Thrombocytosis
- Leukocytosis
- Increased or normal serum LAP
- Serum vitamin B12 >900 pg/mL

Diagnosis of PV requires a patient to meet all three major criteria or two major criteria plus at least two minor criteria. This patient with all three major criteria meets the requirements for diagnosis of PV.

How is PV treated?

First-line therapy for PV is repeated phlebotomy to lower HCT (target HCT is $\leq 45\%$ in men and $\leq 42\%$ in women). Also, administer aspirin unless contraindicated to prevent thrombosis. Other therapies are as follows:

- Hydroxyurea: Administer to patients with increased risk of thrombosis (prior thrombosis, platelets >1.5 million, age >70 years, or multiple CV risk factors).
- Anegrelide: Consider for refractory thrombocytosis.
- Interferon-A: Consider in patients with refractory pruritus.
- Allopurinol: Consider for urine uric acid >1100 mg/day or symptomatic hyperuricemia.

What would have been the diagnosis if the patient with fatigue, headache, blurry vision, erythromelalgia, and splenomegaly had a normal RBC count but platelet count was 700,000/ μ L?

Isolated thrombocytosis can cause signs and symptoms of hyperviscosity, including thrombosis and bleeding. Increased platelets on CBC can be caused by:

- Pseudothrombocytosis: Caused by laboratory error. Patient does not have signs of hyperviscosity. Platelets are normal on repeat testing.
- Reactive thrombocytosis: The most common causes of increased platelets are IDA, splenectomy, infections, and inflammatory disorders (malignancies, autoimmune disorders).
- Essential thrombocythemia (ET): In this rare idiopathic myeloproliferative disorder, diagnostic criteria are platelet count consistently >600,000/ μ L and no evidence of reactive thrombocytosis. Patients may also have increased RBCs and WBCs. The first step is to rule out pseudothrombocytosis and reactive thrombocytosis. Then obtain cytogenetics and bone marrow biopsy to confirm the diagnosis and rule out the other three myeloproliferative disorders (myelofibrosis, CML, and PV). First-line therapy for symptomatic patients is hydroxyurea plus aspirin (no therapy is necessary in asymptomatic patients).

ANALYSIS

Considerations

This patient presents with mucosal bleeding, petechiae, and thrombocytopenia. She has no other history, symptoms, or physical examination findings of any systemic disease, so her problem appears to be an isolated hematologic problem. Review of her CBC is important to ensure that other cell lines (white blood cell count [WBC] and red blood

cell count [RBC]) are normal - if they are abnormal, processes, such as acute leukemia or a bone marrow infiltrative process must be considered. Her coagulation studies (PT and PTT) are also normal - if they were deranged, we would suspect a consumptive coagulopathy causing the thrombocytopenia and a serious underlying disorder. Her current level of thrombocytopenia does not place her at risk for spontaneous hemorrhage, but at platelet counts less than between 5000 and 10,000/mm³, she is risk for life-threatening bleeding.

APPROACH TO

DEFINITIONS

IMMUNE THROMBOCYTOPENIA PURPURA: A hematological disorder characterized by the destruction of blood platelets due to the presence of antiplatelet autoantibodies.

THROMBOTIC THROMBOCYTOPENIA PURPURA: A life-threatening syndrome of uncertain etiology characterized by a pentad of microangiopathic hemolytic anemia, thrombocytopenia, neurologic abnormalities, fever, and renal dysfunction.

HEMOLYTIC UREMIC SYNDROME: A clinical complex consisting of progressive renal failure that is associated with microangiopathic hemolytic anemia and thrombocytopenia

CLINICAL APPROACH

A careful history is the most effective way to determine the presence and significance of a bleeding disorder. For a patient with abnormal bleeding, the most important history relates to any prior history of bleeding. One should inquire about history of abnormal bleeding, epistaxis, menorrhagia, excessive prolonged bleeding from minor cuts, bruising, prolonged or profuse bleeding after dental extraction, excessive bleeding after major surgery or obstetric delivery, or trauma. Excessive mucosal bleeding (eg, gum and nose bleedings) and petechiae are suggestive of thrombocytopenia, or abnormal platelet function such as von Willebrand disease (vWD). On the other hand, hemarthrosis, deep hematomas, and retroperitoneal bleeding more likely reflect a severe coagulation abnormality, such as hemophilia, deficiencies of factors VIII or IX.

The causes of thrombocytopenia can be divided into (a) decreased platelet production, (b) decreased platelet survival, (c) sequestration (hypersplenism), and (d) dilutional. Impaired platelet production is caused by a bone marrow abnormality, such as infiltration caused by malignancy or myelofibrosis, marrow suppression as a result of chemicals, drugs, or radiation, and viruses. In these cases, a deficit of platelet production is rarely seen without abnormalities in the production of white and red cells. Therefore, when impaired platelet production is the result of a bone marrow abnormality, we also expect abnormalities in the number of leukocytes and red cells. Decreased platelet survival is another cause of thrombocytopenia. Thrombocytopenia is defined as a platelet count of less than $150,000/\text{mm}^3$, although spontaneous bleeding usually occurs at much lower levels. Mild thrombocytopenia may be seen in pregnancy and much more significant thrombocytopenia with HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome. Decreased platelet survival can be a result of increased destruction of platelets, such as immune-mediated destruction triggered by medications, various infections, autoimmune diseases like systemic lupus erythematosus (SLE) or for uncertain causes as in idiopathic thrombocytopenic purpura (ITP). Decreased platelet survival can also be due to sequestration in an abnormally enlarged spleen.

ITP: Acute ITP is most common in early childhood, often following an antecedent upper respiratory infection, and usually is self-limiting. In children, ITP usually resolves spontaneously within 3 to 6 months. ITP in adults is more likely to have an insidious or subacute presentation, is most likely to occur in women ages 20 to 40 years old, and is more likely to persist for months to years, with uncommon spontaneous remission. The patient will present with the clinical manifestations of thrombocytopenia, such as petechiae and mucosal bleeding, but with no systemic toxicity, no enlargement of nodes or abdominal organs, and a normal blood count and normal peripheral blood smear except for thrombocytopenia. Laboratory testing is usually focused on a search for secondary causes of thrombocytopenia such as HIV, hepatitis C, ANA (for SLE), and a direct Coombs test to evaluate for autoimmune hemolytic anemia with ITP (Evans syndrome). Bone marrow examination is generally performed on older patients to exclude myelodysplasia, and often reveals increased megakaryocytes but otherwise normal findings.

In 80% of children affected with ITP, spontaneous remission occurs within 6 weeks, but spontaneous recovery in adults is less common. Many physicians elect to treat affected patients, especially adults, with oral steroids, such as prednisone 1 to 2 mg/kg of body weight. Platelet transfusions usually are unnecessary and should be reserved for rare life-threatening situations because survival of transfused platelets in ITP may be as short as a few minutes. Intravenous immunoglobulin (IVIg) is often used when platelet counts are less than $10,000/\text{mm}^3$ and is used concurrently with steroids. Because the spleen removes the antibody-bound platelets, patients who do not respond to steroids may be candidates for splenectomy.

Drug-induced thrombocytopenia: When a patient presents with thrombocytopenia, any drug that the patient is using should be considered a possible cause. Common drugs known to cause thrombocytopenia, include H2 blockers, quinine, and sulfonamides. In general, the diagnosis is made by clinical observation of the response to drug withdrawal. Discontinuation of the offending medication should lead to improvement in the platelet count within a time frame consistent with the drug's metabolism, almost always within 7 to 10 days.

Heparin-induced thrombocytopenia (HIT): There are two types of HIT: HIT-1 which is non-immune mediated usually occurring shortly after initiation of heparin (<48 hours), and caused by platelet clumping. Usually the patient is not clinically affected. HIT-2 is caused by platelet-activating antibodies and occurs 3 or more days after heparin is begun, and sooner if the patient had been sensitized by prior heparin use. HIT-2 can cause serious consequences. HIT differs from other drug-induced causes of thrombocytopenia in that it is not associated with bleeding, but rather with increased risk of thrombosis. HIT typically develops 5-10 days after exposure to either unfractionated heparin (UFH) or low-molecular-weight heparins (LMWH), when an antibody forms against the complex of heparin and platelet factor IV. Typically, UFH puts the patient at increased risk for HIT. These HIT antibodies activate platelets and endothelial cells, and can cause thrombosis. Up to half of patients with HIT will develop clinically evident thrombosis. Diagnosis depends on clinical suspicion, and utilization of an enzyme-linked immunosorbent assay (ELISA) for the HIT antibodies. Treatment includes discontinuation of the heparin (one cannot switch from UFH to LMWH because HIT

antibodies will cross-react), and instead use a direct thrombin inhibitor such as argatroban or lepirudin to treat thrombosis.

Thrombocytopenia may also be caused by consumptive coagulopathy, the most common of which is disseminated intravascular coagulation (DIC). DIC usually is triggered by serious underlying conditions such as bacterial sepsis, malignancy such as acute promyelotic leukemia, or with obstetric catastrophes such as abruptio placentae. Any of these disease processes can produce blood exposure to pathologic levels of tissue factor, triggering uncontrolled thrombin generation with systemic fibrin deposition in the microcirculation. This uncontrolled activation of coagulation results in consumption of platelets and clotting factors, leading secondarily to bleeding. Laboratory findings include thrombocytopenia and elevated PT and PTT (reflecting the consumptive coagulopathy), and decreased fibrinogen and elevated fibrin split products and D-dimer (reflecting uncontrolled fibrin deposition). Usually, the cause of DIC is obvious, and treatment should be directed toward correcting the underlying cause, as well as replacement of platelets and coagulation factors if there is clinically significant bleeding.

A less common disease process which may be confused with DIC is Thrombotic Thrombocytopenic Purpura (TTP). TTP may be triggered by infection such as HIV, or medications such as clopidogrel, or it may be idiopathic. As originally described, TTP has a pentad of findings : (a) thrombocytopenia; (b) microangiopathic hemolytic anemia with elevated lactate dehydrogenase (LDH) level and schistocytosis in the peripheral blood smear; (c) fever; (d) fluctuating central nervous system (CNS) deficits with altered mental status; and (e) renal failure. Patients may be acutely ill, and differentiation from DIC may be challenging, except that the PT and PTT are typically normal in TTP, but elevated in DIC. Plasma exchange is the standard treatment and has reduced the mortality of this condition greatly. Table 5-1 compares DIC, TTP, and ITP.

Table 5-I Comparison of DIC, TTP, and ITP

	Etiology	Clinical course	Treatment
Disseminated intravascular coagulopathy	Secondary to some other process: sepsis, trauma,	Can be relatively mild indolent course or severe life- threatening process; ongoing coagulation and	Treatment aimed at underlying cause. No proven specific treatment

(DIC)	metastatic malignancy, obstetric causes	fibrinolysis can cause thrombosis or hemorrhage; consumption of coagulation factors is seen as prolonged PT and PTT.	for the coagulation problem: if bleeding, replace factors and fibrinogen with fresh-frozen plasma (FFP) or cryoprecipitate; if clotting, consider anticoagulate with heparin.
Thrombocytopenic thrombotic purpura (TTP)	Multiple causes, many seemingly trivial: drugs/infection lead to endothelial injury and release of von Willebrand factor (vWF), triggering formation of microvascular thrombi	May present as septic- appearing patient with fever, altered mental status, thrombocytopenia, microangiopathic hemolytic anemia, and renal failure. Previously a very high mortality, mainly because of CNS involvement. Normal PT and PTT.	Plasmapheresis (removal of the excess/abnormal vWF), most patients recover. Corticosteroids.
Immune thrombocytopenic purpura (ITP)	Antiplatelet antibody leading to platelet destruction	Children: following a viral illness with resolution; in adults, a more indolent course with progression and rarely spontaneous resolution. Isolated thrombocytopenia, normal PT, PTT. Increased megakaryocytes on bone marrow aspiration.	Oral corticosteroids; splenectomy if resistant to steroids. Intravenous immunoglobulin (IVIg).

Von Willebrand disease patients, who appear to have impaired primary hemostasis (ie, petechiae, easy bruising, mucosal bleeding, menorrhagia) yet have normal platelet counts, should be suspected of having impaired platelet function, as in vWD. vWD is the most common inherited bleeding disorder.

It may occur as often as 1 in 1000 individuals. It is an autosomal dominant disorder but often is not recognized because of relatively mild bleeding symptoms or because of

excessive bleeding attributed to other causes, for example, menorrhagia attributed to uterine fibroids. von Willebrand factor (vWF) is a large complex multimeric protein that has two major functions: it allows for platelet adhesion to endothelium at sites of vascular injury, and it is the carrier protein for coagulation factor VIII, which stabilizes the molecule. vWD is a heterogeneous group of disorders, but a common feature is deficiency in the amount or function of vWF. Clinical features are those of primary hemostasis as discussed. Typical laboratory features are reduced levels of vWF, reduced vWF activity as measured by ristocetin cofactor assay, and reduced factor VIII activity. The platelet count is usually normal, bleeding time is increased, and pTT may or may not be prolonged. Treatment is desmopressin acetate (DDAVP) , which causes release of vWF from endothelial stores, or use of factor VIII concentrate, which contains large amount of vWF.

Comprehension Questions

1 A 28-year-old woman complains of excessive bleeding from her gums and has petechiae. Here CBC shows a platelet count of $22,000/\text{mm}^3$ with a hemoglobin of 8.9 g/dL and a WBC count of $87,000/\text{mm}^3$. Which of the following is the most likely etiology of her low platelet count?

- A. Immune thrombocytopenia purpura
- B. Systemic lupus erythematosus
- C. Drug-induced thrombocytopenia
- D. Acute leukemia

2 A 50-year-old man has been treated for rheumatoid arthritis for many years. He currently is taking corticosteroids for the disease. On examination, he has stigmata of rheumatoid arthritis and some fullness on his left upper abdomen. His platelet count is slightly low at $105,000/\text{mm}^3$. His white blood cell count is $3100/\text{mm}^3$ and hemoglobin level 9.0 g/dL. Which of the following is the most likely etiology of the thrombocytopenia?

- A. Steroid induced
- B. Splenic sequestration

- C. Rheumatoid arthritis autoimmune induced
- D. Prior gold therapy

3 A 30-year-old woman with ITP has been taking maximum corticosteroid doses and still has a platelet count of $20,000/\text{mm}^3$ and frequent bleeding episodes. Which of the following should she receive before her splenectomy?

- A. Washed leukocyte transfusion
- B. Intravenous interferon therapy
- C. Pneumococcal vaccine
- D. Bone marrow radiotherapy

4 A 65-year-old man who has a prosthetic heart valve is hospitalized for a knee replacement surgery, and placed on IV heparin for anticoagulation before the procedure. He drinks one glass of wine each weekend and has been diagnosed with osteoarthritis for which he takes acetaminophen. His platelet count was normal, but now is $32,000/\text{mm}^3$. Which of the following is the most likely cause of the thrombocytopenia?

- A. Prosthetic heart valve
- B. Alcohol intake
- C. Acetaminophen
- D. Heparin

ANSWERS

1 D. The thrombocytopenia is seen with other hematologic abnormalities, the most abnormal of which is a markedly elevated WBC count, suggesting acute leukemia.

2 B. This patient with rheumatoid arthritis likely has splenomegaly, also known as Felty syndrome. Splenomegaly from any etiology may cause sequestration of platelets, leading to thrombocytopenia.

3 C. Patients who undergo splenectomy are at risk for infections of encapsulated organisms such as *Streptococcus pneumoniae* and thus should receive the pneumococcal vaccine. It usually is given 2 weeks prior to splenectomy so that the

spleen can help in forming a better immune response.

4 D. The patient likely has heparin-induced thrombocytopenia, which may be confirmed by assay for HIT antibodies. Treatment consists of stopping the heparin.

Clinical Pearls

- Disorders of primary hemostasis (thrombocytopenia or von Willebrand disease) are characterized by mucosal bleeding and the appearance of petechiae or superficial ecchymoses.

- Disorders of secondary hemostasis (coagulation factor deficiencies such as hemophilia) usually are characterized by the development of superficial ecchymoses as well as deep hematomas and hemarthroses.

- Immune thrombocytopenic purpura is a diagnosis of exclusion. Patients have isolated thrombocytopenia (ie, no red or white blood cell abnormalities), no apparent secondary causes such as systemic lupus erythematosus, human immunodeficiency virus (HIV), or medication-induced thrombocytopenia, and normal to increased numbers of megakaryocytes in the bone marrow.

- Spontaneous hemorrhage may occur with platelet counts of less than 10,000/mm³.

- Platelet transfusion in immune thrombocytopenic purpura is generally ineffective and is used only when there is severe life-threatening bleeding.

- Corticosteroids are the initial treatment of immune thrombocytopenic purpura. Patients with more severe disease can be treated with intravenous immunoglobulin; chronic refractory cases are treated with splenectomy.

ANSWERS TO CASE 24:

What is your most likely diagnosis and the best initial treatment?

A 26-year-old woman is seen in the emergency room because of persistent epistaxis. She denies excessive bleeding with menses or childbirth, easy bruisability, or bleeding into her joints. There is no family history of abnormal bleeding. The patient does not take any medications. Physical examination is significant only for the blood oozing from her nose and for the petechiae on her legs. There is no lymphadenopathy or hepatosplenomegaly. Her CBC shows thrombocytopenia, but the other cell lines are

normal.

- > Most likely diagnosis: Immune thrombocytopenia purpura (ITP).
- > Best initial treatment: Oral corticosteroids.

ANSWERS TO CASE 25:

How would you proceed with the evaluation of this patient's bleeding problem?

While emergency medical management of his bleeding is being provided through the placement of a nasogastric tube, together with the intravenous administration of fluids for blood pressure support as needed and typing and crossmatching in preparation for the administration of packed red blood cells, this patient with apparent chronic liver disease needs to have his coagulation status evaluated. Both the PT and PTT should be determined promptly and measurement of the fibrinogen level should be considered because it can be decreased in the setting of chronic liver failure. In this case, if the PT and PTT prove to be elevated, as expected, there is probably little reason for a 1:1 mix in this acutely ill patient because a deficiency state is very likely.

What blood products would you give this patient, if any?

If his PT or PTT proves to be elevated, the best blood product for replacing the deficient factors is fresh frozen plasma. In addition, if his fibrinogen level is measured and found to be less than 100 mg/dL, cryoprecipitate may also be indicated. Finally, it may become necessary to administer platelets if his count falls below 20,000/mm³ in the face of active bleeding.

What other medicines, if any, would you give this patient to manage his bleeding?

If history and physical examination findings are consistent with alcoholism and liver disease, vitamin K should also be given.

What factors may be contributing to this patient's low platelet count?

His low platelet count may stem from multiple causes. First, the platelet count can fall in the face of massive bleeding (consumption). Second, he may be chronically underproducing platelets owing to either chronic alcohol suppression of the bone marrow or folic acid deficiency. Finally, he has an enlarged spleen, which may be sequestering his platelets.

DISCUSSION

What are the major divisions of the coagulation system?

The coagulation system is quite complex, but can be viewed as consisting of at least three major components: the vascular endothelium, the blood coagulation proteins (both those that promote clotting and those that lyse clots by means of the fibrinolytic system), and the platelets. The coagulation cascade represents a series of proteins that, when initiated, forms a fibrin clot. A simple outline of the cascade is shown in Table 25-1. Complex issues such as the exact mechanisms by which anticoagulants, such as protein C and protein S, function and how factor VII may activate factor IX are not completely understood.

Vascular endothelial integrity can be assessed using the bleeding time. In this test, a nick is made in the skin under standardized conditions, and the time to cessation of bleeding is measured.

The blood coagulation proteins are usually evaluated by in vitro studies using the patient's citrate-anticoagulated plasma. This is done by adding back various components of the coagulation cascade to the patient's plasma to induce clot, and the procedure is standardized against plasma from an individual with normal plasma coagulation components. The two most common tests for doing this are the prothrombin time (PT) and the partial tissue thromboplastin time (PTT). The PT measures the extrinsic pathway of the coagulation cascade, and this is done by adding tissue thromboplastin to the patient's plasma. If there is a deficit in any of the common pathway components or factor VII, the clotting time is prolonged abnormally. The PTT measures the intrinsic and common pathways; a deficit in the common or intrinsic pathway proteins results in a prolonged PTT. A third, less commonly used, screening test is the thrombin time, which measures only the last step in the cascade the conversion of fibrinogen to fibrin and is done by adding thrombin to the patient's plasma. Therefore, if the patient has too little fibrinogen or a dysfunctional fibrinogen protein, the time is prolonged. Finally, each of the components of the cascade, including factors I to XIII, can be assayed directly to evaluate for deficits.

Platelets can be evaluated both quantitatively (by the platelet count) and

functionally. Platelet function can be assessed by the bleeding time; qualitatively defective platelets do not form an adequate platelet plug and the bleeding time is prolonged. In addition, platelets can be analyzed in vitro for their aggregability using platelet stimulants (e.g., ristocetin).

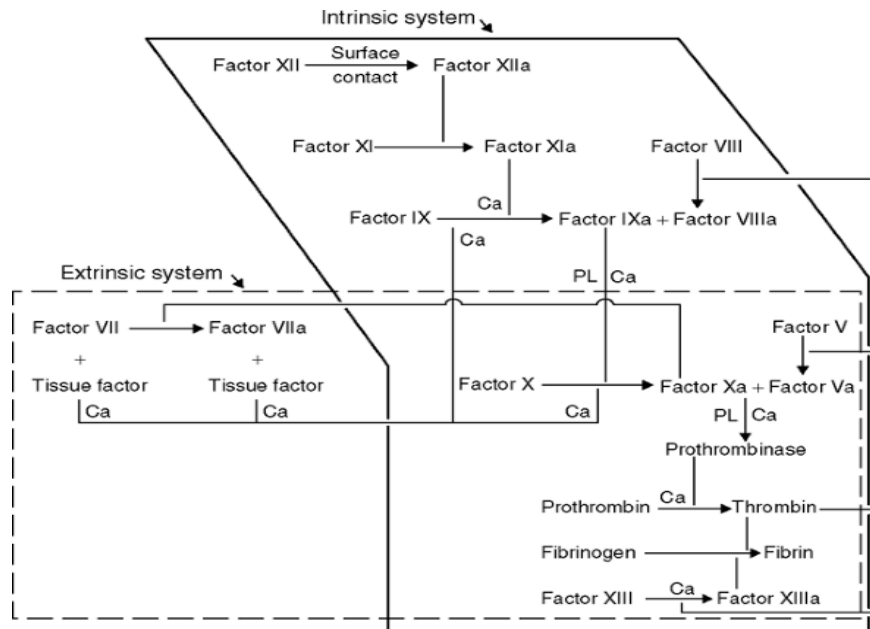
What common disorders are associated with each of the major divisions of the coagulation system?

The vascular endothelium may be fragile in the setting of several acquired conditions, including vasculitis and long-term steroid use. This is important to realize because it may cause the bleeding time to be prolonged despite normal platelet number and function.

Deficits in the blood coagulation proteins may be congenital or acquired. The most common congenital disorders consist of deficiencies in factor VIII (hemophilia A) or factor IX (hemophilia B, or Christmas disease), which are inherited in an X-linked manner. Another common congenital disorder is von Willebrand's disease, in which there is a deficit in von Willebrand's factor. This factor is bound to factor VIII and is necessary for both platelet function and for clotting to take place by the intrinsic pathway.

Deficiencies in various factors can be acquired when their production is antagonized, as occurs with sodium warfarin therapy, a substance that inhibits the production of activated vitamin dependent factors (factors II, VII, IX, X, and protein C and S). Another common situation that causes deficiencies in various factors is liver disease; because the liver is the site for the synthesis of nearly all the coagulation factors, severe liver disease results in deficient production of factors. Malnutrition, malabsorption, and liver disease can all lead to a deficit in vitamin K, with a subsequent deficit in the vitamin dependent factors. Finally, the overwhelming consumption of all factors can result in a coagulopathy, as occurs in disseminated intravascular coagulation (DIC).

Table 25-1



The platelet population can be depressed because of either underproduction or excessive destruction. Underproduction occurs as a consequence of bone marrow suppression (brought about by chemotherapy, infections, drugs, or infiltration with other cells, such as occurs in the setting of leukemia or cancer). Excessive destruction can occur in the setting of an enlarged spleen (sequestration), bleeding (consumption) or consumptive disorders (DIC or thrombotic thrombocytopenic purpura/hemolytic uremic syndrome), and on an autoimmune basis [idiopathic thrombocytopenic purpura (ITP)].

Qualitative defects can be congenital, but are more often acquired and due to drug exposure (aspirin, nonsteroidal antiinflammatory drugs, and some antibiotics) or uremia.

What are the clinical manifestations of various bleeding disorders?

Although any of the bleeding disorders may result in excessive hemorrhage associated with such events as surgical procedures, trauma, or gastrointestinal bleeding, each displays some characteristic features. Vascular fragility is typically associated with subcutaneous ecchymoses. Plasma coagulation protein deficiencies in patients with hemophilia are associated with spontaneous soft tissue and joint bleeds. Other plasma factor deficiencies, as well as platelet deficits, are associated with diffuse ecchymoses (cutaneous and soft tissue). Platelet deficits are also manifested by petechiae (small capillary hemorrhages in mucosal surfaces and areas of increased hydrostatic pressure, such as the ankles and feet) and purpura (larger areas of hemorrhage). Von Willebrand's disease is unique in that it may present with both soft tissue bleeding (factor VII deficiency) and mucosal bleeding (platelet dysfunction).

What workup is indicated for a bleeding patient?

Evaluation of the bleeding patient begins with a good history taking. It needs to be determined if the condition is of long standing or is new. Questions about previous bleeding episodes (nosebleeds, bruising, menstrual flow, bleeding with trauma, surgery, and delivery) as well as family history are vital for determining the nature of the disorder. A careful drug history, including over-the-counter drug use, must be taken. The patient's medical history and a review of symptoms may reveal evidence of autoimmune disorders or intercurrent illness.

Physical examination is important in evaluating the sites of bleeding (cutaneous, mucosal, soft tissue, or joint bleeding sites, as well as petechiae). An enlarged spleen and evidence of liver disease (e.g., spiders or hemangiomas) or malnutrition should be sought, and the patient's overall medical condition should be assessed.

A screening for bleeding disorders should include a platelet count, PT, and PTT; if any of these results are abnormal or if there is evidence of mucosal bleeding, determination of a bleeding time may also be indicated.

If the PT or PTT is prolonged, the next step in the evaluation should be a 1:1 mix in which the patient's plasma is mixed with normal plasma and the PT and PTT are determined again. If the patient is deficient in some factor, the normal plasma partially corrects this deficiency and the PT or PTT are corrected to a normal value. If an inhibitor to a particular factor is present, this inhibitor also blocks the action of the normal plasma, and the PT or PTT are not corrected. The most common inhibitor is the lupus anticoagulant, which is seen in the presence and absence of autoimmune disease; it is usually associated with an elevated PTT that is not corrected with a 1:1 mix. It is associated with an increased risk of clotting, not bleeding.

If the platelet count is very low ($20,000/\text{mm}^3$) and the PT and PTT are normal, a bone marrow biopsy may be indicated to determine whether there are adequate platelet precursors in the bone marrow. If platelet precursors are absent, an underproduction state exists; if precursors are present, this implies that the low platelet count stems from peripheral destruction. Using the detection of antiplatelet antibodies as evidence for the autoimmune destruction of platelets is not reliable because some normal people have antiplatelet antibodies without peripheral destruction, whereas the titers in people with

ITP may be low.

What therapies are available for the management of bleeding disorders?

Blood components can be used to correct deficiencies in the divisions of the coagulation system. Fresh frozen plasma contains various percentages of each of the coagulation proteins and can be used when more than one factor is deficient (e.g., vitamin dependent factors). Cryoprecipitate contains von Willebrand's factor, fibrinogen, and factor VIII, but is most commonly used in people with an acquired fibrinogen deficiency (e.g., DIC and liver disease). Because of the risk of viral infection (it is pooled from multiple donors), cryoprecipitate is no longer used as frequently for patients with mild hemophilia and von Willebrand's disease. Instead, desmopressin (DDAVP) is now used in the treatment of these diseases, as well as in the platelet dysfunction associated with uremia and other qualitative defects. This drug works by stimulating the release of von Willebrand's factor (factor VIII) from the endothelium. There are also specific heat-treated factor concentrates for factors VIII and IX, which can be used in the management of hemophilia.

Quantitative platelet problems caused by underproduction, as well as some consumptive states such as uncontrolled bleeding, can be treated with platelet transfusions. This is often futile in the setting of autoimmune destruction until the autoimmune process is arrested; in fact, platelet transfusion may accelerate destruction by stimulating the immune system. The usual initial treatment for ITP is with high-dose prednisone, followed by splenectomy if the prednisone fails to block the immune destruction. Transfusing platelets into a patient who has uremia or who is taking a drug that renders his or her own platelets dysfunctional is also futile because the transfused platelets quickly become affected as well.

ANSWERS TO CASE 26:

What is the next step in diagnosis?

The next step in a patient with unexplained increase in PT or PTT is to perform a mixing study (mix patient's plasma 1:1 with normal plasma). If coagulation studies normalize, the patient has an inherited clotting factor deficiency (vWD or hemophilia). Otherwise, suspect an acquired clotting factor inhibitor such as heparin.

Mixing study shows correction when normal plasma is mixed with the patient's plasma, so he is suspected to have an inherited coagulopathy (clotting factor deficiency).

What is the next diagnostic step?

Obtain vWF assays (positive only in vWD) and factor VIII levels (factor VIII coagulant, factor VIII antigen, and factor VIII vWF). In hemophilia A, factor VIII coagulant level is low, but other factor VIII levels are normal. In vWF all three levels are low. If all three factor VIII levels are normal, obtain factor IX coagulant level (decreased in hemophilia B).

DISCUSSION

How is hemophilia treated?

Both hemophilia A and B are inherited in an X-linked recessive pattern (hemophilia A is much more common). Most cases are detected in childhood, but milder cases may not be diagnosed until early adulthood. Management of hemophilia A is as follows:

- Bleeding: DDAVP is the first line therapy in mild disease (>5% factor VIII). Factor VIII concentrates are first-line therapy in moderate to severe disease. Also, treat pain from hematomas or hemarthroses with non-NSAID analgesics.
- Head trauma: Obtain CT scan to rule out intracranial bleed, even in minor trauma.
- Pre-operative treatment: administer factor VIII until level is at least 30% to 50%.

ANSWERS TO CASE 27:

On the basis of the physical examination and laboratory findings, what is the differential diagnosis in this patient?

The neck adenopathy in this patient can represent a normal finding; 50% of patients can have lymph nodes that are less than 0.5 cm in diameter. It can also signify acute infection stemming from acute viral infections, mononucleosis, toxoplasmosis, or pulmonary infections, but in this setting the nodes are usually firm and tender and recede within 2 to 4 weeks. Solid tumors are also a consideration in the differential diagnosis, and include head and neck cancer, as well as thymic, lung, and breast cancer; lung and breast cancers are more commonly associated with supraclavicular and axillary

adenopathy. A fourth possibility is Hodgkin's disease or non-Hodgkin's lymphoma. Patients with lymphoma can have lymph nodes that come and go.

DISCUSSION

How and when does Hodgkin's disease typically present?

Hodgkin's disease typically presents in adolescence or young adulthood. However, a bimodal age distribution has been observed, especially in developed countries. The first peak is in adolescence or young adulthood, whereas the second peak occurs at 55 years of age. Hodgkin's disease typically presents as a waxing and waning adenopathy, most commonly in the neck or supraclavicular area. Fifty percent of patients present with a mediastinal mass visible on chest radiography, and 40% present with B symptoms (fever, night sweats, and 10% weight loss in the preceding 6 months).

Of what should the staging evaluation in patients with Hodgkin's disease consist, and how do the findings have an impact on therapy?

The staging evaluation in patients with Hodgkin's disease includes a complete history and physical examination. Laboratory investigations should include a complete blood count and evaluation of the smear for changes indicating anemia, hemolysis, or abnormal white blood cells as well as a differential, determinations of the sedimentation rate and alkaline phosphatase level, and evaluation of liver and renal function. The radiologic evaluation should always include CT studies of the chest, abdomen, and pelvis or CT/PET scans.

A diagnosis based on tissue findings is a must. Needle aspiration or cytologic findings is not adequate because the tissue obtained by these methods yields no information about the nodal architecture. It is preferable to obtain a lymph node or wedge of a large mass, but even then it may take more than one lymph node biopsy to document the presence of the disease if only reactive hyperplasia is seen. Bone marrow biopsy is a required part of the staging workup, particularly in symptomatic patients, but should not be substituted for the tissue examination because, again, the nodal architecture cannot be observed. General guidelines no longer suggest performing a staging laparotomy unless if the results would affect the nature of therapy. This may happen in early stage disease

(i.e., stages IB, IIB, and IIIA), when the findings from laparotomy could alter a decision to use radiation therapy alone.

The choice of therapy in patients with Hodgkin's disease is governed by stage. Patients with stage I and II disease can be treated with radiation therapy alone. If there is bulky disease, combined chemotherapy and irradiation should be used. For patients with stage III and IV disease, chemotherapy should be used with radiation delivered to sites of bulky disease. There is still some controversy about what is the best treatment for stage IIB and IIIA disease. Most therapeutic options have high remission rates, and frequently long-term side effects dictate the choice.

What are the known causes or diseases associated with the development of non-Hodgkin's lymphoma?

The risk of lymphoma is increased in patients with certain connective tissue and immunologic disorders. These include human immunodeficiency virus (HIV) infection, Klinefelter's syndrome, acquired hypogammaglobulinemia, iatrogenic immunosuppression (especially after organ transplantation), ataxia-telangiectasia syndrome, Sjgren's syndrome, rheumatoid arthritis and systemic lupus erythematosus, Swiss-type agammaglobulinemia, common variable immunodeficiency disease, acquired immunodeficiency syndrome, and the X-linked lymphoproliferative syndrome.

A viral etiology of lymphoma has been proposed, but no clear proof of this virus exists except for human T-cell leukemia virus type 1 (HTLV-1) infection. Certain types of more common lymphomas have been associated with a viral etiology (e.g., Burkitt's lymphoma and Epstein-Barr virus and HIV or post organ transplantation lymphomas). The search to establish a viral cause has implicated oncogenes, leading to the identification of various cytogenetic abnormalities in lymphoma. The common pattern is for a known oncogene to be translocated into an immunoglobulin gene locus. The common translocations are listed in Table 27-1.

1. **Table 27-1.** Common Translocations in Patients with Lymphoma

Translocation Histologic	Type of Lymphoma
t(8;14) chromosome	Burkitt's and non-Burkitt's
t(2;8) chromosome	Burkitt's and non-Burkitt's
t(8;22) chromosome	Burkitt's and non-Burkitt's

t(14;18) chromosome	Follicular
t(2;5) chromosome	Anaplastic large cell

How does the World Health Organization's working formulation of non-Hodgkin's lymphoma differ from the older classifications?

The non-Hodgkin's lymphomas are classified according to histologic type. The newer World Health Organization working formulation is based on the morphologic features of each type of lymphoma. This classification divides the lymphomas into three major subgroups: low grade, intermediate grade, and high grade. Therefore, the lymphomas are classified according to both their morphologic features and their behavior. Newer classifications examine molecular characteristics, as shown in Table 27-2.

Table 27-2. WHO Classification of the Non-Hodgkin's Lymphomas

The indolent lymphomas

○ **B-cell neoplasms**

- Small lymphocytic lymphoma/B-cell chronic lymphocytic leukemia
- Lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinemia)
- Plasma cell leukemia
- Hairy cell leukemia
- Follicular lymphoma (grade 1 and 2)
- Marginal cell lymphoma

○ **T-cell neoplasms**

- T-cell large granular lymphocyte leukemia
- Mycosis fungoides
- T-cell prolymphocytic leukemia

○ **Natural killer cell neoplasms**

- Natural killer cell large granular lymphocyte leukemia

The aggressive lymphomas

○ **B-cell neoplasms**

- Follicular lymphoma (grade 3)
- Diffuse large B-cell lymphoma
- Mantle cell lymphoma

- **T-cell neoplasm**

- Peripheral T-cell lymphoma
- Anaplastic large cell lymphoma, T/null cell

The highly aggressive lymphomas

- **B-cell neoplasms**

- Burkitt's lymphoma
- Precursor B-lymphoblastic leukemia/lymphoma

- **T-cell neoplasms**

- Adult T-cell lymphoma/leukemia
- Precursor T-lymphoblastic leukemia/lymphoma

ANSWERS TO CASE 28:

What is the likely diagnosis?

Transient small nodes in the neck or groin are common benign findings. However, a 3 X 4 cm mass of nodes for 2 months is undoubtedly abnormal. Persistent lymphadenopathy and constitutional symptoms suggest a likely diagnosis of lymphoma or chronic leukaemia. Sarcoidosis and tuberculosis are possible but less likely diagnoses. Lymph nodes are normally barely palpable, if at all. The character of enlarged lymph nodes is very important. In acute infections the nodes are tender and the overlying skin may be red. Carcinomatous nodes are usually very hard, fixed and irregular. The nodes of chronic leukaemias and lymphomas are non-tender, firm and rubbery. The distribution of enlarged lymph nodes may be diagnostic. Repeated minor trauma and infection may cause enlargement of the locally draining lymph nodes. Enlargement of the left supraclavicular nodes may be due to metastatic spread from bronchial and nasopharyngeal carcinomas or from gastric carcinomas (Virchow's node). However, when there is generalized lymphadenopathy with or without splenomegaly, a systemic illness is most likely. The typical systemic symptoms of lymphoma are malaise, fever, night sweats, pruritus, weight loss, anorexia and fatigue. Fever indicates extensive disease, and may be associated with night sweats. Severe skin itching is a feature of some cases of lymphoma and other myeloproliferative illnesses.

The incidence of lymphoma is greatly increased in patients who are immunosuppressed, such as organ transplant recipients and patients with HIV infection.

Major differential diagnosis of generalized lymphadenopathy.

- Infections: infectious mononucleosis or 'glandular fever'(caused by Epstein-Barr virus infection), toxoplasmosis, cytomegalovirus infection, acute HIV infection, tuberculosis, brucellosis and syphilis.
- Inflammatory conditions: systemic lupus erythematosus, rheumatoid arthritis and sarcoidosis.
- Lymphomas or chronic lymphocytic leukemia.

How would you investigate and manage this patient?

The most likely clinical diagnosis in this man is lymphoma. The patient should be referred to a local haemato-oncology unit. He should have a lymph-node biopsy to reach a histological diagnosis, and a computed tomography (CT) scan of the thorax, abdomen and bone marrow to stage the disease. CT scanning is a non-invasive and effective method of imaging retroperitoneal, iliac and mesenteric nodes. Positron-emission tomography (PET) combined with CT increases the sensitivity for detecting disease (Fig. 35.1), and is useful for assessing response to treatment. The patient will require treatment with radiotherapy and chemotherapy. Radiotherapy alone is reserved for patients with limited disease, but this patient has widespread disease. He should be given allopurinol prior to starting chemotherapy, to prevent massive release of uric acid as a consequence of tumor lysis, which can cause acute renal failure.

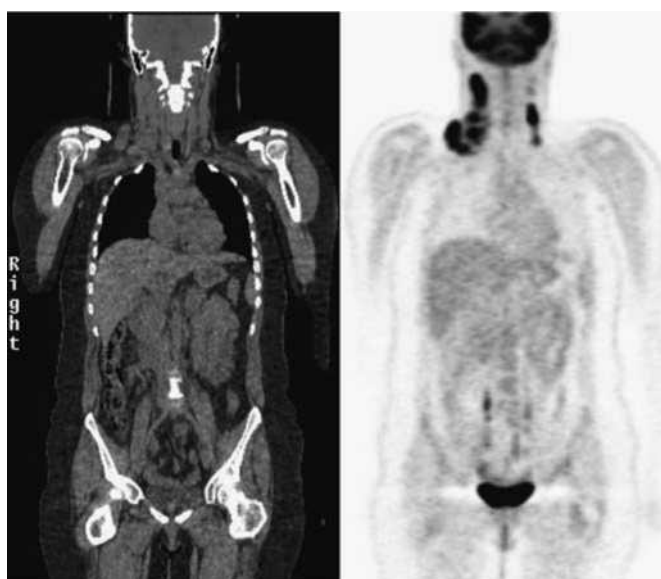


Figure 35.1 CT-PET image showing increased activity in enlarged lymph nodes, particularly in the right side of the neck.

Clinical pearls

- The character and distribution of abnormal lymph nodes is helpful in reaching a diagnosis.
- Lymphadenopathy affecting two or more separate groups of nodes suggests lymphoma or a systemic infection.
- CT-PET scanning allows accurate staging of disease and assessment of maintenance of remission in response to treatment.
