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TWO CASES OF THYROID COLLISION TUMORS WITH DIFFERENT DIFFERENTIATION PATHWAYS

Collision tumors of the thyroid gland are rare and characterized by the coexistence of two distinct neoplasms with different histopathological origins within the same anatomical region. We report two cases of synchronous thyroid carcinomas demonstrating divergent differentiation pathways: papillary thyroid carcinoma (PTC) combined with follicular carcinoma in one case, and PTC combined with a poorly differentiated component in the other case. Both cases presented with a long-term history of multinodular goiter but displayed rapid recent growth. Surgical treatment with total thyroidectomy was performed in both cases. Histopathology confirmed dual tumor composition with sharp topographic demarcation, supporting the diagnosis of collision tumors. We discuss clinicopathological features, diagnostic challenges, and potential mechanisms underlying synchronous tumorigenesis. While the exact pathogenesis remains unclear, environmental and molecular factors may contribute to divergent malignant transformation within a susceptible thyroid gland. Awareness of this phenomenon is crucial for accurate diagnosis and management.

Keywords: thyroid collision tumor, papillary carcinoma, follicular carcinoma, synchronous neoplasms.

Collision tumors [1] are diagnosed when two or more neoplasms of different histological origin coexist in the same anatomical location but arise independently and are not intermingled at the molecular level. Unlike combined or mixed tumors, the components of which have a common origin, collision tumors represent two separate neoplastic processes. Despite their proximity, their cell populations remain distinct and separated by normal tissue [2].

Collision tumors can consist of two benign, one benign and one malignant, or two malignant neoplasms. They can occur in various organs, including the stomach, liver, adrenal glands, lungs, ovaries, kidneys, colon, skin, and thyroid gland [3].

Synchronous medullary and papillary collision thyroid carcinomas were first described by Lamberg in 1981 [4]. Since then, several combinations have been reported, including well-differentiated carci-

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noma with Hürthle cell carcinoma, minimally invasive follicular carcinoma with papillary microcarcinoma, follicular and anaplastic carcinomas, and primary squamous cell carcinoma coexisting with papillary carcinoma [5—9]. There are also reports of primary carcinomas coexisting with synchronous metastases to the thyroid gland, such as papillary carcinoma with metastatic liposarcoma [10], osteosarcoma [11], or lung adenocarcinoma [6].

Synchronous medullary, papillary, and follicular thyroid carcinomas are extremely rare, with a reported incidence of less than 1% [8]. Therefore, each observation has an important scientific and clinical significance. We present two cases of synchronous coexistence of medullary and micropapillary carcinomas, as well as follicular and papillary thyroid carcinomas, in two women and discuss the hypothesis of factors contributing to their development.

Clinical case presentation

Case 1. A 67-year-old female patient was found to have a thyroid nodule in the left lobe during an ultrasound examination; however, she did not receive any treatment for the following 20 years. In 2025, a biopsy of the nodule was performed, and cytology revealed features consistent with medullary thyroid carcinoma (MTC): binucleated monomorphic small-to-medium cells arranged in cohesive sheets, with well-defined borders, eccentrically located nuclei, and absence of colloid. There was no family history of hereditary thyroid cancer.

Thyroid function was preserved, as evidenced by TSH 2.07 μIU/mL, anti-TPO 14.1 IU/mL, anti-TG 17.5 IU/mL, and T4 0.734 ng/dL. Serum calcitonin was markedly elevated at 502.0 pg/mL (normal value: ≤6.0 pg/mL).

The patient underwent total thyroidectomy with central and bilateral lateral neck dissection. Pathological examination of the left thyroid lobe revealed a nodular tumor without a distinct capsule, composed of round and spindle-shaped cells with eosinophilic cytoplasm and clear borders. The tumor cells had hyperchromatic, monomorphic nuclei. The stroma was dense and eosinophilic. This morphology is typical of a neuroendocrine tumor and most consistent with medullary carcinoma. Microscopically, the tumor was confined to the thyroid gland (Fig. 1).

To confirm the diagnosis, immunohistochemistry was performed. Tumor cells demonstrated positive staining for neuroendocrine markers (synaptophysin and chromogranin A) as well as for calcitonin, confirming the diagnosis of medullary thyroid carcinoma (Figs. 2 and 3).

In the right thyroid lobe, a very small (approximately 2 mm) focus of tumor was identified, composed of rounded, clear nuclei containing intranuclear inclusions. There was no necrosis, and mitotic figures were not observed. This histological pattern was characteristic of papillary thyroid microcarcinoma (Fig. 4).

Thus, histopathological evaluation confirmed medullary carcinoma of the left thyroid lobe and an incidental papillary microcarcinoma of the right lobe. Metastatic deposits of medullary carcinoma were found in the lymph nodes.

Pathology report: MTC (1.8 cm), pT1b N1b LVI0 Pn0 R0 (AJCC/TNM 8th edition), ICD-O code 8510/3. Papillary thyroid microcarcinoma (0.2 cm), pT1a R0 (AJCC/TNM 8th edition), ICD-O code 8260/3.

One week after surgery, the serum calcitonin decreased to 11.10 pg/mL, and after one month — to 3.26 pg/mL.

The patient was prescribed L-thyroxine 100 mg/day (replacement, not suppressive therapy after thyroidectomy) and is now under follow-up.

Case 2. A 31-year-old female patient was found to have two nodular lesions within both thyroid lobes during an ultrasound examination. Fine-needle aspiration confirmed the presence of well-differentiated carcinoma in each nodule. There was no history of neck irradiation or family history of thyroid cancer.

Baseline laboratory tests (including TSH, free T3 and T4, calcitonin) were within normal limits. A total thyroidectomy with central neck dissection was performed without complications.

Pathological examination: In the left thyroid lobe, a tumor nodule measuring up to 2 cm was identified. It was surrounded by a dense fibrous capsule of uneven thickness with areas of hyalinization. The nodule demonstrated a heterogeneous micro- and macrofollicular architecture, with colloid present in most follicles. The tumor cells were monomorphic, with round hyperchromatic nuclei; nucleoli were present in most cells. The cytoplasm was scant, mildly variable, pale eosinophilic, with

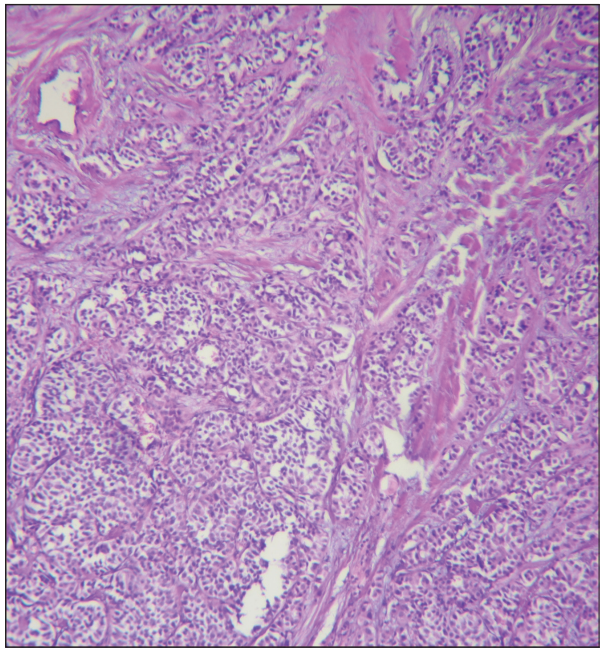

Fig. 1. Medullary thyroid carcinoma (case 1). H&E staining. ×100

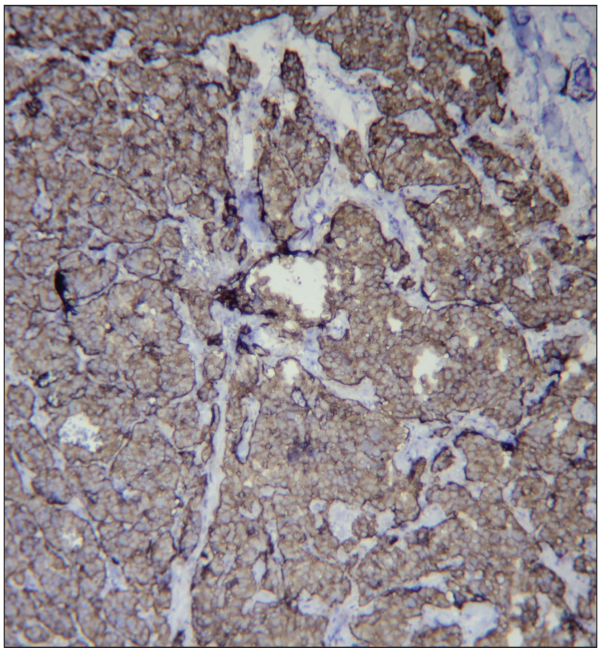

Fig. 2. Medullary thyroid carcinoma (case 1). Positive immunohistochemical staining for synaptophysin. ×100

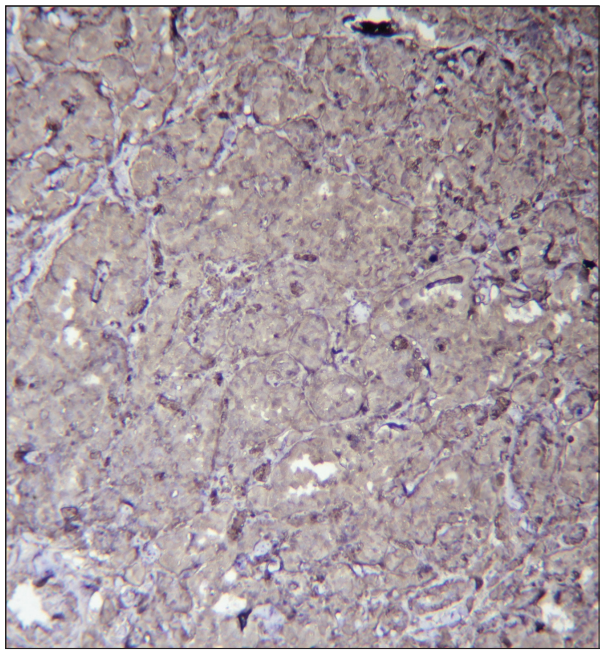

Fig. 3. Medullary thyroid carcinoma (case 1). Positive immunohistochemical staining for calcitonin. ×100

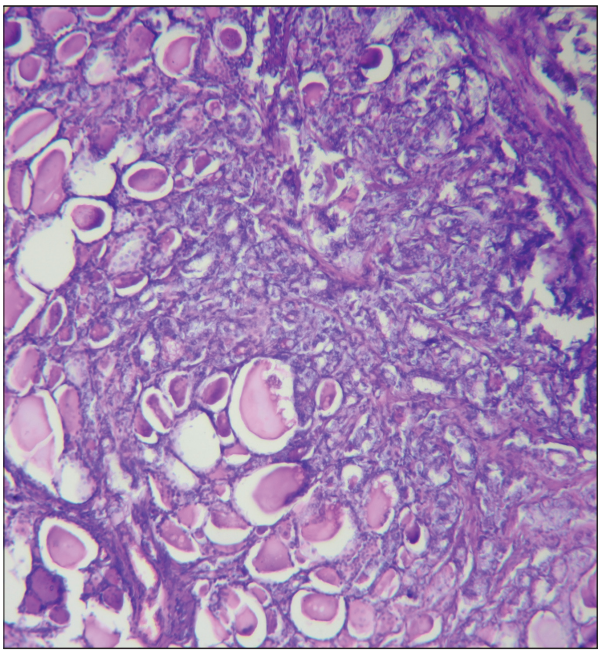

Fig. 4. Papillary thyroid microcarcinoma (case 1). H&E staining. ×100

well-defined borders. Mitoses were rare (1—2 per 10 HPF). The capsule showed multiple foci of capsular invasion; no vascular invasion was detected. The histologic pattern corresponded to follicular carcinoma. Thyroid tissue outside the nodule demonstrated diffuse lymphocytic infiltration.

Immunohistochemistry showed diffuse positivity of tumor cells for thyroglobulin, confirming their origin from thyroid follicular epithelium. Thus, the morphology and immunophenotype were consistent with follicular thyroid carcinoma (Fig. 5).

In the right thyroid lobe, a tumor nodule demonstrated histological features of papillary carcinoma, follicular variant. No evidence of lymphovascular or perineural invasion was found. The maximum tumor diameter was 1.0 cm. The tumor was

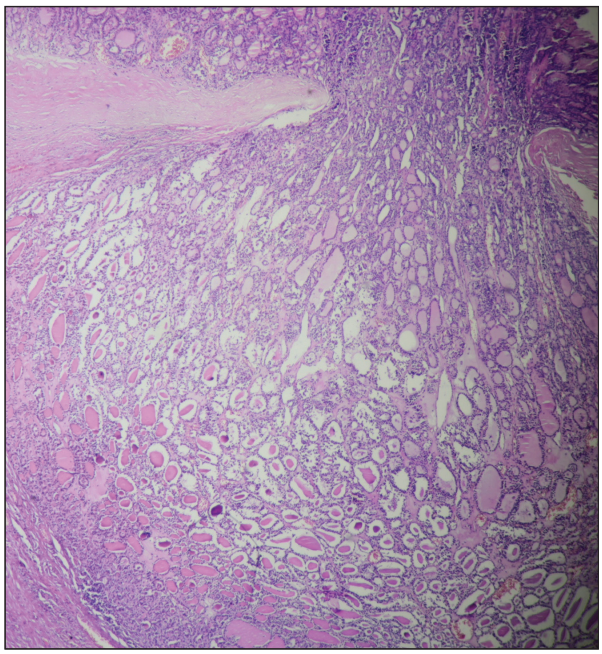

Fig. 5. Follicular thyroid carcinoma (case 2). Extracapsular tumor extension. H&E staining. ×40

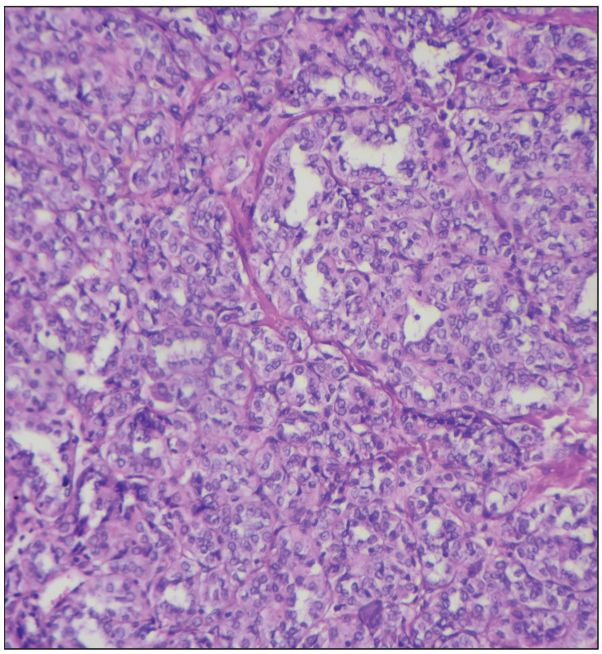

Fig. 6. Papillary thyroid carcinoma (case 2). Nuclear features characteristic of papillary carcinoma. H&E staining. ×200

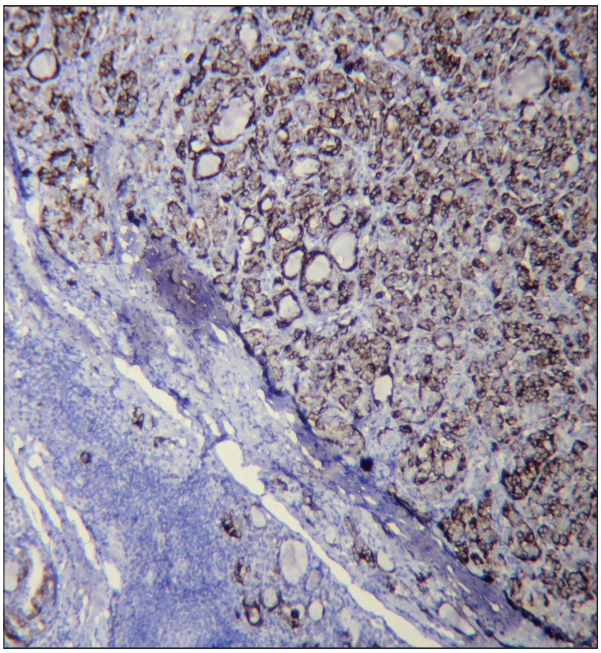

Fig. 7. Papillary thyroid carcinoma (case 2). Positive immunohistochemical staining for cytokeratin-19. ×100

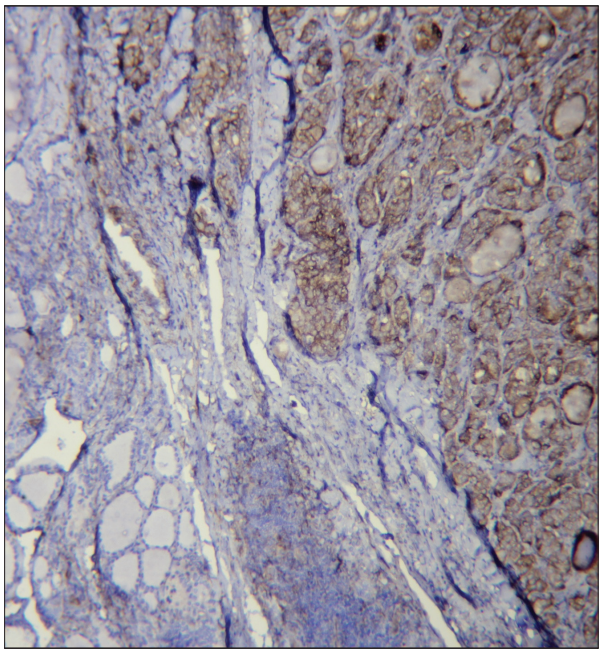

Fig. 8. Papillary thyroid carcinoma (case 2). Positive immunohistochemical staining for galectin-3. ×100

confined to the thyroid lobe with no capsular invasion. Thyroid parenchyma outside the tumor showed diffuse lymphocytic infiltration.

Immunohistochemistry revealed strong positivity of tumor cells for cytokeratin 19 (with weak staining of internal controls in scattered normal thyroid cells). Tumor cells also demonstrated strong positive staining for galectin-3 (Figs. 6—8).

Thus, the pathological evaluation of the resected specimen confirmed synchronous malignancies within both thyroid lobes. One nodule represented papillary thyroid carcinoma, pT1a N0 Mx LVI0 Pn0 R0 (ICD-O code 8340/3), and the other represented minimally invasive follicular carcinoma, pT1a N0 Mx LVI0 Pn0 R0 (ICD-O code 8335/3), according to the AJCC/TNM 8th edition.

No metastatic involvement was found in cervical lymph nodes. The patient began radioiodine therapy. At present, there are no signs of recurrence or metastatic progression.

Discussion

Collision tumors represent the physical apposition of two morphologically independent neoplasms within a single anatomical organ. They differ from combined or composite tumors, in which the components share a common origin or have mixed histology [1].

In the thyroid gland, such associations most often include papillary and follicular carcinoma or the coexistence of well-differentiated carcinoma with medullary carcinoma or even non-epithelial tumors [12]. Collision tumors of the thyroid gland are more common in women (ratio 1:2) and typically present in the fifth, sixth, and seventh decades of life [13].

Accurate diagnosis is crucial, especially for medullary, pseudopapillary, follicular, and oncocytic subtypes; however, in non-oncology centers, many synchronous cancers are likely underdiagnosed or misclassified [14]. Clinically, collision tumors tend to be more aggressive, making the treatment more challenging. The presence of two tumors with different phenotypes can increase the risk of metastasis and recurrence, especially if both cancers exhibit aggressive features.

Papillary thyroid cancer typically metastasizes to the cervical lymph nodes, while follicular cancer spreads hematogenously to the lungs and bones. Medullary cancer metastasizes not only to the regional lymph nodes but also to the lungs, liver, and bones. It can also spread to the brain (usually the pituitary gland) and, less commonly, to the skin or breast [15]. Therefore, a synchronous disease can potentially manifest itself as both lymphatic and hematogenous metastases to internal organs or bones.

Each synchronous cancer should be staged as an independent primary tumor [14]. The treatment strategy (surgery, adjuvant radioiodine therapy) is selected based on the most aggressive cancer variant. Prognosis can be refined using molecular markers such as mutations in the *BRAF* and *TERT* gene promoters, but such testing is not routinely performed in clinical practice.

The mechanisms of the development of synchronous collisional tumors remain a subject of fundamental research. Three main hypotheses are discussed: the role of cancer stem cells, microenvironmental disruption, and stochastic coexistence.

One of the theories suggests that collisional tumors arise due to the ability of cancer stem cells to differentiate along divergent lineages after the activation of driver mutations, leading to the formation of two separate tumors in a single organ [14, 16, 17]. Molecular hallmarks of such tumors include the absence of transitional forms between components, genetic and epigenetic heterogeneity, and a high prevalence of environmentally induced mutations (e.g., *BRAF, RAS, RET/PTC*) [18].

The "pluripotent progenitor cell" theory explains the origin of carcinomas from the follicular and parafollicular cell lines, but it does not account for synchronous tumors of different embryological origins, such as papillary and primary squamous cell thyroid carcinomas [19]. The "field cancerization" theory suggests that the presence of a primary tumor can cause changes in surrounding tissues — decreased oxygen tension, altered pH, impaired microcirculation, impaired metabolism, and altered stem cell differentiation — thereby creating a favorable environment for the development of another malignant tumor de novo [6]. In many patients, synchronous thyroid cancer occurs in the setting of Hashimoto's thyroiditis, suggesting that a chronic inflammatory microenvironment may promote the development of collision tumors.

A limitation of this theory is that it does not define the precise conditions under which one tumor can promote the development of the other [19] and does not explain why collision tumors are rare.

The stochastic (random) theory proposes that two independent primary tumors develop in the thyroid gland by chance, and carcinogenesis is initiated by a combination of chemical, physical, biological, and psychosocial influences that can contribute to the development of diseases, including cancer [20].

Even sublethal doses of radiation can induce mutations in the *RET/PTC* genes (increasing the risk of papillary carcinoma) or *CALCA* (associated with medullary carcinoma) [21].

Exposure to toxic substances (heavy metals, dioxins, combustion products) can exert endocrine-

disrupting effects, promoting oncogenic mutations in thyrocytes or C cells [22].

Polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs), dioxins, and heavy metals can independently induce epigenetic changes in various cell lines, including the hypermethylation of tumor suppressor gene promoters such as *CDKN2A*, thereby promoting the development of heterogeneous collision-induced tumors [23]. Iodine deficiency can promote the proliferation of various cell populations (thyrocytes and C cells), thereby increasing the likelihood of collision tumors such as papillary thyroid carcinoma (arising from thyrocytes) and MTC (arising from C cells) [8].

The combined action of these factors creates conditions in which simultaneous mutagenic effects can occur on different thyroid cell types, triggering independent neoplastic clonal processes.

Epidemiological data have shown an increase in the incidence of thyroid cancer during wartime. Previous studies have demonstrated a higher incidence of papillary thyroid carcinoma among US military personnel compared to the general population [24, 25]. Given the rarity of collisional carcinomas, their documentation is critical for understanding the heterogeneity of thyroid neoplasms and the potential influence of exposome-related factors and for improving clinical approaches.

To sum up, collision thyroid carcinomas are a rare diagnosis complicating staging and selection of optimal treatment strategies.

The studied tumors require increased diagnostic vigilance, as treatment must take into account differences in their biological behavior. Surgical excision followed by adjuvant therapy specific to the tumor subtype remains the standard. Further research into the environmental and molecular factors that contribute to disease development is needed.

Conflict of interest statement

The authors declare no competing interests.

Consent

Written informed consent for publication of these clinical cases and accompanying images was obtained from the patients. A copy of the signed consent form is available to the journal's Editor-in-Chief upon request.

Author contributions

KO: Conceptualization and study design; data analysis and interpretation; writing the manuscript; critical revision of the manuscript; final approval of the manuscript. ZS: Data collection and/or data assembly; critical revision of the manuscript; final approval of the manuscript. TO: Data collection and/or data assembly; data analysis and interpretation. AA: Data analysis and interpretation. KM: Data collection and/or data assembly; data analysis and interpretation. DM: Data collection and/or data assembly; data analysis and interpretation. KK: Data collection and/or data assembly; data analysis and interpretation; writing the manuscript.

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ДВА ВИПАДКИ КОЛІЗІЙНИХ ПУХЛИН ЩИТОПОДІБНОЇ ЗАЛОЗИ З РІЗНИМИ ШЛЯХАМИ ДИФЕРЕНЦІАЦІЇ

Колізійні пухлини щитоподібної залози є рідкісними та характеризуються співіснуванням двох різних новоутворень з різним гістопатологічним походженням у межах однієї анатомічної області. Ми повідомляємо про два випадки синхронних карцином щитоподібної залози, що демонструють дивергентні шляхи диференціації: папілярна карцинома щитоподібної залози (ПЩЗ) у поєднанні з фолікулярною карциномою в одному випадку та ПЩЗ у поєднанні з низькодиференційованим компонентом у другому. В обох випадках спостерігався тривалий анамнез багатовузлового зоба, але нещодавно спостерігався і швидкий ріст. В обох випадках було проведено хірургічне лікування з тотальною тиреоїдектомією. Гістопатологія підтвердила подвійний склад пухлини з чіткими топографічними межами, що підтверджує діагноз колізійних пухлин. Ми обговорюємо клініко-патологічні особливості, діагностичні проблеми та потенційні механізми, що лежать в основі синхронного туморогенезу. Хоча точний патогенез залишається незрозумілим, екологічні та молекулярні фактори можуть сприяти дивергентній злоякісній трансформації в межах чутливої щитоподібної залози. Усвідомлення цього явища має вирішальне значення для точної діагностики та лікування.

Ключові слова: колізійна пухлина щитоподібної залози, папілярна карцинома, фолікулярна карцинома, синхронні новоутворення.