

Synchronous Medullary Carcinoma and Primary Follicular Lymphoma in the Same Thyroid Lobe: A Case Report and Literature Review

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Case Report

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Abstract

Primary thyroid lymphoma (PTL) and medullary thyroid carcinoma (MTC) are rare malignancies. Their synchronous development as a collision tumor within a single thyroid lobe is exceptionally uncommon. We present a unique case of a 53-year-old female with a long-standing history of autoimmune thyroiditis who was simultaneously diagnosed with MTC and primary follicular lymphoma (FL, grade 3b) following histological examination of a surgical specimen. The diagnosis was confirmed using immunohistochemistry. Notably, the lymphoma cells lacked BCL2 expression despite a high histological grade, characteristic of a specific localized subgroup of extranodal FLs. This case highlights the critical importance of comprehensive histological and immunohistochemical evaluation of thyroid nodules, particularly in patients with chronic lymphocytic thyroiditis, to guide optimal therapeutic management.

Introduction

Primary thyroid lymphoma (PTL) and medullary thyroid carcinoma (MTC) are rare malignancies. MTC accounts for less than 2% of all thyroid cancers. Conversely, PTL represents approximately 2–5% of primary thyroid malignancies and less than 3% of all extranodal non-Hodgkin lymphomas. The vast majority of thyroid lymphomas are diffuse large B-cell lymphomas (DLBCL) and extranodal marginal zone lymphomas (MALT lymphomas) [1, 2]. Follicular lymphoma (FL) is an extremely rare histological subtype in this location, comprising only 3–5% of all PTL cases [3].

Cases of the simultaneous development of two distinct malignant tumors in the thyroid gland (so-called "collision tumors") are uncommon. The literature describes clinical observations of MTC combined with systemic or primary lymphomas, such as Hodgkin's lymphoma, DLBCL, mantle cell lymphoma, and small lymphocytic lymphoma (SLL) [4-10]. However, the synchronous occurrence of MTC and primary FL in the same thyroid lobe is exceptionally rare. Given the low incidence of both diseases, their coexistence presents a significant diagnostic and therapeutic challenge. In this article, a clinical case of the simultaneous detection of MTC and FL in one thyroid lobe is presented, and the pathogenesis, differential diagnosis, and morphological features of such tumors are discussed. To the best of our knowledge, this is the first description of such a combination in the English-language literature.

Case Report

A 53-year-old female patient was admitted to the surgical department of the National Medical Research Center for Endocrinology in July 2025 for elective surgical treatment. According to her medical history, small thyroid nodules were initially discovered during a routine examination in 2020. Based on hormonal profiling, overt hypothyroidism secondary to autoimmune thyroiditis was diagnosed, and levothyroxine sodium replacement therapy was initiated (75 mcg/day; 50 mcg/day at the time of admission).

In 2022, an elevated serum calcitonin level above reference ranges was documented. A thyroid ultrasound in 2025 revealed a hypoechoic area measuring 21 × 17 × 13 mm in the right lobe, alongside a 7 × 6 mm nodule (TI-RADS 3). Bilateral hyperplastic lymph nodes up to 31 × 9 mm were visualized.

Further laboratory evaluation demonstrated a basal calcitonin level of 49.0 pg/mL (reference range: 0.0–9.8 pg/mL) and a carcinoembryonic antigen (CEA) level of 2.7 ng/mL. Genetic testing for germline mutations in the *RET* gene (exons 10, 11, 13, 14, and 15) was negative for pathogenic variants. Fine-needle aspiration cytology (FNAC) of the isoechoic nodule in the right lobe was consistent with a malignancy (Bethesda VI), whereas the other nodule was classified as benign (Bethesda II). Calcitonin measurement in the needle washout fluid from one of the right lobe nodules revealed extremely high values (2000.0 pg/mL), with no evidence of metastatic involvement in the lymph nodes (lymph node washout calcitonin: 0.5 pg/mL).

The patient underwent a right extrafascial hemithyroidectomy with microsurgical neurolysis of the recurrent laryngeal nerve and an ipsilateral central lymph node dissection.

Macroscopic examination revealed a right lobe measuring 4.0 × 2.7 × 1.8 cm. A poorly circumscribed gray-white nodule measuring 1.9 × 1.5 × 2.0 cm was identified on the cut surface. Histological examination demonstrated that the nodule consisted of two distinct tumor components: a predominant (major) component comprising an abundant lymphoid infiltrate with large pleomorphic cells (centroblasts) forming nodular aggregates with focal necrosis and apoptotic bodies. A high mitotic rate was observed (up to 10 mitoses per high-power field); and a minor component consisting of areas of mildly pleomorphic polygonal cells with amphophilic cytoplasm forming solid, trabecular, and follicular structures within a fibrotic stroma (Fig. 1A-D). No metastases were found in the 16 excised central compartment lymph nodes (pN0). The non-neoplastic thyroid parenchyma showed features of severe lymphocytic thyroiditis.

To accurately verify the diagnosis, an immunohistochemical (IHC) study with an extended antibody panel was performed. The minor component cells exhibited strong cytoplasmic expression of calcitonin and chromogranin A, and strong nuclear expression of TTF-1 (Fig. 2 A-D). The Ki67 proliferation index was less than 1%. CD45 expression was absent. This profile is entirely consistent with MTC (pT1a). The predominant lymphoid component showed massive membranous expression of the pan-B-cell marker CD20, combined with co-expression of germinal center markers BCL6, CD10, and HGAL, as well as weak expression of LMO2 and CD23 on follicular dendritic cells. Notably, the tumor cells lacked the expression of the anti-apoptotic protein BCL2 and MUM1 (Fig 3 A-F). The Ki67 proliferation index in this component reached 70%. These findings established the diagnosis of primary follicular lymphoma (grade 3b).

Based on the IHC analysis, the final diagnosis was established: Multiple primary synchronous malignancies of the right thyroid lobe: 1) Medullary thyroid carcinoma (pT1a, L0, V0, Pn0, R0); 2) Follicular lymphoma, grade 3b.

Discussion

The synchronous development of MTC and FL in a single thyroid lobe represents a unique example of a collision tumor—a neoplasm composed of two histologically and ontogenetically distinct populations of malignant cells. MTC arises from parafollicular C cells (neural crest derivatives) possessing

neuroendocrine properties, whereas FL originates from germinal center B cells of the lymphoid follicle. The exact mechanisms underlying the development of collision tumors remain incompletely understood. Three main hypotheses are considered: 1) the "tumor induces tumor" theory; 2) the common stem cell theory; and 3) the stochastic collision effect theory [8, 11-13].

Chronic autoimmune thyroiditis is traditionally considered a key risk factor for PTL, increasing the risk of development tenfold compared to the general population. It is hypothesized that chronic antigenic stimulation leads to reactive lymphoid proliferation, with subsequent acquisition of genetic mutations initiating malignant transformation [14]. The present patient had a long-standing history of autoimmune thyroiditis, and marked lymphocytic infiltration outside the tumor was histologically confirmed, providing a favorable background for lymphomagenesis. However, a direct link between autoimmune thyroiditis and the development of MTC has not been established [15].

Diagnosing the combination of FL and MTC requires thorough histological and IHC analysis. FNAC often lacks sufficient sensitivity for diagnosing lymphoma due to the similarity of its cytomorphological features with severe lymphocytic thyroiditis, potentially leading to false-negative results. Core needle biopsy remains the gold standard for lymphoma diagnosis.

The global literature contains only a few unique clinical observations of MTC combined with various types of lymphomas, which can be broadly divided into metachronous and synchronous occurrences. Metachronous tumor development was reported in two cases. In a 33-year-old male, MTC was detected following previous chemotherapy for Hodgkin's lymphoma [4]. Another case was described in a 56-year-old patient who was diagnosed with MTC associated with multiple endocrine neoplasia type 2 (MEN2) syndrome in his twenties, and more than thirty years later developed mantle cell lymphoma [5].

Cases of synchronous development of MTC and lymphoproliferative disorders are of significantly greater clinical and pathogenetic interest. Such diagnostic scenarios were described in a 52-year-old female with mesenteric DLBCL and in a patient with splenic marginal zone lymphoma (SMZL), who additionally had a verified MTC metastasis [6]. More complex collision combinations include the simultaneous presence of MTC, papillary thyroid carcinoma, and small lymphocytic lymphoma (SLL) involving the same neck nodes [7]. A similar clinical case was recently described involving an MTC nodule, classic papillary carcinoma, and a cervical lymph node demonstrating the simultaneous presence of papillary carcinoma metastasis and SLL [8]. In another observation, synchronous MTC and Hodgkin's lymphoma with massive bilateral involvement of cervical lymph nodes and only focal infiltration of the thyroid tissue were reported [9].

However, the greatest rarity is the simultaneous development of MTC specifically with PTL, where the lymphoid neoplasia initially arises directly within the organ tissue rather than involving it secondarily. The first extensively documented clinical observation involved an 84-year-old female synchronously diagnosed with an MTC nodule and a massive primary DLBCL almost completely replacing the left lobe [10].

A careful analysis of all published data reveals that no descriptions of the synchronous development of MTC and primary FL of the thyroid within the same organ have been available to date. This circumstance underscores the uniqueness of our clinical observation, which demonstrates for the first time the possibility of the coexistence of these entities as a true collision tumor.

Of particular interest is the phenotype of the identified FL. Historically, FL is associated with the t(14;18) (IGH-BCL2) translocation and BCL2 protein overexpression. However, large studies have shown that follicular lymphomas arising primarily in the thyroid gland are heterogeneous and divided into two clinical and morphological subgroups. The first group exhibits features typical of systemic FL and is prone to dissemination. The second group is characterized by the absence of BCL2 expression and IGH-BCL2 translocation, often has a high histological grade (WHO grade 3), and is typically detected at a localized stage (stage IE) [3]. Our patient's lymphoma (CD10+, BCL6+, BCL2-negative, grade 3b without lymph node involvement) clearly fits into the second, atypical subgroup of localized extranodal FLs.

The therapeutic strategy upon detecting a collision tumor is a complex task. For localized MTC, the standard of care is surgical intervention followed by serum calcitonin monitoring [2]. In the case of FL, the strategy depends on the Ann Arbor stage. For strictly localized stage I FL, the treatment of choice may be active surveillance or adjuvant radiation therapy to the thyroid bed. More aggressive variants require systemic chemoimmunotherapy (e.g., R-CHOP) [1].

Conclusion

In conclusion, this clinical case highlights the critical importance of a comprehensive pathomorphological and immunohistochemical evaluation of thyroid nodules. The presence of one tumor type does not rule out the coexistence of a second malignancy of completely different histogenesis. Oncological vigilance regarding lymphoproliferative disorders in patients with long-standing autoimmune thyroiditis presenting with rapid nodule growth is highly relevant. Meticulous multidisciplinary collaboration among surgeons, endocrinologists, and pathologists allows for the development of an optimal, personalized treatment strategy for such patients.

Declarations

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Author Contributions: N.P., A.V. and L.U. conceived and designed the project. A.V., D.A. and D.K. collected clinical data and/or performed morphological and immunohistochemical analysis. N.P. and E.Ch. wrote the manuscript. All authors agreed to the content of the manuscript.

Ethics approval: This case report was approved by the Institutional Ethics Committee of the Endocrinology Research Centre (protocol code 10, dated 26 May 2020). All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.

Consent to participate: Written informed consent was obtained from the patient included in this case report.

Consent to publish: The patient provided written informed consent for the publication of this case report and any accompanying images in a de-identified form.

Data Availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability: Not applicable.

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Figures

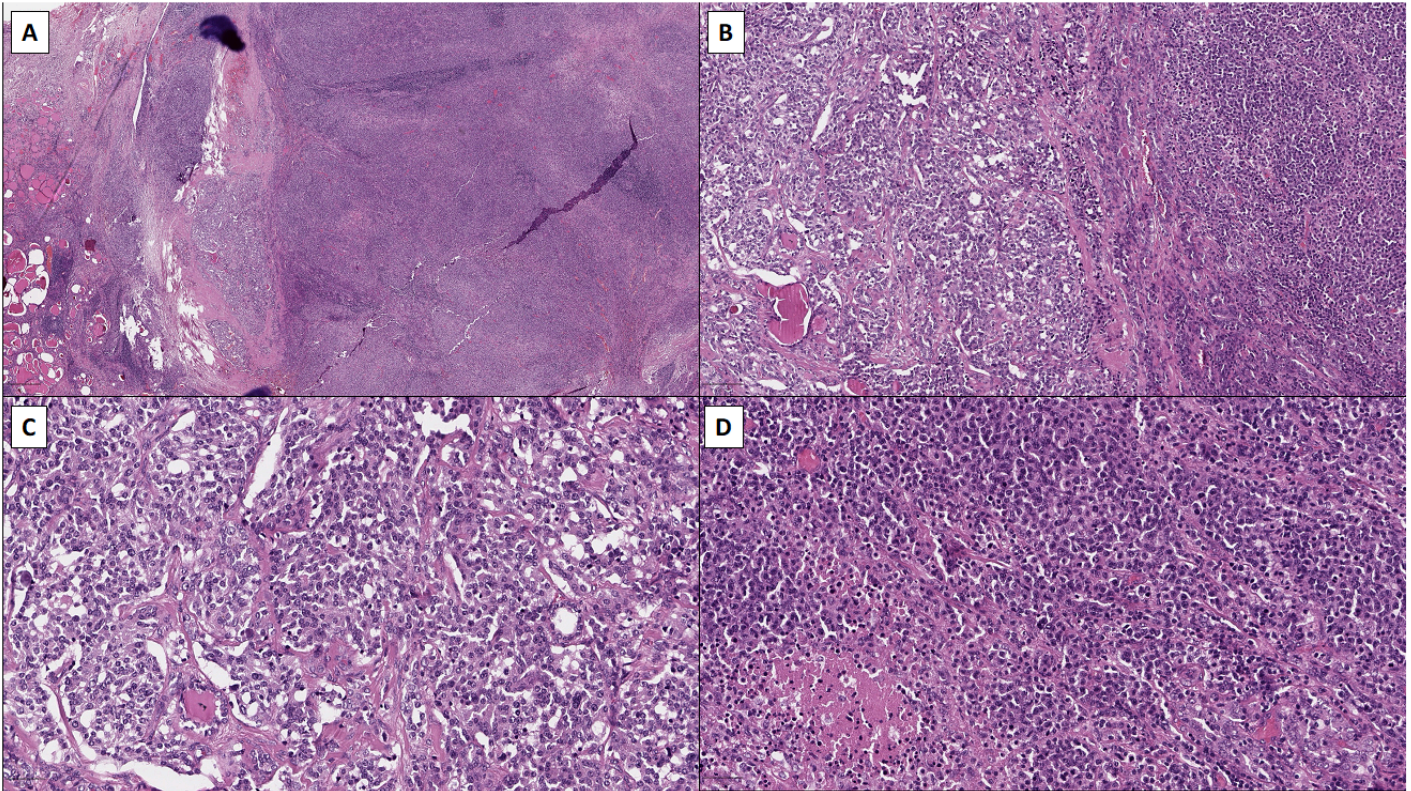


Figure 1

Tumor histology: (A) The tumor consists of two components. (B) At higher magnification, the two tumor components are clearly visualized. (C) The minor component is represented by polymorphic polygonal tumor cells with amphophilic cytoplasm. (D) The predominant component consists of abundant lymphoid infiltrate with large polymorphic cells and foci of necrosis. Hematoxylin-eosin.

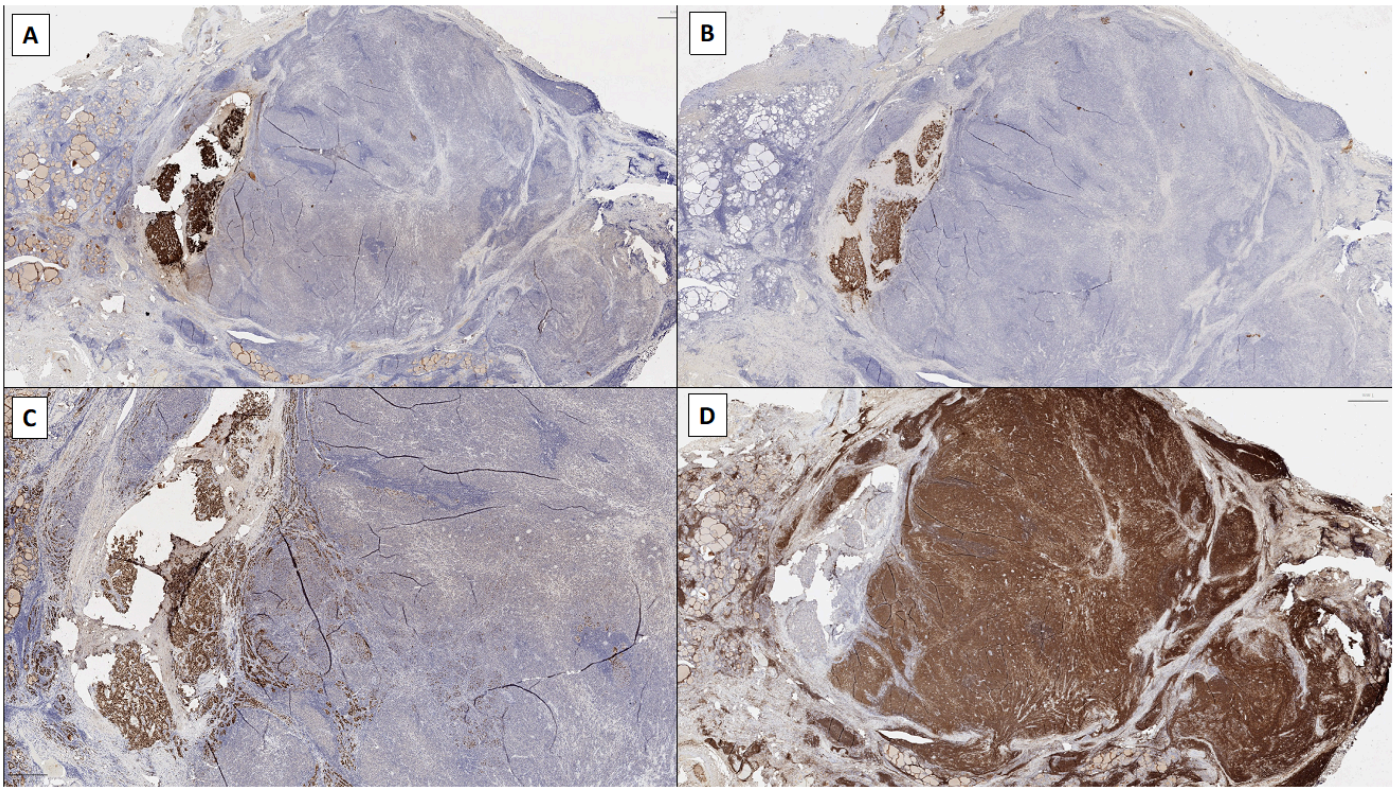


Figure 2

Immunohistochemical findings of the tumor: (A) Strong positive cytoplasmic expression in cells of the minor tumor component with antibodies to Chromogranin A. (B) Strong positive cytoplasmic expression in cells of the minor tumor component with antibodies to Calcitonin. (C) Strong positive nuclear expression in cells of the minor tumor component with antibodies to TTF1. (D) Strong positive expression in cells of the major tumor component with antibodies to CD45, while the reaction in the minor component is negative.

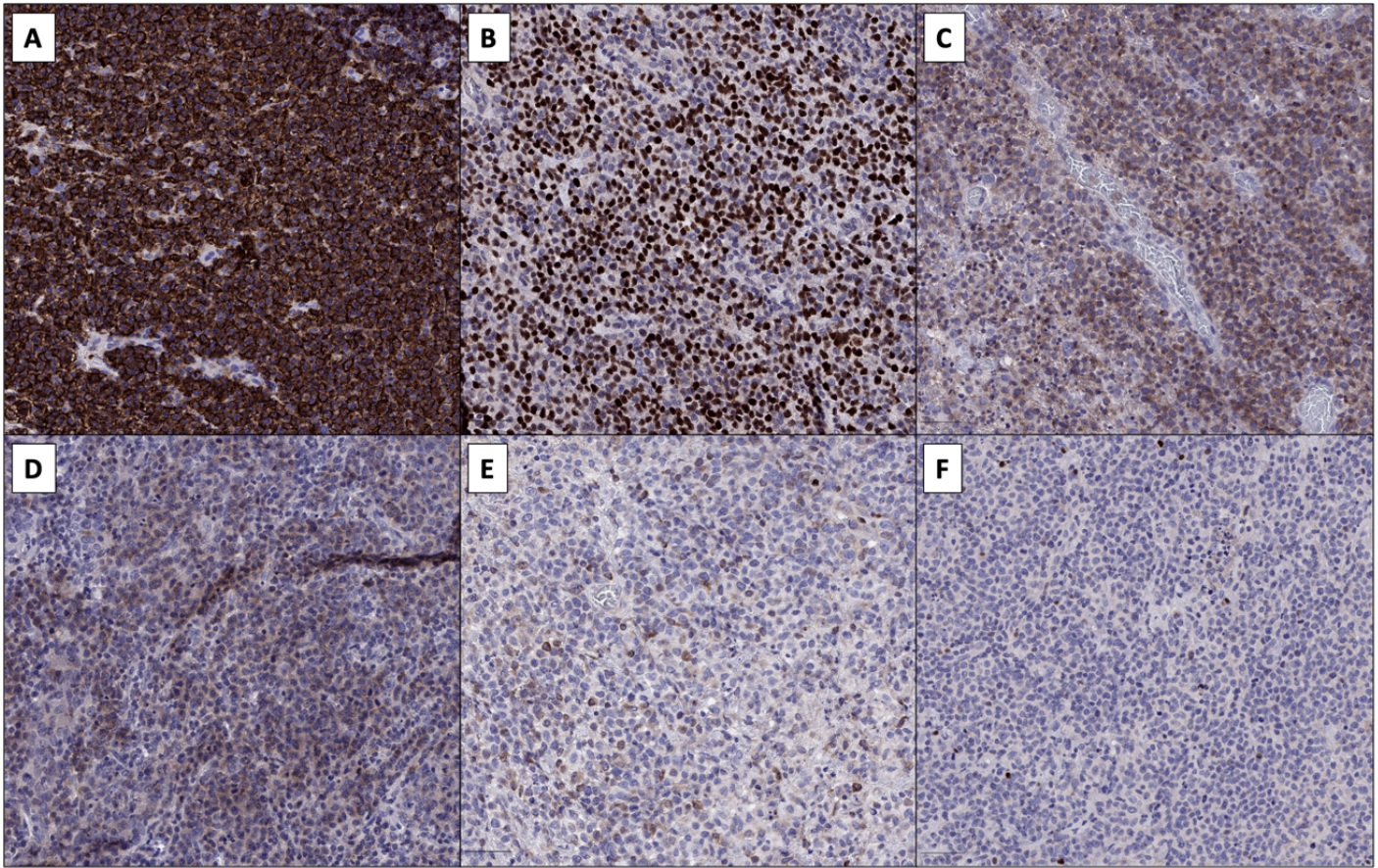


Figure 3

Immunohistochemical findings of the tumor: (A) Strong positive expression in cells of the major tumor component with antibodies to CD20. (B) Strong positive expression in cells of the major tumor component with antibodies to BCL6. (C) Positive expression in cells of the major tumor component with antibodies to CD10. (D) Positive expression in cells of the major tumor component with antibodies to HGAL. (E) Negative expression with antibodies to BCL2 in cells of the major tumor component. (F) Negative expression with antibodies to MUM1 in cells of the major tumor component.