Case Report

Navigating the rare: a case report of intrathyroidal thymic carcinoma

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Background: Intrathyroidal thymic carcinoma (ITTC) is an exceedingly rare malignancy of the thyroid, which presents significant diagnostic challenges. ITTC often has nonspecific clinical manifestations and histological features similar to other thyroid neoplasms, making its diagnosis difficult. This rarity and complexity result in a lack of consensus on its diagnostic criteria and management strategies. ITTC typically arises from ectopic thymic tissue, and despite its malignancy, it generally has a relatively favorable prognosis when accurately diagnosed and treated in a timely manner.

Case Description: This case report discusses a rare instance of ITTC in a 38-year-old male patient who presented with a 2-month history of neck lumps, accompanied by symptoms of neck compression and hoarseness. Clinical imaging, including ultrasound, suggested the possibility of lymphoma due to the appearance of a hypoechoic lesion encasing the carotid artery. However, after conducting immunohistochemical analysis, including markers such as CD5 and CD117, a definitive diagnosis of ITTC was made. The case highlights the diagnostic challenges posed by this rare malignancy and the critical role of histopathology in its identification.

Conclusions: ITTC is a rare, low-grade malignant tumor that can often be mistaken for other types of thyroid cancers. Multidisciplinary collaboration is essential for accurate diagnosis and optimal treatment planning. While the diagnosis of ITTC can be complex, immunohistochemical markers are instrumental in confirming the presence of this tumor. Despite its rarity, ITTC generally carries a favorable prognosis, with a 5-year survival rate of approximately 90%. This case report contributes to the limited body of literature on ITTC and underscores the importance of recognizing its unique immunophenotype in achieving an accurate diagnosis.

Keywords: Intrathyroidal thymic carcinoma (ITTC); immunohistochemical diagnosis; thyroid neoplasms; case report

Submitted Dec 16, 2024. Accepted for publication Mar 03, 2025. Published online Mar 26, 2025.
doi: 10.21037/gs-2024-540
View this article at: https://dx.doi.org/10.21037/gs-2024-540

Introduction

Intrathyroidal thymic carcinoma (ITTC) is an uncommon malignancy of the thyroid that was first characterized by Miyauchi *et al.* in 1985 (1). ITTC is defined as a malignant epithelial tumor of the thyroid exhibiting thymic epithelial differentiation, and its occurrence is relatively rare. Despite its relatively indolent biological behavior, the prognosis for patients with ITTC is generally favorable (2). However, the clinical manifestations and histopathological features

of ITTC closely resemble those of thyroid squamous cell carcinoma and undifferentiated carcinoma, which can result in misdiagnosis and potentially excessive treatment (3). ITTC is a malignant neoplasm, previously referred to as intrathyroid epithelial thymoma (ITET) or thyroid carcinoma showing thymus-like differentiation (CASTLE) (4). The etiology of ITTC remains largely unknown, with the majority of reported cases originating from Asia, particularly China and Japan, suggesting a possible link to genetic, racial, or environmental factors (5). The clinical characteristics, imaging findings, and fine needle aspiration cytology (FNAC) results of ITTC are often indistinguishable from those of other advanced thyroid malignancies (6). Consequently, accurate preoperative diagnosis of ITTC may be challenging, necessitating postoperative pathological and immunohistochemical evaluations for definitive diagnosis (7). Given the rarity of ITTC, there is a paucity of research on this condition both nationally and internationally, and clear guidelines for its diagnosis and treatment are currently lacking (8). This study presents a clinical case of ITTC encountered at Beijing Tsinghua Changgung Hospital, with the aim of enhancing the understanding of this malignancy through a comprehensive account of the patient's history, diagnostic challenges, and treatment approaches. We present this article in accordance with the CARE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-2024-540/rc).

Highlight box

Key findings

- The study presents a case of intrathyroidal thymic carcinoma (ITTC) in a 38-year-old male, emphasizing the diagnostic challenges due to its non-specific symptoms and its similarities to other thyroid neoplasms. The diagnosis was confirmed through immunohistochemical analysis, which demonstrated positive expression of CD5 and CD117, specific biomarkers for ITTC.

What is known and what is new?

- ITTC is a rare, low-grade malignant neoplasm of the thyroid gland that is characterized by a favorable prognosis. This study contributes to the limited literature on ITTC and highlights the importance of identifying its unique immunophenotype for accurate diagnostic purposes.

What is the implication, and what should change now?

- This study's findings highlight the significance of multidisciplinary collaboration in diagnosing ITTC. Achieving an accurate preoperative diagnosis is complex and depends on immunophenotyping. Heightened clinician awareness of early and precise diagnosis can impact treatment strategies and enhance patient outcomes.

Case presentation

The patient is a 38-year-old male who had been experiencing neck lumps for a duration of 2 months, accompanied by discomfort due to neck compression and hoarseness. On March 26, 2024, he presented to the General Surgery Clinic of Beijing Tsinghua Changgung Hospital. A physical examination revealed diffuse hardness in the thyroid region, and a palpable enlarged lymph node was noted in the left neck area (level IV), which exhibited a hard texture. The patient was otherwise healthy, with no known chronic diseases, immune diseases, or such. His systemic review was unremarkable.

On the day of the patient's consultation, a neck ultrasound examination was conducted in the ultrasound department of Beijing Tsinghua Changgung Hospital (*Figure 1*). The examination revealed a hypoechoic lesion measuring approximately 6.0 cm × 5.5 cm × 7.2 cm located in the lower pole of the left thyroid gland. The echogenicity of the lesion was heterogeneous, and its inferior margin extended towards the aortic arch and partially towards the sternum, exhibiting indistinct boundaries and irregular contours. The lesion was found to encase the common carotid artery and the vertebral artery; however, no compression, displacement, or deformation of the blood vessels was noted. Blood flow signals were detected within the lesion. Additionally, multiple enlarged lymph nodes were identified in the IV and V regions of the left neck and the tracheoesophageal groove, with some measuring approximately 2.1 cm × 1.3 cm. The structural integrity of the lymph nodes was compromised, with certain lymph nodes exhibiting abundant blood flow signals localized along the lymphatic hilum, whereas others displayed dispersed blood flow signals. The ultrasound report revealed a highly solid mass located beneath the left thyroid gland, encasing both the common carotid artery and the vertebral artery, which is consistent with findings indicative of lymphoma. Additionally, multiple enlarged lymph nodes were observed in the left cervical region, further supporting the diagnosis of lymphoma.

On the day of the patient's consultation, laboratory test results revealed that the calcitonin (CT) level was within the normal range at 4.04 ng/L, and the parathyroid hormone level was elevated at 87.2 ng/L. Simultaneously, the patient

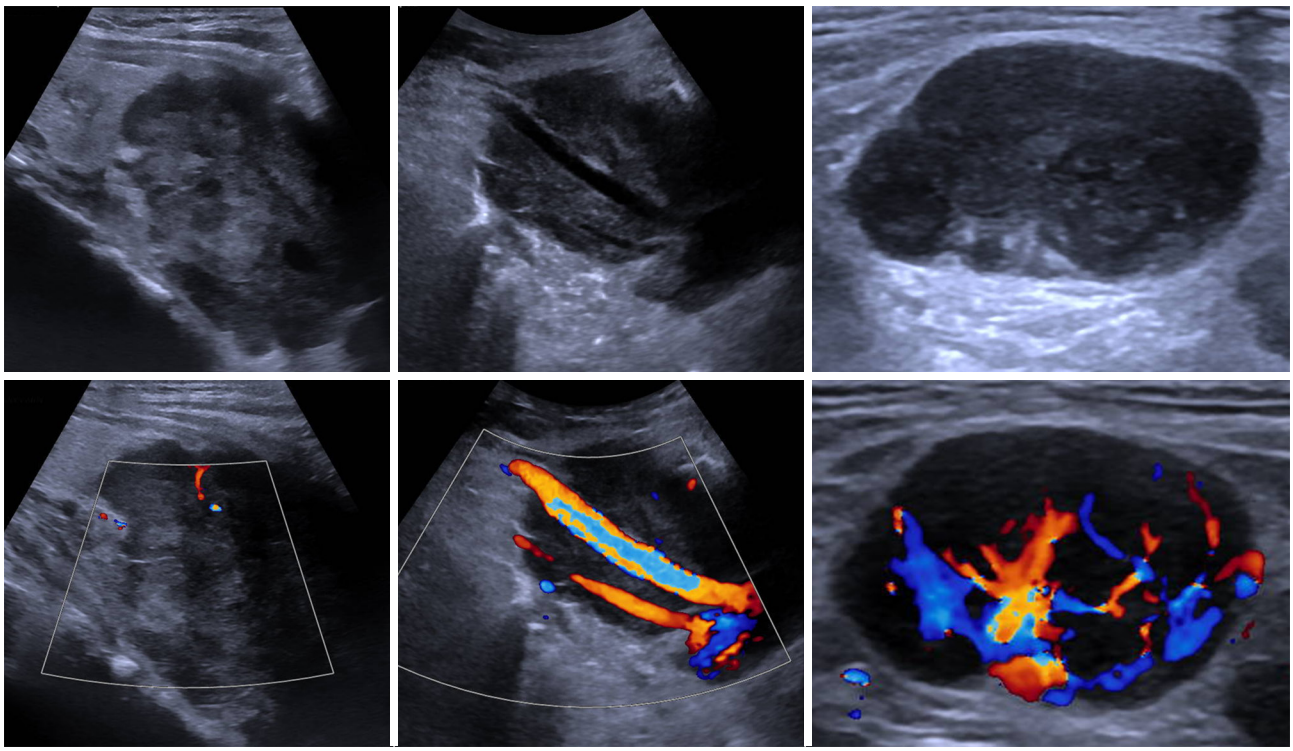

Figure 1 Ultrasound findings in Beijing Tsinghua Changgung Hospital. A hypoechoic mass could be seen in the lower pole of the left lobe of the thyroid gland. The echo of the lesion was uneven, and its lower edge extended towards the aortic arch, with fuzzy boundaries and irregular contours. The lesion surrounded the common carotid artery and vertebral artery, but no vascular compression, displacement or deformation was found. A small amount of blood flow signal can be detected within the mass. Enlarged lymph node could be seen in the left neck, and the structural integrity of the lymph node was damaged. The lymph node showed rich blood flow signals distributed along the lymphatic hilum.

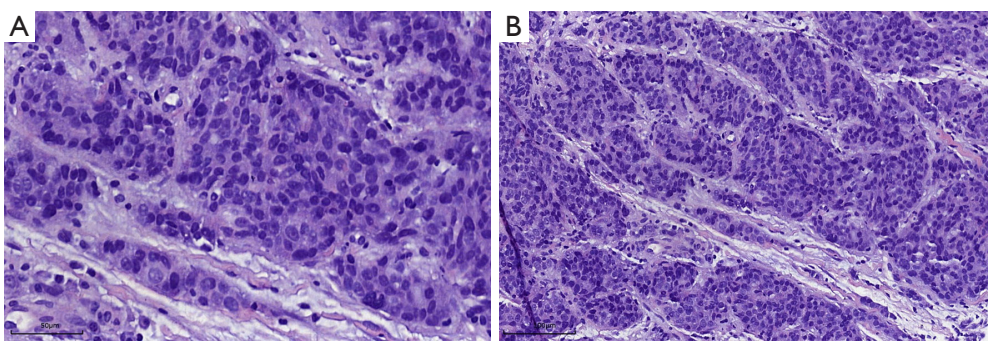

Figure 2 Histological examination of ITTC. Hematoxylin and eosin staining showed that nest like tumor cells could be seen in the proliferative fibrous tissue, with moderate nuclear atypia, elevated nuclear cytoplasmic ratio, and visible mitotic figures (A, ×20; B, ×40). ITTC, intrathyroidal thymic carcinoma.

underwent a biopsy of a left neck mass at the general surgery outpatient department of our hospital, during which three specimens were collected, each measuring approximately 2.2 cm × 0.1 cm. The pathological analysis of the biopsy indicated that the tumor cells were organized in a nested pattern within the punctured fibrous tissue, demonstrating moderate to severe cellular atypia, the presence of mitotic figures, and intravascular tumor thrombus (*Figure 2*).

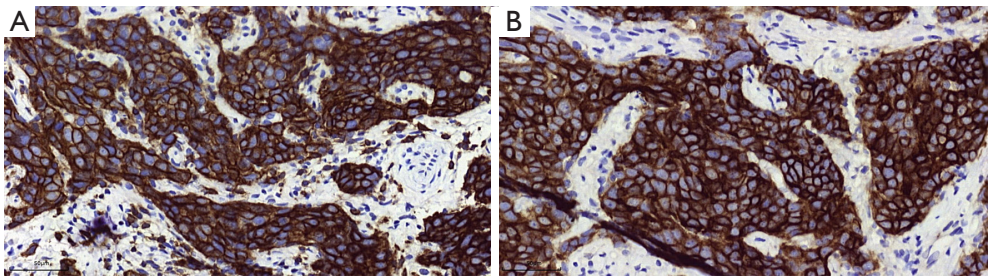

Figure 3 Immunohistochemical detection of ITTC. The tumor cells showed positive immunoreactivity to CD5 (A) (×40), CD117 (B) (×40) and PAX8 (C) (×40). ITTC, intrathyroidal thymic carcinoma; PAX8, paired box gene 8.

The immunohistochemical profile is delineated by the following markers: AE1 + AE3 (positive), P40 (positive), cytokeratin (CK) 5 + 6 (positive), CK19 (positive), Vimentin (negative), thyroid transcription factor-1 (TTF-1) (negative), Glt-3 (positivity observed in individual cells), synaptophysin (Syn) (positivity observed in individual cases), chromogranin A (CgA) (positivity observed in individual cases), and Ki67 (70% positivity).

In conclusion, the diagnosis of moderately differentiated squamous cell carcinoma should be integrated into clinical practice. Furthermore, the incorporation of paired box gene 8 (PAX8) or P16 may be necessary to clarify the origin of the carcinoma. A negative P16 test can help rule out other potential malignancies, such as poorly differentiated carcinoma or squamous cell carcinoma. Subsequently, supplementary immunohistochemical testing was performed, which demonstrated positive expression of PAX8, CD5, and CD117 (*Figure 3*). Based on the clinical manifestations, pathological characteristics, and immunohistochemical findings, the patient received a definitive diagnosis of ITTC.

Following a definitive diagnosis, the patient was transferred to Japan, where he underwent radiation therapy as an adjunct treatment.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). The study was approved by the Institutional Ethics Board of Beijing Tsinghua Changgung Hospital (No. 24781-6-01). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

ITTC was initially described by Miyauchi *et al.* in 1985 as an ITET, demonstrating histological similarities to thyroid squamous cell carcinoma (1). In 1991, Chan *et al.* noted that the tumor exhibited histological characteristics akin to thymic carcinoma, lymphoepithelioma, or squamous cell carcinoma, suggesting that it may arise from ectopic thymic tissue or residual gill sacs, while still possessing the potential for thymic differentiation. This tumor was subsequently designated as CASTLE (2). The third edition of the World Health Organization (WHO) Endocrine Organ Tumor Classification, published in 2004, recognized CASTLE as a low-grade malignant tumor and classified it as an independent category within thyroid tumor classifications (9). According to the European Rare Cancer Surveillance Project (RARECARE), CASTLE is classified as a rare form of thyroid cancer (10). In 2017, the updated WHO classification of endocrine organ tumors redefined CASTLE as ITTC (11).

The etiology of ITTC remains inadequately understood. Most tumors are typically located within the thyroid gland, predominantly in the lower pole of the unilateral lobe. However, a limited number of reports document occurrences in extrathyroidal locations, including the parotid gland, sublingual gland, submandibular gland, and parapharyngeal space (12). Due to the insidious nature of ITTC's onset, the associated mass is often not easily palpable during physical examinations, and the majority of cases exhibit a slow progression, resulting in an extended clinical course (13). Initial clinical manifestations are generally subtle, primarily presenting as painless neck masses, although some patients may experience neck discomfort. When the mass becomes sufficiently large to

compress or invade the trachea and esophagus, patients may encounter difficulties in breathing and swallowing, and hoarseness may arise if the recurrent laryngeal nerve is affected (14). Preoperative diagnostic methods for thyroid cancer predominantly include laboratory tests, imaging studies, and FNAC (15). Notably, laboratory tests for ITTC typically reveal no specific abnormalities, and thyroid function is generally within normal limits (16). Ultrasound is the most commonly utilized imaging modality in clinical practice. The patient described in this report presented with a solid hypoechoic mass on thyroid ultrasound, characterized by indistinct boundaries and heterogeneous internal echoes (6). Yamamoto *et al.* documented the sonographic characteristics of three cases of ITTC, which exhibited low echogenicity, irregular margins, and slightly increased echogenicity within the mass compared to the surrounding tissue, mirroring the sonographic features observed in the current patient (6). Differentiating primary thyroid lymphoma from ITTC poses a challenge; however, lymphoma typically manifests with low echogenicity, indistinct margins, heterogeneous internal echoes, and patterns of high echogenicity resembling a grid or cords (6). This condition may also present with abundant vascular signals and can result in diffuse destruction of thyroid architecture, frequently associated with Hashimoto's thyroiditis (12). Although ITTC is classified as a low-grade malignant tumor with relatively indolent biological behavior, it has the potential for regional lymph node metastasis and invasion of adjacent tissues (17).

Given the rarity of ITTC, many pathologists have diagnosed it as poorly differentiated carcinoma, squamous cell carcinoma, undifferentiated carcinoma, or malignant thyroid tumors, without a definitive classification (16). Consequently, when pathologists encounter thyroid tumors exhibiting poorly differentiated morphology, squamous differentiation, and a lymphocytic background, it is imperative to consider the potential diagnosis of ITTC in the preoperative differential diagnosis (17). The definitive diagnosis of ITTC predominantly relies on postoperative pathological examination, particularly through immunohistochemical analysis (12). ITTC masses are generally larger, and the lesions exhibit a pushing growth pattern (15). Typically, ITTC tumors are solid, lacking calcification or cystic features (18). These tumors usually present with well-defined margins, an absence of a capsule, and are often gray-white in cross-section, characterized by a tough and hard texture (13). An early lesion characteristic is the distinct boundary between the tumor and the thyroid parenchyma. Patients diagnosed with ITTC frequently demonstrate high expression levels of CD5 and CD117, which are currently regarded as specific biomarkers for ITTC (4). However, there are isolated cases of ITTC that do not express CD5. Additionally, tumor cells may express epithelial markers such as CK and P63, with a minority of cases expressing neuroendocrine markers such as neuron-specific enolase (NSE), Syn, and CgA (5,8,10). Almost all cases do not express thyroid-related markers such as TTF-1, thyroglobulin (TG), or CT (5). The Ki-67 labeling index is relatively low, typically ranging from 10% to 30%, whereas undifferentiated carcinoma and primary squamous cell carcinoma often exceed 50% (11). Previous studies reported that immunohistochemical staining has shown PAX8 to be expressed in thymic tissue and carcinomas, but it was not specific for identifying ITTC (19).

The expression of these markers further substantiates the origin of ITTC in thymic tissue and confirms that ITTC is a low-grade malignant tumor exhibiting characteristics of squamous cell differentiation and neuroendocrine differentiation, thereby aiding in the differentiation of ITTC from poorly differentiated thyroid cancer, undifferentiated thyroid cancer, and squamous cell carcinoma (6).

The biological behavior of ITTC is typically characterized as indolent, with a generally favorable prognosis for the majority of cases (12). Research indicates that the 5- and 10-year survival rates for ITTC are 90% and 82%, respectively (16). However, due to the rarity of ITTC, there is a significant paucity of research both domestically and internationally, which has resulted in a lack of clear guidelines for its diagnosis and treatment (14). While ultrasonography is a vital initial tool for thyroid tumor screening, its capacity for full tumor staging is limited. The diagnostic approach for ITTC should include advanced imaging techniques like computed tomography and positron emission tomography (PET)-computed tomography. These methods are essential for comprehensive staging, evaluating tumor boundaries, assessing surrounding structures, and detecting distant metastases. Their integration enhances diagnostic accuracy and improves treatment planning and patient prognosis. At present, the clinical management of ITTC is primarily informed by clinical experience rather than empirical evidence. Surgical intervention is considered the preferred treatment modality for ITTC (19). In instances where locally advanced ITTC is deemed unsuitable for curative surgery, radiotherapy, either alone or in combination with

chemotherapy, may be considered as alternative treatment options.

Conclusions

ITTC is a rare, low-grade malignant primary thyroid tumor with a generally good prognosis. Preoperative diagnosis is challenging. Accurate diagnosis relies on immunophenotyping, and surgery is the cornerstone of treatment. This case report underscores the importance of recognizing the unique characteristics of ITTC for accurate diagnosis.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-2024-540/rc

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-2024-540/prf

Funding: None.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-2024-540/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). The study was approved by the Institutional Ethics Board of Beijing Tsinghua Changgung Hospital (No. 24781-6-01). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Cite this article as: Wang X, Zhang H, Wang B, Zhang L. Navigating the rare: a case report of intrathyroidal thymic carcinoma. Gland Surg 2025;14(3):570-576. doi: 10.21037/gs-2024-540