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Review Article

Follicular Cell Derived Thyroid Carcinoma: Common Things Present in Uncommon Ways

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Abstract

Follicular cell derived thyroid carcinomas, including papillary thyroid carcinoma and follicular thyroid carcinoma, are common in daily pathology practice and the incidence of this entity is dramatically increased due to the wide application of more sensitive diagnostic procedures. However, uncommon presentations of thyroid cancers can be seen occasionally and without awareness of those scenarios, traps, and pitfalls that can easily compromise the patient's care. We reviewed the English literature through PubMed search based on three uncommon presentations identified during our routine diagnostic service for patients with or without thyroid nodules: (1) Phosphatase and tensin homolog immunoreactivity loss initially identified on common follicular nodules, and follicular thyroid carcinoma leading to the identification of a phosphatase and tensin homolog hamartoma tumor syndrome, (2) metastatic thyroid carcinoma incidentally identified in the specimens of neck lymph node dissection of head and neck squamous cell carcinoma, and (3) a papillary thyroid carcinoma incidentally identified in the specimen of laterally located thyroglossal duct cyst. We discussed the representative case scenarios, which include clinicopathologic, immunophenotypic, some with genomic features, diagnostic pearls, and patient management. Follicular cell-derived thyroid carcinoma is commonly diagnosed at a younger age than most other adult cancers. The awareness of those pitfalls would significantly improve the diagnostic accuracy leading to better patient outcomes.

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Keywords: Papillary thyroid carcinoma; Follicular thyroid carcinoma; Phosphatase and tensin homolog; PTEN hamartoma tumor syndrome; Cowden syndrome; Thyroglossal duct cyst; Head and neck squamous cell carcinoma.

Abbreviations: CS, Cowden syndrome; CT, computer tomography; FTC, follicular thyroid carcinoma; HNSCC, head and neck squamous cell carcinoma; KPNC, Kaiser Permanente northern California; MRI, magnetic resonance imaging; PET, positron emission tomography; PHTS, PTEN hamartoma tumor syndrome; PTC, papillary thyroid carcinoma; PTEN, phosphatase and tensin homolog; RECQL4, RecQ like helicase 4; TDC, thyroglossal duct cyst; TT, total thyroidectomy.

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Introduction

Thyroid carcinoma is a common malignancy with about 43,800 new cases (11,860 in men and 31,940 in women) and about 2,230 deaths from thyroid cancer (1,070 men and 1,160 women) in 2022, based on the American Cancer Society's most recent estimates of thyroid cancer in the United States (USA).[1] It has been recognized to be the most rapidly increasing cancer in the USA, mainly due to increased detection by more sensitive diagnostic procedures, including advanced computer tomography (CT) or magnetic resonance imaging (MRI) scans that can detect incidental small thyroid nodules.

Follicular cell derived thyroid carcinomas including papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) are commonly diagnosed at a younger age than most other adult cancers. Moreover, women are three times more likely to develop thyroid carcinoma than men. Pathologically, PTC and FTC are the two most common thyroid malignancies arising from thyroid follicular epithelial cells.[2] The pathogenesis of the thyroid carcinoma still remains to be elucidated. For example, there is a heterogenous group of familial predisposition cancer syndromes that have thyroid gland manifestations and other clinical findings.

Diagnosis of thyroid carcinomas on the specimens of fine needle aspiration/biopsy, lobectomy, and total thyroidectomy is an important part of the routine service of pathologists. Although a PTC and FTC are common diseases of the thyroid, some uncommon presentations exist and without awareness of them, traps and pitfalls could easily compromise optimal patient care. This review focused on three uncommon presentations identified during our routine diagnostic service for patients with or without thyroid nodules: (1) Phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome (PHTS) initially identified on common follicular nodules, (2) metastatic thyroid carcinoma incidentally identified in the specimens of the neck lymph node dissection of head and neck squamous cell carcinomas (HNSCC), and (3) a PTC incidentally identified in the specimen of the thyroglossal duct cyst.

Loss of PTEN initially identified on common follicular nodules leading to the identification of the PTEN hamartoma tumor syndrome

PHTS is caused by a germline inactivation mutation in the

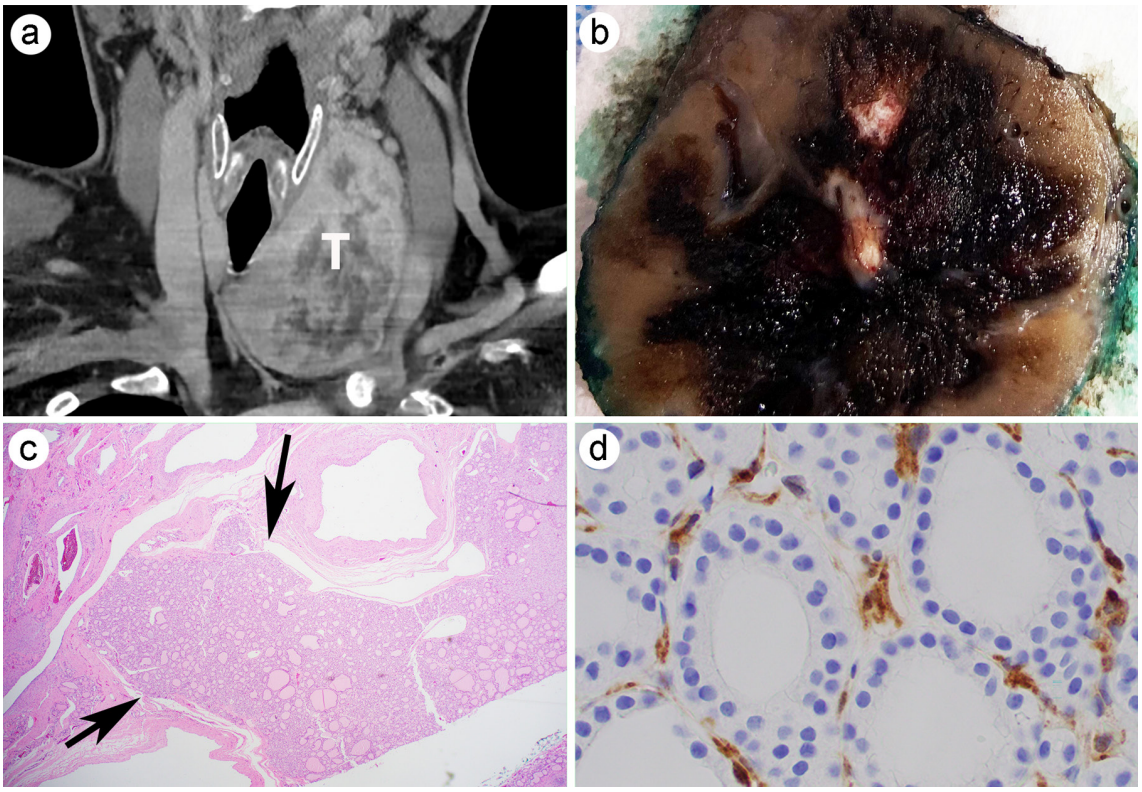

Fig. 1. Follicular thyroid carcinoma (FTC) with loss of PTEN. (a) Computer tomography scan (coronal) showing a 10 cm left lobe thyroid mass (T), (b) thyroid lobectomy showing a hemorrhagic and heterogeneous cut surface of the mass, (c) H&E stein section showing a capsular invasion of the tumor (arrows), and (d) immunohistochemical stain showing loss of PTEN in the FTC cells with intact PTEN in the stromal and endothelial cells (c, 40×; d, 400×).

PTEN gene, and patients have highly variable hamartomatous conditions characterized by macrocephaly, Lhermitte-Duclos disease, mucocutaneous lesions, gastrointestinal hamartomas, lipomas, benign thyroid lesions, macular pigmentation of the glans penis, cerebrovascular malformations, and several types of cancer.[3] Associated cancers include breast (up to 85% risk), thyroid (typically follicular up to 38% risk), renal (up to 34%), endometrial (up to 28% risk), colorectal (9–16% risk), and melanoma (6% risk).[3] PHTS is also associated with developmental delay, intellectual disability, and autism spectrum disorder. Biological relatives are at risk for PTEN-related conditions and further diagnostic tests are warranted if clinically appropriate. First-degree relatives to the patient (siblings, children, and parents) have a 50% penetration of carrying this genetic mutation.[3,4] Furthermore, PTEN loss is highly suggestive of Cowden syndrome (CS); however, it is not diagnostic of CS and an additional clinical correlation would be required to confirm the diagnosis.

Recently, we encountered a unique case of a 31-year-old male with a long-standing history of thyroid enlargement.[2] At 14 years old, he had thyroid gland enlargement and was sent for a thyroid gland fine needle aspiration (FNA). It was diagnosed as benign. He was presented with breathing difficulty, and a physical examination showed an enlarged left thyroid gland lobe and macrocephaly. He did not have penile freckling, generalized skin pigmentation, or papillomas. An ultrasound (US) examination and CT scans showed a 10 cm hypervascular, heterogeneous appearing mass (Fig. 1a). The FNA of the left thyroid gland mass was interpreted as a benign thyroid nodule (Bethesda II). For symptomatic relief, a left hemithyroidectomy was performed. The macroscopic hemithyroidectomy showed a 10 cm encapsulated mass with a heterogeneous and hemorrhagic cut surface along with a calcified center (Fig. 1b). Microscopically, a well-formed tumor capsule was identified with smooth muscle-walled vessels within the fibrous connective tissue, thus suggesting the presence of a true capsule. The tumor was arranged in a follicular architecture with easily identified colloid throughout. A capsular invasion (Fig. 1c) was identified in four areas, but there were no nuclear features diagnostic of PTC. Additionally, no areas of lymphatic or vascular invasion were identified, there were not any tumor necrosis or increased mitoses. These changes supported the diagnosis of minimally invasive FTC with nuclear loss of PTEN (Fig. 1d). In addition, there was a microscopic focus (0.2 mm) of a classical PTC, which showed all the characteristic nuclear and architectural features that were diagnostic of a PTC. The margins were free from tumor. It was the background non-neoplastic thyroid gland parenchyma that was of note with about 50 adenomatous (hamartomatous) nodules that ranged from 0.2 mm (Fig. 2a) to 5 mm. These nodules were cellular, hence showing a monotonous follicular architecture with nuclei that were round and regular with nuclear hyperchromasia. These nodules were quite different from the surrounding parenchyma (Fig. 2a). With such tight, well-formed nodules lacking any fibrous connective tissue capsules and having a general monotony to them, the possibility of a PTEN or DICER1 abnormality was suspected. Immunohistochemistry (IHC) for the PTEN also showed the nuclear loss of the PTEN in the small benign hamartomatous nodules from the submitted parenchyma (Fig. 2b). A PCR test for the Invitae Kaiser Permanente Northern California (KPNC) Hereditary Cancer Panel, which included 62 genes, was performed. In addition to the pathogenic PTEN mutation [PTEN c.388C>T (p.Arg130)], two mutations in RecQ Like Helicase 4 (RECQL4) [RECQL4 c.2755G>A (p.Ala919Thr);

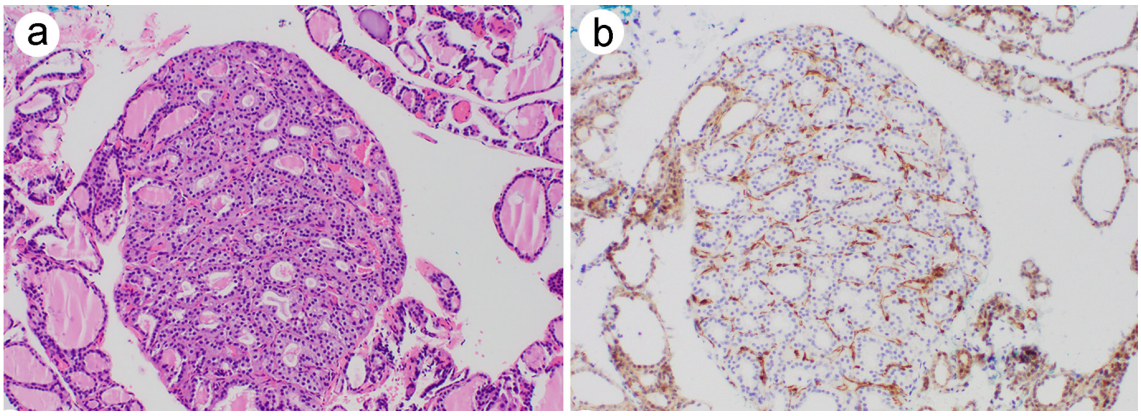

Fig. 2. PTEN loss in the benign adenomatous nodule. (a, b) H&E stain showing a 0.2 mm benign adenomatous nodule (a) with loss of the PTEN immunoreactivity while intact PTEN is present in the adjacent follicles (a, b, 100×).

RECQL4 c.940C>T (p.Pro314Ser)] of uncertain significance were also identified. A genetic consultation developed a family pedigree. The patient's family was of Hispanic ancestry, and the patient's mother was diagnosed with breast cancer at 40 years old and died of the disease two years later. The patient's father is currently cancer free. The patient's son had macrocephaly with speech delay. The histological findings, molecular test, and genetic consultation with pedigree supported CS and were consistent with a PHTS.[2]

Barletta *et al*.[5] showed a PTEN loss by IHC has a sensitivity of 100% and a specificity of 92.3%. As CS confers a significant risk for cancer,[5,6] a PTEN loss by IHC would be useful to recognize CS patients to initiate genetic counseling and enable gene–informed management, particularly as related to high-risk cancer surveillance and to monitor neurodevelopment symptoms.[5] Individuals with PTEN mutations should undergo cancer screening at the time of diagnosis to enable healthcare providers to detect any tumors at the earliest, most treatable stages, as in our case. Due to the patient's young age and family history of early presentation of breast carcinoma, genetic testing for hereditary cancer predisposition (Invitae KPNC Hereditary Cancer 62 gene panel) was performed, which showed a pathogenic variant, c.388C>T (p.Arg130*), identified in PTEN. This result was consistent with a predisposition to, or diagnosis of the PTEN-related conditions.

Our unique case of PTHS presented multiple disease processes, including a FTC, PTC, and adenomatous nodules which suggested that thyroid nodules were very common and a small proportion of patients, particular in young patients (<20 years of age), with the findings as in this case could have PTEN immunostaining for screening purposes. This could eventually lead to diagnosis of a family PTEN hamartoma tumor syndrome. This was the first case report of a RECQL4 mutation[7] in a PTEN associated minimally invasive FTC or PTHS. With accumulated data, those mutations may shed light on the mechanism, prognosis, and potential treatment options. Therefore, pathologists should be aware that the thyroid nodules in some young patients with loss of nuclear PTEN immunostaining could be the first manifestation of PTHS.

Metastatic thyroid carcinoma incidentally identified in the specimens of a neck lymph node dissection for head and neck squamous cell carcinoma

Occult or subclinical thyroid carcinomas are not uncommon. Metastasis from thyroid carcinoma may be found incidentally during a neck dissection for HNSCC, and the reported prevalence of thyroid metastasis has been 0.3% to 7.9% estimated by different groups.[8–11] This may be due to the histopathological methods employed. Moreover, the management of patients should be discussed in the light of thyroid ultrasonography and prognosis of HNSCC, as the therapeutic implications remain poorly defined because of the frequently poor prognosis of HNSCC.[8]

In our practice, we have encountered several cases of incidentally identified PTC in the neck lymph nodes dissection specimen of patients with HNSCC.[11] One of them was a 73-year-old man with a history of obesity, Barrett's esophagus, and 30-pack-year smoking history who presented a lower lip lesion with a biopsy confirming a moderately differentiated squamous cell carcinoma (SCC). A CT scan and full-body positron emission tomography (PET) (PET/CT) scan showed bilateral enlarged and hypermetabolic cervical lymph nodes measuring 1.2 cm (right 1b, with SUV max 4.0) and 6.5 cm (left 1b, with SUV max 14.8) (Fig. 3a). The FNA of the lymph node was performed and showed a well differentiated SCC that was positive for p40. A lower lip SCC resection (with a clear margin on the frozen section diagnosis) and bilateral neck dissection were then performed. Pathology demonstrated keratinizing SCC metastasis to two of 71 bilateral lymph nodes (Fig. 3b). The largest tumor deposit was 6.5 cm with an extranodal extension. An additional incidental finding was a metastatic PTC to one (Fig. 3c, d) of 10 lymph nodes identified at the right neck level IIA that were negative for SCC. The final pathologic diagnosis was a lower lip SCC with neck lymph node metastasis with extranodal extension (tumor stage: pT2N3cM0) and incidentally identified neck metastasis of PTC. Post-surgery, the patient recovered well, and no discernable thyroid mass or nodule was seen clinically or on imaging. He completed a course of adjuvant chemotherapy with cisplatin and radiation therapy. At the one-year follow-up, the patient was doing well with a stable weight. No tumor recurrence was identified, and no thyroid nodules were identified on the imaging.

In our case, the identified neoplasm demonstrated a follicular formation lined by enlarged and overlapping cells with nuclear clearing, grooving, and intranuclear pseudoinclusion, which were classic features for a PTC. The high prevalence of cervical thyroid metastases found in the neck dissection for HNSCC was due to the careful histopathological assessment. The impact of occult thyroid cervical lymph node metastasis on patient management was difficult to assess, especially as prognosis in HNSCC is often severe.[11] There was no consensus regarding therapeutic decisions motivated by the incidental discovery of thyroid metastases. Furthermore, total thyroidectomy should be

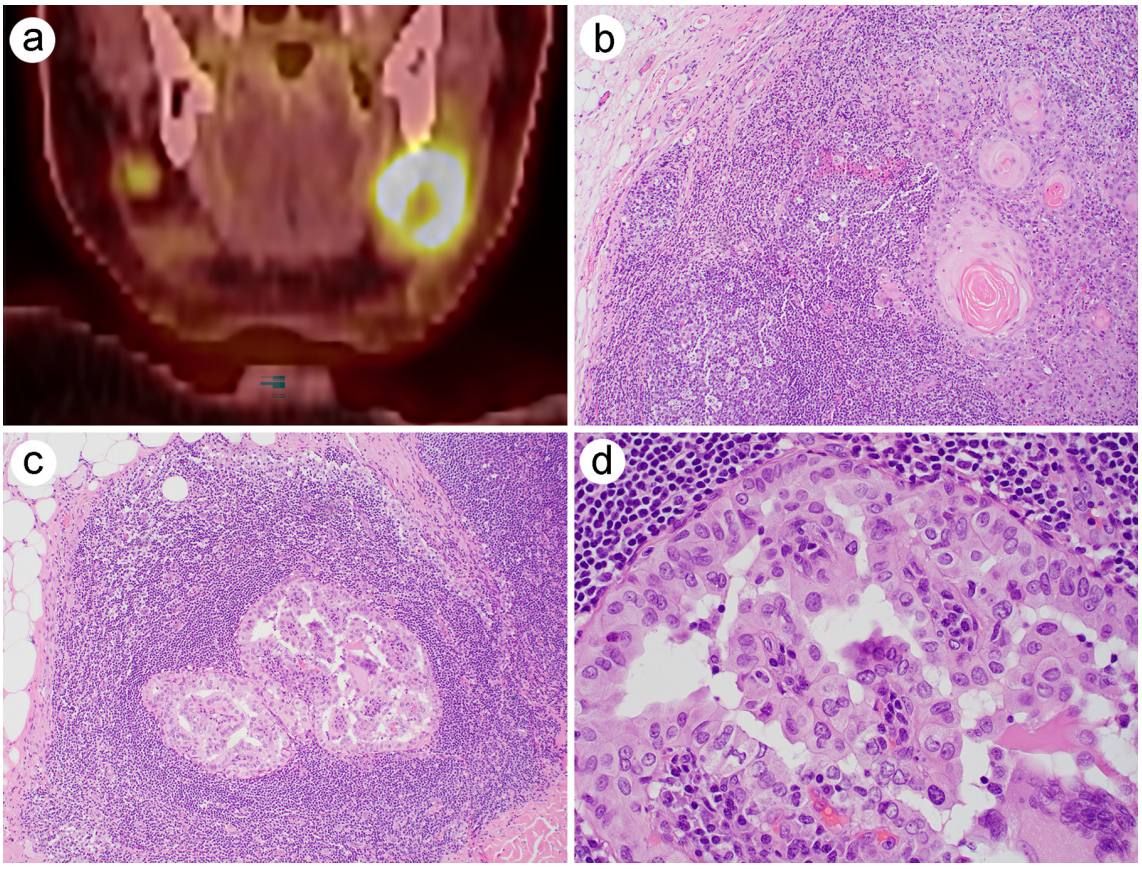

Fig. 3. Incidental identified papillary thyroid carcinoma in the neck lymph node dissection of a 73-year-old male with s history of a lower lip squamous cell carcinoma. (a) PET/CT showing the bilateral hypermetabolic lymph nodes; (b-d) H&E stain sections showing the lymph node with metastatic keratinizing squamous cell carcinoma, (b) and papillary thyroid carcinoma (c, d) (b, c, 100×; d, 400×).

systematic according to some authors, while others consider that no aggressive therapy on the thyroid gland is necessary in most cases. Although several patients have died from HNSCC or from secondary cancer in case series, no deaths were related to thyroid carcinoma. We and others have previously reported the good prognosis of metastases of thyroid carcinoma discovered during a neck dissection for HNSCC. The therapeutic impact of the incidental discovery of histological thyroid metastasis may be discussed in the light of the thyroid ultrasonographic results during the follow-up, the prognosis of the HNSCC, and the risks of surgery. Hence, the discovery of a thyroid nodule would justify thyroidectomy and histological confrontation.[8]

PTC incidentally identified in the specimen of a laterally located thyroglossal duct cyst

The thyroglossal duct is a developmental anomaly in which a remnant of the thyroid anlage is left in the neck during its descent from the foramen cecum of the tongue to the final pretracheal position.[12] A persistent duct can lead to the thyroglossal duct cyst (TDC). TDC accounts for 7% of the midline neck swellings, and laterally located TDC is uncommon. Carcinoma arising from TDC is also rare, and reported in 1% to 7 % of all TDCs.[12,13]

From our practice, we encountered an unusual case of a 19-year-old male with a left thyroid lobe mass. An US and MRI examination showed a 2.5 cystic mass at the left lobe of the thyroid (Fig. 4a). FNA was performed and showed a benign thyroid lesion (Bethesda Category II). Due to a family history of cancer, the patient underwent surgical resection starting with a midline incision. During the surgery, it was found the left lobe cystic mass could be isolated from the left thyroid lobe with minimal adhesions, and the cystic mass was connected to the base of the tongue through a thyroglossal duct beneath the hyoid bone. The duct and cyst were entirely resected (Fig. 4b). In surgical pathology, the duct and cystic wall were entirely submitted for microscopic evaluation. Interestingly, a 2 mm focus of follicles showed a nuclear enlargement, nuclear overlapping, clearing, and occasional intranuclear pseudoinclusion in a fibrotic background (Fig. 4c, d). The tumor cells were positive for CK19 and HBME1, while the adjacent benign thyroid tissue was negative. The pathology diagnosis was a PTC arising in a lateral located TDC (pT1a) with negative margin. Post-surgery, the patient recovered well, and no thyroid nodule or metastatic disease was identified in the imaging. At the one-year follow-up, the patient was doing well, and no recurrent or metastatic tumor was identified in the imaging.

Most recently, Wong *et al*.[13] reported 86 patients who underwent surgery for TDC with a median age of 48 years and a female preponderance (62%). A preoperative US examination was used in 85% of the patients, and FNA cytology in 57%. There were six cases (7%) of TDC PTC. The US examination in five TDC carcinoma cases showed a solid nodule within the cyst wall. FNA cytology was undertaken in five TDC carcinoma cases from the solid nodule; malignant in one, and suspicious malignancy in two. Two PTC

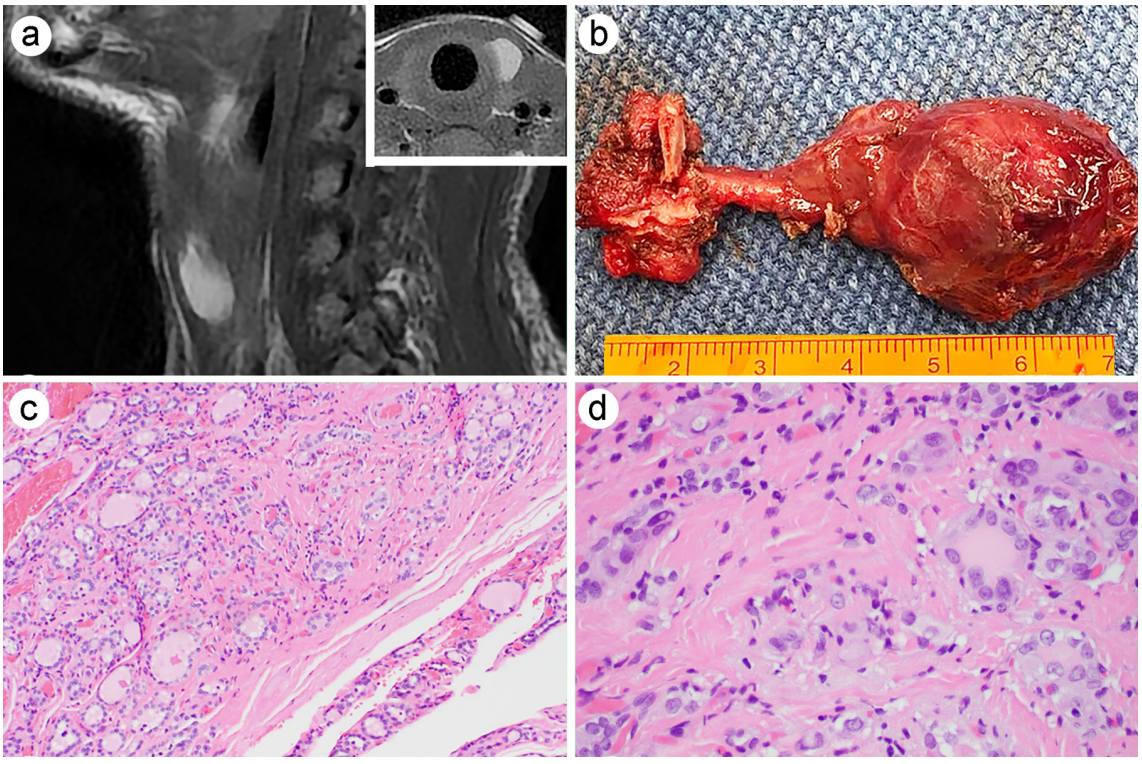

Fig. 4. Incidental identification of a papillary thyroid carcinoma (PTC) in a laterally located thyroglossal duct cyst. (a) MRI (sagittal, T2) showing a cystic lesion on the left lobe of the thyroid (inset, Axial, T2), (b) intraoperatively, the cyst was identified as a thyroglossal duct cyst with a resection of the overlying hyoid bone; (c-d) H&E staining sections showing a focus (2 mm) of classical PTC present in the cystic wall with negative margin (c, 100×; d, 400×).

patients had concurrent total thyroidectomy (TT), and three subsequently had a TT. Multifocal thyroid PTC was found in two patients. One patient had a recurrence in the lateral lymph nodes nine years after the excision of the TDC papillary carcinoma and TT. All patients were alive and well with no distant metastases (median follow-up 11 years).[13] They recommended a preoperative US examination to evaluate the TDC, thyroid gland, and cervical lymph nodes, and an FNA cytology to target the solid component of the TDC, and favored a total thyroidectomy for all patients with a TDC carcinoma. In our case, no solid lesion was preoperatively identified in the US and MRI examinations, but an incidental microscopic PTC was identified. No total thyroidectomy was performed, and no tumor recurrence or metastasis was identified at the one-year follow-up.

The majority of TDC carcinoma was a PTC, and most likely arose from a thyroid gland remnant.[14] Thompson *et al*.[15] reported 22 cases (17 females and five males; aged 12–64 years) with carcinomas identified among 685 resected TDC cases (3.2% incidence). An anterior midline neck mass was the presenting symptom in all patients. A Bethesda Category V or VI classification was conducted preoperatively by FNA in five of the 12 cases tested. The final pathology showed that all 22 carcinomas were PTCs made after the Sistrunk procedure (SP), and they were classical PTCs showing a sclerotic and infiltrative pattern, as in our case. A SP was performed on all patients with a concurrent (n = 4) or subsequent (n = 12) total thyroidectomy. Of the patients who had a thyroidectomy, a synchronous PTC was identified in six (thus, six out of 22 patients had synchronous thyroid gland primaries). This supported the origin from extrathyroidal remnants (cyst origin) rather than a metastatic tumor from a thyroid gland primary. Follow-up radioactive iodine therapy was performed on 13 patients. Metastatic disease to the local lymph nodes 57 months after presentation was seen in one patient with all others alive and disease free (mean 3.8 years; range 0.4–10.8 years). Thompson *et al*. suggested that for "microcarcinomas" (≤1 cm), conservative management could be used for patients <45 years (i.e., the SP only); for >1 cm tumors, and due to the high incidence of a concurrent PTC and higher stage at presentation in older patients, completion thyroidectomy was recommended for patients ≥45 years. Thus, even though a good prognosis could be expected for a PTC developing in TDCs, staging was advocated to more appropriately therapeutic interventions.[15] Our case was unusual, and the TDC was laterally located and clinically mimicking a thyroid lobe nodule. A 2-mm focus of classical PTC was identified with a negative margin. Based on Thompson *et al*.'s suggestion,[15] no total thyroidectomy was performed in our case.

Conclusions

We reviewed the literature regarding the above three uncommon presentations associated with follicular cell derived PTC and FTC. (1) Thyroid nodules are very common and a small proportion of patients, particularly young patients (<20 years of age) may have the histologic findings as in our case. Therefore, PTEN immunostaining could be considered for screening purposes, and this could lead to the diagnosis of family PTEN hamartoma tumor syndrome. RECQL4 mutation was also identified in the PTEN associated minimally invasive FTC or PTHS. With the accumulated data, those mutations may shed light on the mechanism, prognosis, and potential treatment options. (2) Metastatic thyroid carcinoma could be incidentally identified in the specimens of neck lymph node dissection for a HNSCC, and the reported prevalence of thyroid

cancer metastasis was 0.3% to 7.9% as estimated by different groups. This large variation may be due to the histopathological methods employed. The management of the patients should be discussed in the light of thyroid ultrasonography and prognosis of a HNSCC, as the therapeutic implications of metastatic thyroid carcinoma still remained poorly defined because of the frequently severe prognosis of a HNSCC. (3) TDC accounted for 7% of the midline neck swellings, and laterally located TDC was uncommon. Carcinoma arising from TDC was also rare. The majority of them were classical PTC, and most likely arose from a thyroid gland remnant. A portion of patients may have a good prognosis without a thyroidectomy. In conclusion, awareness of these uncommon presentations by pathologists would lead to an early, accurate diagnosis and ultimately improve the patient's outcome.

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Conflict of interest

Dr. Lai has been an Associate editor and Dr. Wang has been a Deputy Editor-in-Chief of the *Journal of Clinical and Translational Pathology* since May 2021. The authors have no other conflicts of interest to disclose.

Author contributions

JL designed the study, made the diagnoses, collected and analyzed the data, wrote and finalized the manuscript. FF, LS, and HW critically reviewed the manuscript. All authors have made a significant contribution to this study and have approved the final manuscript.

Ethical statement

This is a review article that needs no Institutional Review Board approval. However, this article contains some personal information from the patients, and the authors have obtained the written informed consent for publication of the patients' history and the accompanying images.

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