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Review Article

Thyroid tissue outside the thyroid gland: Differential diagnosis and associated diagnostic challenges

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ABSTRACT

The presence of thyroid tissue outside of the thyroid gland may occur in various clinical settings and anatomic locations and includes both benign and malignant differential diagnoses. Some of these entities include thyroglossal duct cyst, lingual thyroid, parasitic nodule, thyroid tissue within a lymph node and struma ovarii. In routine daily practice, these entities do pose diagnostic challenges for the pathologists. Differential diagnostic considerations depend largely on the location of lesion and the histologic features. A definitive diagnosis may remain unclear in some cases while knowledge is still evolving in others i.e., incidentally detected bland appearing thyroid follicles in a lateral neck lymph node. This article aims to elaborate on the various entities characterized by thyroid tissue outside of the thyroid gland, both benign and malignant, and the relevant differential diagnostic considerations.

1. Introduction

The thyroid gland is an important endocrine gland located in the neck. The presence of benign thyroid tissue outside of the thyroid gland is relatively infrequent but can be seen in ectopic thyroid tissue in the head and neck and mediastinum including parasitic nodules, and struma ovarii (Table 1). This may be relevant as these entities may be difficult to distinguish from metastatic thyroid carcinoma. This review article seeks to address these diagnostic challenges when encountered in clinical practice.

2. Development of the thyroid gland

The thyroid gland is located anterior to trachea at the level of the C5-T1 vertebrae. It comprises right and left lobes connected at the midline by the isthmus. Additionally, a *pyramidal lobe*, which is a remnant of thyroglossal duct, can be seen in 15–75% [1]. In our practice, we see it in about 40% of cases (unpublished data). When present, the pyramidal lobe is connected with the isthmus and may be to the left or right of the midline [2], especially when the gland is distorted by nodules. Follicular cells and parafollicular C-cells comprise the functional endocrine component of the gland and secrete thyroid and calcitonin hormones, respectively.

Development of the gland starts around the third week of gestation from a median anlage and endodermal cell proliferation, which forms a diverticulum at the level of the foramen cecum [3]. The downward migration of thyroid diverticulum starts around the 24th day of embryogenesis and finishes by day 50 when it reaches the midline at the level of anterior upper trachea [3]. During this caudal movement, the thyroid diverticulum remains attached to the tongue via the thyroglossal duct. While the duct usually involutes around the 10th week of gestation, a portion may remain and give rise to the pyramidal lobe, which is considered a normal anatomic variant [4].

Two lateral anlages are derived from ultimobranchial bodies which develop in the fourth and fifth pharyngeal pouches during the 5th week of gestation. Ultimobranchial bodies migrate form their site of origin and join to the midline thyroid gland and give rise to parafollicular C-cells. C-cells are usually present in the lateral thyroid lobes and are considered to be neural crest origin, but recent work suggests an endodermal derivation [4]. Many genes and transcription factors regulate thyroid gland organogenesis. In the early stages of development, this includes FOXE1 (Forkhead domain transcription factor, TTF-2), NKX2-1 (Homeodomain transcription factor, TTF-1), PAX-8 (Paired domain transcription factor), and HHEX (homeodomain transcription factor). The late stages of development include regulator genes comprised of HOXA3 (homeobox protein), TSHR along with Thyroglobulin (Tg), other NKX2 genes, and FGFR2 (Tyrosine kinase receptor) [3]. Mutations in these molecular pathways can result in abnormal development of thyroid and involve multiple organs in syndromic association [5].

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Table 1
Thyroid tissue outside the thyroid gland.

Thyroglossal duct cyst	**Location:** Anterior midline neck in relation to hyoid bone **Imaging:** Well circumscribed on imaging **Histology:** Lined by benign squamous epithelium or ciliated pseudostratified columnar epithelium, cyst wall may contain inflammatory cells, macrophages, thyroid follicles, and seromucinous glands and bone **D/D**: Epidermal inclusion cyst, dermoid cyst, branchial cleft cyst
Thyroglossal duct cyst carcinoma	**Incidence:** Malignancy is rare (mostly PTC) **Location:** Midline neck **Imaging:** Complex cyst or with solid elements **Histology:** Malignant tumor with background TGDC remnants. **D/D:** Metastasis to Delphian lymph node or carcinoma arising in pyramidal lobe
Lingual thyroid	**Location:** Base of tongue. **Histology:** Benign thyroid follicles, overlying squamous epithelium and grows in skeletal muscle **D/D:** Metastatic thyroid carcinoma in patients with known history of thyroid carcinoma
Parasitic nodule	**Location:** Lateral neck **Histology:** Benign thyroid tissue with no evidence of surrounding lymph node or lymph node involvement and has no subcapsular sinus. Background lymphocytic thyroiditis can be seen **D/D:** Metastatic thyroid carcinoma
Struma ovarii	**Location:** Ovary **Histology:** Benign or hyperplastic thyroid tissue as a component of teratoma. **Malignancy:** Rare (PTC > FC). For FC look for vascular invasion, ovarian serosal involvement or extra-ovarian disease **D/D:** Metastatic thyroid carcinoma (very rarely especially in bilateral ovarian involvement or with prior history of thyroid cancer)
Thyroid tissue in lymph node	Favor benign thyroid inclusion: ***After***, • Obtaining multiple deeper section • Close evaluation to look for focal/or subtle abnormal cytomorphologic features and ***If***, • No morphologic features of malignancy • No psammoma bodies • No architecture or cytomorphologic abnormality • Subcapsular or subcortical • Small in size (few follicles) • Seen in one or two lymph nodes only • In midline • No molecular/or immunohistochemical evidence of thyroid carcinoma **D/D:** Metastatic thyroid carcinoma

D/D: differential diagnosis, TGDC: thyroglossal duct cyst, PTC: papillary thyroid carcinoma, FC: follicular carcinoma.

3. Thyroglossal duct cyst

The thyroglossal duct remains attached to the thyroid diverticulum during caudal migration in early embryogenesis and obliterates by the 10th week [6]. Persistence of the thyroglossal duct can be seen in 7% of the population, mostly in the pediatric age group, but also in adults [7]. *Thyroglossal duct cyst* can be found anywhere in the midline neck from foremen cecum to the area around the hyoid bone, which is the most common (65% at infrahyoid and 20% at suprahyoid locations) [8]. Imaging features are helpful in identifying midline well circumscribed cysts, cyst contents and relationship to the hyoid bone [6]. Clinically, it usually presents as a painless midline non tender mass which moves on swallowing. However, on rare occasions (2%) can be seen as a lateral neck mass swelling [9]. Size of the cyst is variable and may range from less than a cm to as large as 10 cm on imaging [9]. Morphologically, the cyst wall is lined by ciliated respiratory type, squamous or cuboidal epithelium (Fig. 1A). The cyst lining may be denuded or show squamous metaplasia in cases with abundant inflammation. In addition, the cyst lining may show thyroid tissue (71%), hyoid bone, salivary gland type seromucinous glands, fibrosis and inflammation [9].

Thyroglossal duct cysts (TGDC) are rarely associated with malignancy (Fig. 1B–C). The reported malignancy rate ranges from 1% to 7.4% with majority of cases showing papillary thyroid carcinoma [9]. In a study of 242 cases of thyroglossal duct associated lesions, Wei et al. found that 31% had thyroid tissue in the cyst wall and 18 cases (7.4%) had papillary thyroid carcinoma (PTC) [10]. Thompson et al. identified 22 (3.2%) PTCs in 685 thyroglossal duct cysts [9]. Ewing et al. reported a series of 11 cases of thyroglossal duct cysts with 2 showing PTC [7]. Other less frequent carcinomas reported in literature include follicular thyroid carcinoma, squamous cell carcinoma and mucoepidermoid carcinoma [11]. Squamous cell carcinoma probably arises from the cyst lining cells rather than the ectopic thyroid tissue as reported cases show a background of benign cyst lining epithelium [12]. P16 positivity can be seen in squamous cell carcinoma arising in a thyroglossal duct cyst, as well as in the basal cells in benign squamous lining [12]. It is important to exclude the possibility of metastasis before diagnosing carcinoma arising from a TGDC. Cases of carcinoma arising in a TGDC should have background normal remnants of TGDC or benign thyroid tissue and the thyroid gland should also be evaluated, both clinically and radiologically [13]. These cases should be separated from isolated cystic metastasis to the Delphian lymph node located above the isthmus in the midline neck [14]. Regional lymph node metastasis to central compartment lymph nodes (level VI) can be seen in PTC arising in TGDC [13]. Interestingly, medullary carcinoma is not seen in TGDC as it is C-cell related process, which develop from ultimobranchial bodies and moves to lateral lobes of thyroid gland. They are not related to caudal migration of thyroid diverticulum from base of the tongue. Stein et al. in a study of 41 cases of TGDC did not find any parafollicular C-cells or medullary thyroid carcinoma despite finding thyroid tissue in 34 cases upon TTF-1 and calcitonin immunohistochemical staining [15].

Fine needle aspiration (FNA) cytology can be helpful in establishing a preoperative diagnosis, especially in cases with suspicious imaging features. Thompson et al. identified 144 of 685 TGDC cases that underwent preoperative FNA and of those the majority (n = 123) were non-diagnostic. Of the twelve TGDC associated with malignancy that underwent FNA, six categorized as malignant, two were non-diagnostic and four were called benign [9]. Similarly, Wei et al. reported preoperative FNA in 39 of 242 TGDC cases with only two cases demonstrating scant thyroid follicular cells [10]. Cytologic evaluation of

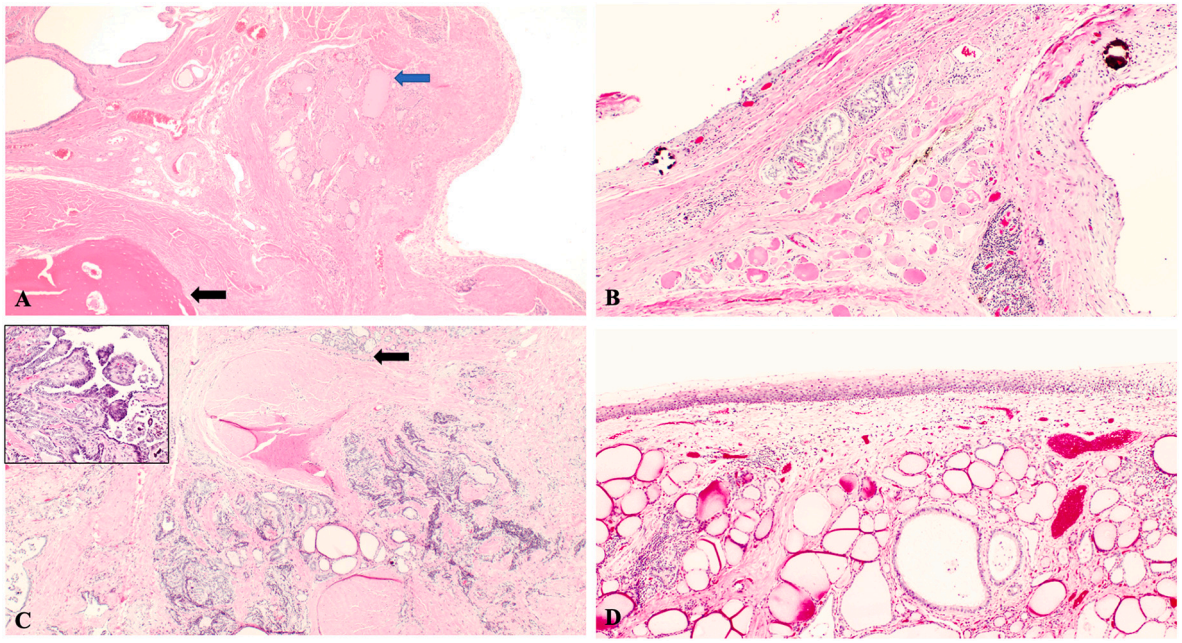

Fig. 1. Thyroglossal duct cyst (A) Thyroglossal cyst with focus of benign thyroid follicles (blue arrow) within the cyst wall, hyoid bone (black arrow) and skeletal muscle (H&E stain ×40). Thyroglossal duct cyst with associated papillary thyroid carcinoma (B–C), (B) Cyst lining consists of cyst lining epithelium, fibroconnective tissue, muscle, and thyroid follicles and psammoma bodies (H&E ×40). (C) Papillary thyroid carcinoma (PTC, lower side) and associated benign appearing thyroid follicular cells (arrow) and PTC with papillae formation and associated nuclear changes in high power view (H&E ×40 and 400). (D) Benign squamous epithelium and underlying thyroid follicular cells (lingual thyroid) (H&E ×40). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

TGDC can show low cellularity, cyst fluid, inflammatory cells (mostly macrophages and lymphocytes), thyroid follicular cells and cyst lining epithelial cells. Cases with PTC shows similar cytologic features as seen in thyroid gland which include nuclear crowding, overlapping, elongation, grooves, irregular nuclear membranes, chromatin clearing and intranuclear pseudoinclusions. Overall, the true positive and false negative rates of preoperative FNA diagnosis of TGDC associated PTC is 53% and 47%, respectively [16]. Thyroid tissue and malignancy is often not represented on the FNA sample due to smaller size leading in a low FNA efficacy. Additionally, the cystic nature of the lesion and lack of epithelial lining cells especially when associated with inflammatory process can produce a low cellularity specimen [17].

Diagnosis of TGDC is usually straight forward based on the clinical and imaging features [9]. However, identifying malignancy on preoperative imaging can be challenging. On imaging, cystic midline neck lesions with associated solid elements raise consideration of concomitant malignancy [18]. The likely differential diagnosis of TGDC includes dermoid cyst, epidermal inclusion cyst, branchial cleft cyst and bronchial cyst. Dermoid and epidermal inclusion cysts usually show keratinizing squamous epithelial lining while dermoid cysts also contain adnexal structures and their location is not related to hyoid bone. On the other hand, TGDC has mostly nonkeratinizing squamous lining, may contain thyroid follicles in the cyst wall and location is usually in close proximity to hyoid bone. Branchial cleft cyst is usually located laterally in the anterior neck unlike TGDC, which is located along the midline. Bronchial cyst may show seromucinous glands, cartilage and smooth muscle in the cyst wall while TGDC may rarely show some of these components and lack the smooth muscle wall. Data is limited regarding the formal staging system for TGDC associated carcinoma [18]. However, TGDC associated carcinoma usually treated by Sistrunk procedure alone in low risk cases which include those less than 45 years old with no soft tissue extension or lymph node metastasis and a normal thyroid gland. However, high risk cases with extensive disease can be managed with completion thyroidectomy [18].

4. Ectopic thyroid

Lingual thyroid, most common location of ectopic thyroid, is due the failure of caudal migration of thyroid diverticulum which results in the presence of thyroid tissue at the base of tongue (foremen cecum level) [3]. Lingual thyroid can be seen in any age group, including at birth, and is more common in females [19,20]. Cases are mostly asymptomatic but symptomatic cases can manifest as dysphagia, voice change, throat discomfort, sleep apnea and cough [19,20]. Presence of lingual thyroid tissue can be considered in the differential diagnosis of metastatic thyroid carcinoma, especially in a patient having history of PTC [21]. Lingual thyroid tissue usually contains follicular cells (Fig. 1D) that lack a well-defined capsule and grow in the skeletal muscle, which may mimic invasion [21]. Scintigraphy with Tc-99m can used to detect lingual thyroid tissue [22]. However, rare cases have shown increase uptake on radioiodine scan in chin area which later proved to be a benign lingual thyroid tissue [21]. Carcinoma can rarely arise from the lingual thyroid tissue and most of the reported cases are PTC; surgical management approach depends on the extent of disease [23].

Ectopic thyroid tissue consists of follicular cells and colloid and lack parafollicular C-cells. Midline neck area is the most common location of ectopic thyroid tissue. However, less frequently ectopic thyroid tissue can be seen in axilla, submandibular region, intratracheal, thoracic organs, ovaries (struma ovarii), gallbladder, vagina and adrenal gland [21,24]. Two ectopic foci (dual ectopy) of thyroid tissue are rarely reported in the literature. Malignancy rarely occurs in the ectopic tissue and PTC is the most frequent. However, follicular carcinoma, Hurthle cell carcinoma and anaplastic carcinoma cases are also reported [1,25].

Struma ovarii is a type of monodermal teratoma with a peak incidence in fifth decade. This can be asymptomatic but may present as lower abdominal pain or mass [26]. Histologic examination shows thyroid follicular tissue (Fig. 2A) and rarely Hashimoto thyroiditis. These may be cystic with an attenuated lining that necessitates immunostaining for confirmation of thyroid follicular cells (i.e., thyroglobulin). Malignancy is rare in these cases (5%) and predominantly

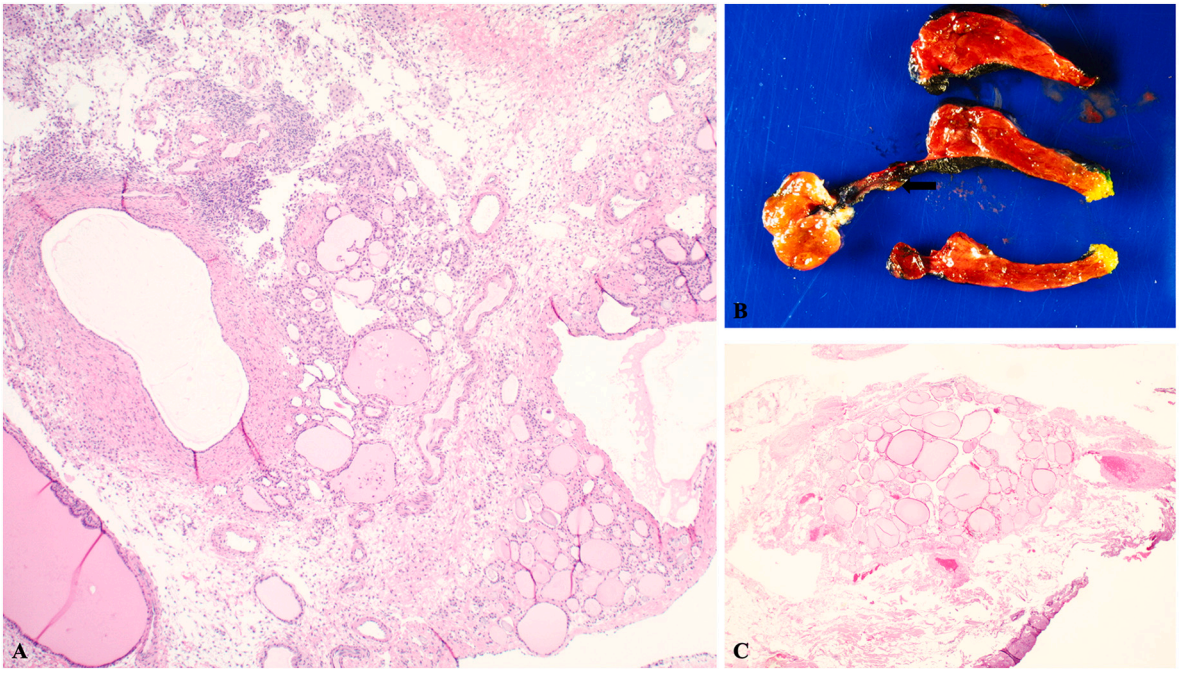

Fig. 2. (A) Struma ovarii with thyroid follicular cells seen in the cyst wall (H&E stain ×40). Parasitic thyroid nodule (B–C), (B) Lateral thyroid nodule attached to the main thyroid gland by a thin fibroconnective tissue (black arrow) (gross image). (C) Benign thyroid tissue within the fibroadipose tissue (H&E stain ×20).

includes PTC followed by follicular carcinoma [27]. The criteria for malignancy are similar to when the diagnosis is made in the thyroid gland. For follicular carcinoma, while either capsular or a vascular invasion is required when diagnosed in the thyroid gland, struma ovarii usually has no true capsule. Vascular invasion is one of the reliable criteria used to diagnose follicular carcinoma arising in struma ovarii and has been reported, albeit rarely [27]. Other features, such as ovarian capsular/serosal involvement, extraovarian disease or recurrent disease indicate malignant behavior [28].

Benign thyroid tissue can be seen in perithyroidal adipose tissue and skeletal muscle. In addition, adipose tissue can be seen within the thyroid gland, entrapped or due to metaplastic changes. Skeletal muscle is usually identified in isthmus and pyramidal lobe regions [29]. The presence of benign thyroid tissue in the skeletal muscle should not be overinterpreted as infiltrating carcinoma. The differential diagnosis of ectopic thyroid tissue in midline neck region includes metastatic PTC and substernal goiter. PTC involving a Delphian lymph node or a cystic papillary thyroid carcinoma with abundant macrophages and scattered clusters of neoplastic cells should exhibit classic nuclear features and other diagnostic features of PTC. Thyroid tissue with benign morphology in the midline of the neck is usually ectopic benign thyroid [30]. However, the presence of PTC in the thyroid gland raises the differential diagnosis of metastasis. Bohinc et al. described a case of a 0.5 cm micropapillary thyroid carcinoma involving the thyroid gland and an incidental finding of benign ectopic thyroid tissue in the adrenal gland [31]. Similarly, Basaria et al. described a case of a 4.5 cm PTC and increased uptake on radioiodine scan in the chin that raised concern for metastasis, but subsequent biopsy proved it to be benign lingual thyroid tissue [21]. Substernal goiter represents extension of the thyroid gland into the mediastinum and may cause airway compressive symptoms necessitating resection.

5. Parasitic thyroid nodules

Benign thyroid tissue in the lateral neck without evidence of a surrounding lymph node or evidence of other lymph node involvement is considered as *parasitic thyroid nodule*; this is also referred to as lateral aberrant thyroid (which also encompasses other entities) [32]. Usually these nodules are loosely connected to the thyroid gland by a thin fibrous band and are present in the same fascial plane as the thyroid gland (Fig. 2B). Originally it was thought that these foci represent metastatic thyroid carcinoma involving lymph nodes. However, more recent literature shows that nodules fulfilling the definition of a parasite nodule are benign [32]. Microscopic examination of these nodules shows benign thyroid parenchyma that is similar to the main thyroid gland (Fig. 2C). Morphologic features of Hashimoto thyroiditis with reactive lymphoid component including germinal centers may be seen and should not be interpreted as evidence of a lymph node and, therefore, as metastatic thyroid carcinoma. Parasitic thyroid nodules lack a subcapsular sinus and other architectural features of a lymph node. Bychkov reported a series of 8 patients with parasitic thyroid nodules; 4 had carcinoma in main thyroid gland. Morphologically, 4 cases showed features of Hashimoto thyroiditis, 3 showed Graves' disease and one was multinodular goiter. Interestingly, the author found many parasitic nodules were located close to vessels and retraction or tissue clefting was noticed around these nodules [33]. Several hypotheses exist to explain the presence of thyroid tissue in lateral neck, including abnormal thyroid rest migration during embryogenesis, lack of fusion of lateral and median anlage, and seeding of thyroid tissue after surgery [34].

Clinically, they can present as single or multiple lateral neck masses that may be interpreted as an enlarged lymph node (s) [33,35]. Imaging studies may raise concern for metastatic carcinoma involving a lymph node. Technetium-99 scan can show increased uptake in hyperfunctioning parasitic nodules in lateral neck, which may be due to thyrotoxicosis thus stimulating a metastatic process [35]. Similarly, thyroglobulin levels are usually elevated in FNA samples hence increases clinical concern for thyroid malignancy. FNA examination may be helpful to evaluate features of malignancy. PTC usually shows classic nuclear features and other morphologic features of malignancy. Lack of such features, absence of lymphocytes and recognizing benign cytologic features of thyroid would make parasitic nodule as a main diagnostic consideration. In our opinion, in such cases a descriptive diagnosis with a note describing the differential diagnosis would be more appropriate and further recommending clinical and radiological correlation. Benign thyroid nodules can show cystic degenerative changes which can be

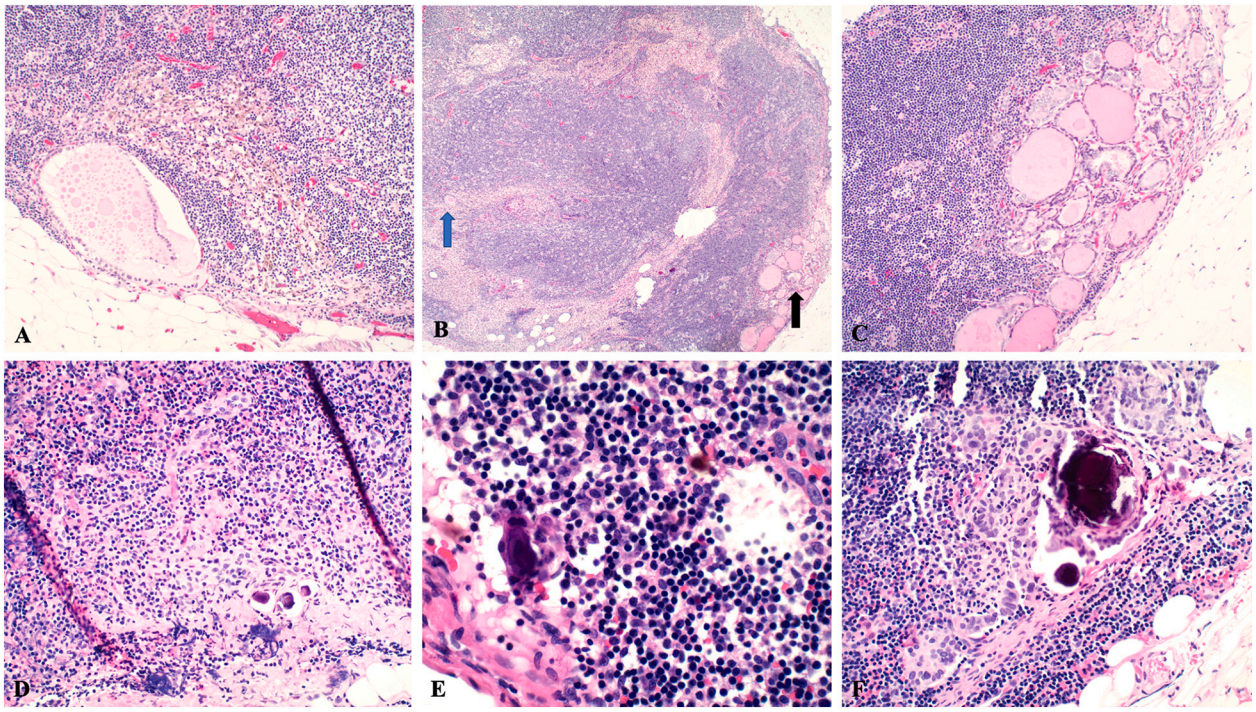

Fig. 3. Thyroid tissue in lymph node (A–C), (A) Benign appearing thyroid inclusion with cuboidal lining and colloid (H&E stain ×100). (B) PTC, Benign appearing thyroid follicular cells (blue arrow) and malignant cells (black arrow) (H&E satin ×20). (C) PTC, malignant glands mixed with benign appearing glands (H&E stain ×100). Psammoma bodies in lymph node, (D) Psammoma bodies in lymph node without epithelial cells and with rare some rare surrounding epithelial cells (E) (D: H &E stain ×200 and E: H&E stain ×400). (F) Psammoma bodies with surrounding malignant epithelial cells (H&E stain ×200). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

seen as macrophages and thyroid follicular cells in FNA cytology sample. This brings concern for a cystic variant of PTC which should exhibit typical nuclear features in cytologic smears. In such circumstances BRAF testing may give additional information. Another consideration is identifying cytologic atypia in parasitic nodule with Hashimoto's thyroiditis which may be overinterpreted leading to unnecessary surgery [36]. Molecular profiling may be helpful in the determination of malignancy.

6. Thyroid tissue in cervical lymph nodes

Incidentally discovered thyroid tissue within the cervical lymph nodes raises the differential diagnosis of benign thyroid inclusion versus a metastatic thyroid carcinoma (Fig. 3A–C). This may be detected during cytologic evaluation of a neck lymph node in a patient with lymphadenopathy for other reasons or histologic evaluation of lymph node dissections performed for other cancer staging. Finding demonstrable features of malignancy, such as psammoma bodies, fibrosis and atypical morphology can be helpful. However, cytologically bland thyroid follicular cells within the lymph node pose a challenge for diagnosis and management. Butler et al. reported 22 patients with head and neck or lung cancers and associated lymph node dissection. They found metastatic thyroid carcinoma in 16 of the patients. Of those, 9 cases showed carcinoma upon subsequent thyroid resection. In addition, 2 had lobectomy and isthmus removed with no tumor and 5 had no excision performed. The authors concluded that any thyroid tissue in a lymph node signifies metastasis, as many of their metastatic foci lacked classic features of malignancy [37]. On the other hand, Meyer et al. noted thyroid inclusions in 5 autopsy cases (either left or right cervical lymph nodes) and only one case had a 0.2 cm papillary microcarcinoma in thyroid gland on contralateral side to the relevant lymph node [38].

Benign thyroid inclusions are usually smaller in size (i.e. 2–3 follicles), located in sub capsular or cortical areas of lymph node, show microfollicles with a wedge-shaped arrangement (base pointing toward the capsule) and may involve two or less lymph nodes, lack psammoma bodies and nuclear features of papillary thyroid carcinoma [38-40]. Benign thyroid inclusions are usually located in midline or medial to jugular vein [38-40] and should not be seen in lymph node lateral to carotid sheath and jugular vein [41]. However, caution should be practiced when morphologic evaluation of lymph node shows benign appearing thyroid follicles replacing majority of the lymph node (more than one third) or involves multiple lymph nodes and goes beyond the above described criteria of benign inclusion [38,39]. Kakudo et al. identified bland appearing thyroid follicles in multiple lateral neck lymph nodes and molecular analysis demonstrated polyclonal origin which suggested non-neoplastic process [42]. León et al. studied 752 patients with lymph node dissections for head and neck cancer and identified 11 cases with thyroid inclusions. Five showed histologic features of malignancy (three lateral and two paratracheal) and three underwent thyroid resection and one had PTC. Six of their cases showed benign thyroid inclusions in the subscapular area involving lateral lymph nodes with no evidence of disease on follow up and suggested a less aggressive management approach [43].

Finding intranodal thyroid tissue in the absence of primary thyroid tumor is a challenging diagnosis for pathologists. If FNA or histologic evaluation shows a few clusters of benign appearing follicular cells associated with lymphocytes in a specimen designated “neck mass”, then benign ectopic thyroid, such as parasite nodule or intranodal inclusion versus metastasis from an occult thyroid primary should be considered. It is essential to correlate the morphologic findings with imaging features to determine location of the mass. Additionally, it is not uncommon to find benign appearing thyroid inclusions along with the malignant thyroid tissue in a lymph node (Fig. 3B). Finding benign appearing thyroid tissue within cervical lymph nodes requires additional work-up that may include obtaining additional deeper H&E levels, to look for morphologic features of malignancy, imaging studies, discussion with clinical team and evaluation of thyroid gland. Wang

et al. described a case with 2.5 cm lateral neck mass that was diagnosed as PTC involving a lymph node on frozen but no tumor in the thyroid upon thyroidectomy. Authors identified morphologically malignant and benign appearing thyroid tissue within the same lymph node and suggest a possible origin of cancer may relate to benign thyroid inclusion [44]. Mojica et al. reported a case of an FNA of a right posterior neck mass diagnosed as metastatic PTC. Thyroidectomy and lymph node dissection showed PTC in the thyroid gland and 19 of 55 lymph nodes showed thyroid tissue. Eleven were histologically malignant and the remaining 8 had normal appearing thyroid tissue. Furthermore, they identified BRAFV600E point mutation in both malignant and benign appearing nodal thyroid tissue [45]. Remarkably, authors also noticed that 8 morphologically benign appearing thyroid inclusion had replaced more than one-third of the lymph node which seems to beyond the cut off criteria of begin inclusions as described above [45]. In our institution, the unexpected finding of a few banal intranodal thyroid follicles in cervical lymph node/nodes prompts a note from the pathologist suggesting ruling out a primary thyroid carcinoma by imaging and cytomorphologic examination, if clinically indicated, before considering it ectopic intranodal thyroid tissue.

Psammoma bodies are frequently seen in papillary thyroid carcinoma. They show concentric lamellation and are basophilic in appearance while dystrophic calcifications are usually irregular and do not show lamellation (Fig. 3D–F). The presence of psammoma bodies either in thyroid or in a lymph node raises a concern of underlying malignancy [39]. Finding an incidental psammoma body in the cervical lymph nodes should prompt additional work-up to get deeper sections and search for an associated epithelial component. Imaging of the thyroid gland may be helpful to identify any thyroid lesions and these cases should be discussed in institutional multidisciplinary teams. Hunt et al. identified 29 thyroid specimens with isolated psammoma bodies located within thyroid parenchyma (n = 27) or perithyroidal lymph nodes (n = 2), away from tumor (if present), and they found tumor in 27 cases (PTC = 25 and Hurthle cell carcinoma = 2). Incidental papillary microcarcinomas were identified in 12 cases (size range = 0.1–0.85 cm). They recommend considering psammoma bodies in lymph nodes as metastasis and cautious evaluation of thyroid including submission of the entire gland for microscopic examination to exclude papillary microcarcinoma [46]. Others suggest the presence of psammoma bodies in PTC with aggressive clinicopathologic features [47]. Currently, the presence of psammoma bodies in the cervical lymph node is considered as pN1a [48]. However, nodal classification (American Joint Committee on Cancer: AJCC Staging Manual, 8th Edition) consists of N1a which corresponds to involvement of levels VI and VII while N1b represents involvement of any lymph node from levels I through V [48]. Some authors suggested categorizing lymph nodal involvement into following groups based on the tumor size: Psammoma bodies only, isolated tumor cells (not greater than 0.02 cm), micrometastasis (greater than 0.02- less than 0.2 cm) and further into small to large lymph node involvement [49]. Tumors with macrometastasis as compared to micrometastasis showed higher regional recurrence rate (32% versus 5%, respectively) leading the authors to conclude that presence of micrometastasis has no definitive clinical significance [50]. Randolph et al. proposed separating low risk N1 nodal disease which includes micrometastatic disease and clinically N0 from high risk nodal disease including macrometastatic foci and a clinical disease [49].

Use of ancillary testing can be helpful that includes galectin-3 (nuclear and cytoplasmic staining) and HBME-1 (membranous or apical luminal staining and cytoplasmic staining) immunostains and BRAF molecular test analysis which are negative in benign inclusions. BRAF immunohistochemistry (cytoplasmic staining) can be used and has overall good sensitivity (89%) as compared to BRAF mutational analysis by PCR (polymerase chain reaction) [51]. Usually, identifying PTC in a lymph node with typical nuclear features and psammoma bodies is straight forward. Less frequently, metastatic carcinoma with papillary architecture and psammoma body, from other sites, such as lung, ovaries can involve neck lymph nodes [52]. In such cases, immunohistochemical stains determining thyroid origin (TTF-1, PAX-8 and thyroglobulin) can be helpful. Finding an incidental thyroid carcinoma in the lymph node should prompt additional work up like imaging of thyroid gland and if imaging is normal then less aggressive approach and follow-up is suggested [40,48]. Others have suggested surveillance in select cases with no or very small thyroid lesions [53].

7. Conclusion

In summary, the presence of thyroid tissue in the midline of the neck may be seen in the setting of thyroglossal duct cyst, lingual thyroid, ectopic thyroid tissue, pyramidal lobe lesions, benign inclusions within the lymph node or metastatic thyroid carcinoma in a lymph node. Thyroid carcinoma can arise form thyroglossal duct cyst and lingual thyroid. Parasite nodules comprises of thyroid parenchymal tissue in lateral neck without features of a lymph node. The presence of Hashimoto thyroiditis in a parasite nodule should not be confused with lymph node metastasis. Benign thyroid inclusions in neck lymph nodes are usually small and are comprised of cytologically bland thyroid follicular cells and are located medial to jugular vein. They lack psammoma bodies and nuclear features of papillary thyroid carcinoma. Incidental thyroid carcinoma in lymph nodes with obvious malignant features requires additional imaging work to exclude occult thyroid primary.

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Andrea Barbieri: Conceptualization, validation, visualization, writing-review and editing

Manju Lata Prasad: Validation, visualization, writing-review and editing

Syed Gilani: Conceptualization, validation, visualization, writing original draft, writing-review and editing

Declaration of competing interest

None.

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