Ectopic thyroid tissue: anatomical, clinical, and surgical implications of a rare entity

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Abstract

Ectopic thyroid tissue is a rare entity resulting from developmental defects at early stages of thyroid gland embryogenesis, during its passage from the floor of the primitive foregut to its final pre-tracheal position. It is frequently found around the course of the thyroglossal duct or laterally in the neck, as well as in distant places such as the mediastinum and the subdiaphragmatic organs. Although most cases are asymptomatic, symptoms related to tumor size and its relationship with surrounding tissues may also appear. Any disease affecting the thyroid gland may also involve the ectopic thyroid, including malignancy. The clinician must distinguish between ectopic thyroid and metastatic deposits emerging from an orthotopic gland, as well as other benign or malignant masses. Thyroid scintigraphy plays the most important role in diagnosing ectopy, but ultrasonography contributes as well. In cases of symptomatic disease, surgery is the treatment of choice, followed by radioiodine ablation and levothyroxine suppression therapy in more refractory cases. This review provides current understanding about the wide clinical spectrum of this rare condition, also referring to optimal diagnostic approach, differential diagnosis, and management strategies.

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Introduction

Ectopic thyroid tissue is a rare developmental abnormality involving aberrant embryogenesis of the thyroid gland during its passage from the floor of the primitive foregut to its final pre-tracheal position (1, 2). Its prevalence is about 1 per 100,000–300,000 people, rising to 1 per 4000–8000 patients with thyroid disease (1, 2). However, in autopsy studies, the prevalence ranges from 7 to 10% (3, 4). More than 440 cases have been reported to date. In 70–90% of cases, it is the only thyroid tissue present (1–6). Ectopic thyroid is most common in females, especially in populations of Asian origin (5, 6). It may occur at any age, from 5 months to 40 years, but it is most common at younger ages.

In the thyroid gland, two different cell types are detected, the thyroid follicular cells and the parafollicular or C-cells. The former derive from the thyroid anlage, which is a region on the midline, on the embryonic mouth cavity, incorporating cells from the endoderm (7). Except for the median anlage, lateral anlages from the two IV branchial pouches form the lateral thyroid, accounting for the 1–30% of the gland’s total weight (4). On the other hand, the C-cells originate from the ultimo-branchial bodies of the IV pharyngeal pouch, located symmetrically on the sides of the developing neck. The initial origin of C-cell precursors, before migrating to this position, is the neural crest. The thyroid follicular cells are responsible for thyroid hormone production, while the C-cells produce calcitonin (7).

From an embryological point of view, an endodermal diverticulum from the median plate of the floor of the pharyngeal gut is formed, during the third or fourth week of gestation. This diverticulum descends in the midline, from the foramen cecum (located between the posterior third and anterior two-thirds of the tongue) to the final location of the gland, anteriorly to the pre-trachea and larynx. This migration begins at embryonic day 24 and; as a result, a narrow channel is created, called thyroglossal duct. The latter undergoes atrophy prior to the definitive thyroid formation (2, 7, 8). Ectopic thyroid tissue is the result of a failure of migration of thyroid, not only along the route of thyroglossal duct but also in subdiaphragmatic organs, such as the gallbladder (9) and the adrenal glands (10).

The exact mechanisms responsible for thyroid morphogenesis have not been clearly elucidated. Transcription factors appear to play a key role in the organogenesis of thyroid gland. These include the
transcription factor TITF1/NKX2-1, which is responsible for the thyroid-specific expression of thyroglobulin (Tg) and thyroperoxidase and the transcription factors PAX8, HHEX, and FOXE1. These factors are expressed not only in functioning thyroid cells but also in their precursors and seem to be essential for the early stages of thyroid morphogenesis (7). TITF1/NKX2-1 seems to play a pivotal role during thyroid gland development, as it controls survival at the beginning of organogenesis as well as the expression of genes specific for thyroid follicular cells in adult life (7). In a similar way, PAX8 is required not only for the survival of thyroid cell precursors but also for their functional differentiation. It plays a key role in the genetic regulatory cascade, which controls thyroid development (7, 11). It is of note that some cases of thyroid dysgenesis may be due to mutations in genes regulated by the aforementioned transcription factors (7). The role of HHEX is not completely elucidated. It seems that it is required to maintain the expression of TITF1/NKX2-1, FOXE1, and PAX8 mRNA in the thyroid anlage (7). As far as FOXE1 is concerned, genetic studies have demonstrated that it is required for thyroid migration. Mice homozygous for Foxe1 mutations have a sublingual thyroid. However, no such mutations have been detected in humans up to now (7). In general, it is speculated that some cases of thyroid dysgenesis may be due to mutations in the genes regulated by the aforementioned transcription factors. Other genes, such as TSH receptor gene, are necessary for thyroid development. Along with PAX8, they have been implicated in a minority of patients with thyroid dysgenesis (7).

This review focuses on ectopic thyroid tissue as a clinical entity, providing current knowledge about the manifestation of its various types. In addition, it tries to optimize the clinician's diagnostic approach and management.

### Clinical presentation of ectopic thyroid tissue

#### Lingual thyroid

The most frequent location of ectopic thyroid tissue is at the base of tongue, in particular at the region of the foramen cecum, accounting for about 90% of the reported cases (12), although lower rates (47%) have also been reported by others (5, 6). The mean age at presentation is about 40.5 years, ranging from birth to 83 years. In 70–75% of cases, lingual thyroid is the only thyroid tissue present (13, 14). Interestingly, lingual thyroid has been found in 10% of 200 consecutive autopsies (15). The most common symptoms are related to the growth of lingual thyroid and include dysphagia, dysphonia, stomatolalia (speech that is produced with clogged nostrils), sensation of foreign body, cough, snoring, sleep apnea (16–20), and, in more severe cases, respiratory obstruction and hemorrhage (21). The patient may be also asymptomatic; thus, lingual thyroid may be an incidental finding, revealed after investigation of non-thyroid-related symptoms (22).

In terms of thyroid function, most patients with lingual thyroid present with hypothyroidism, usually in the absence of orthotopic thyroid (5, 6, 16, 18, 22). They may also be euthyroid, even when no orthotopic thyroid exists (18). Hypothyroidism in a lingual thyroid may also be induced by medications interfering with iodine metabolism and actions of TSH, such as lithium (17). Hyperthyroidism is extremely rare and only two cases have been reported in the literature (23) (Table 1).

#### Other sites

Apart from the foramen cecum, ectopic thyroid has been described in numerous other sites, between the

<table>
<thead>
<tr>
<th>Location</th>
<th>Symptomatology</th>
<th>Age at diagnosis</th>
<th>Thyroidal status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lingual</td>
<td>Dysphagia, dysphonia, stomatolalia, cough, sensation of foreign body, snoring and sleep apnea respiratory obstruction, and hemorrhage</td>
<td>40.5 (0–83)</td>
<td>Usually hypothyroid, less often euthyroid</td>
</tr>
<tr>
<td>Submandibular</td>
<td>Asymptomatic</td>
<td>4–81</td>
<td>Euthyroid</td>
</tr>
<tr>
<td>Thyroglossal duct cyst</td>
<td>Palpable, mobile, usually painless mass</td>
<td>4–75</td>
<td>Hypothyroid or euthyroid</td>
</tr>
<tr>
<td>Intratracheal</td>
<td>Dyspnea, cough, difficulty in swallowing, hemoptysis, and stridor</td>
<td>30–50</td>
<td>Euthyroid</td>
</tr>
<tr>
<td>Intrathoracic (mediastinal, lung, and heart)</td>
<td>Asymptomatic</td>
<td>40–77</td>
<td>Euthyroid</td>
</tr>
<tr>
<td>Struma ovarii</td>
<td>Asymptomatic</td>
<td>45</td>
<td>Euthyroid, hyperthyroid in 5–15%</td>
</tr>
<tr>
<td>Adrenal glands</td>
<td>Lower abdominal pain, palpable lower abdominal mass, and abnormal vaginal bleeding</td>
<td>50–67</td>
<td>Euthyroid</td>
</tr>
<tr>
<td>Duodenum, pancreas, and intestine</td>
<td>Asymptomatic (incidental finding)</td>
<td>50–63</td>
<td>Euthyroid</td>
</tr>
<tr>
<td>Dual ectopy (usually lingual and subhyoid)</td>
<td>Asymptomatic (incidental finding)</td>
<td>18.7 (4–45)</td>
<td>Euthyroid or hypothyroid</td>
</tr>
</tbody>
</table>
base of the tongue and its final pre-tracheal position, as well as in the mediastinum and distant subdiaphragmatic areas (Table 1).

In rare cases, when the cells of the lateral anlage do not join those of the median, a lateral ectopic thyroid gland is formed. When this occurs, its location is usually in the submandibular region (4). These patients usually present with a lateral, palpable, mobile, painless mass in the carotid triangle or the submandibular area (2, 4). Until recently, cases of ectopic thyroid detected in the lateral cervical region were regarded as malignant (metastatic) lesions and were termed ‘lateral aberrant thyroid’ (24). Submandibular thyroid tissue is more common in females at ages ranging from 4 to 81 years and is located mainly on the right side of the neck (2, 4, 25). In most cases, orthotopic thyroid gland usually coexists and the patients are euthyroid (2, 4, 26, 27). Nevertheless, it may also present as the only functional thyroid tissue (25). Possible explanations provided for this ectopy are displacement during the course of embryonal development, spread of tissue during surgery on an orthotopic thyroid gland, and metastasis of a highly differentiated papillary thyroid carcinoma (26).

Thyroid tissue has also been described in other parts of its descending route. These include remnants (cysts) of the thyroglossal duct, being usually asymptomatic (28). On histological examination, ectopic thyroid may be found within the wall of the cyst with an overall frequency of <5%. It produces thyroid hormones, but the concentrations are usually subnormal and patients may be hypothyroid (28, 29). Hashimoto’s thyroiditis (30) and papillary carcinoma (31) have also been described.

Intratracheal thyroid is another rare position of ectopic thyroid described in the literature. Plausible explanations for this entity may be the division of the developing thyroid caused by the trachea and its cartilage rings or an ingrowth of thyroid tissue into the tracheal lumen. The latter is due to a developmental defect of the mesenchymal tissue between the thyroid and the trachea, allowing the primitive thyroid to adhere to the trachea (32). Intratracheal ectopic thyroid can occur at any age, but predominantly between the ages of 30 and 50 years, mainly in females (33). Patients usually present with cough, difficulty in swallowing, dyspnea, hemoptysis, and stridor, as a result of upper airway obstruction, or can be asymptomatic. A normally functioning orthotopic thyroid usually coexists and, hence, patients are euthyroid (32, 33).

Intrathoracic ectopic thyroid is another rare location of ectopic thyroid, accounting for about 1% of all mediastinal tumors. It has been reported in the mediastinum, lungs, and heart, manifesting usually with dry cough, dyspnea, and hemoptysis. Less commonly, patients may present with dysphagia or the superior vena cava syndrome. Intrathoracic thyroid may also be revealed incidentally on chest radiograph (34–36) or on autopsy (37). In cases of mediastinal ectopic thyroid, orthotopic tissue usually coexists and the patients are euthyroid (36). In most of the few cases been reported in the literature, it is located in the anterior mediastinum and in two cases posteriorly (36).

Intracardiac thyroid is an extremely rare finding, involving mainly the right ventricle. Patients present with dyspnea and the tumor is usually revealed on echocardiography examination. Euthyroidal state is reported and orthotopic thyroid gland coexists (38–40). Larger tumors, about 7 cm in diameter, resulting in severe right ventricular outflow tract obstruction (38), as well as de novo development of follicular carcinoma in ectopic intracardial thyroid have been described (40). Paracardiac thyroid mass has also been reported, attached to the ascending aorta, manifesting with chest pain and palpitation, due to irritation of the pericardium and compression of the right atrium (41). The patient can also be completely asymptomatic and the mass may be found incidentally during cardiovascular operations (42). The most plausible explanation for the detection of ectopic thyroid next to or into the heart lies probably on the common embryological origin of these two organs. There is a close anatomic relationship between the thyroid primordium and the developing myocardium in early human embryos. It is known that the ventral pharyngeal endoderm lies in close apposition to the heart mesoderm. As the heart and aorta descend, the thyroid gland is drawn caudally and leading to various anomalies of its final position (7, 41). Interestingly, cardiac malformations represent the most frequent birth defects related to thyroid dysgenesis (7).

Extremely rare locations of ectopic thyroid that have been described in the literature are subdiaphragmatic, involving locations such as the ovaries, adrenals, gallbladder, pancreas, duodenum, and mesentery of the small intestine. The presence of thyroid in the ovaries, also known as ‘struma ovarii’, develops as a teratoma containing a large amount of thyroid tissue, microscopically and biologically identical to normal thyroid. Struma ovarii comprises 1% of all ovarian tumors and 2–4% of all ovarian teratomas, with the thyroid proportion usually accounting for more than 50% of the total tissue (43–45). The mean age at diagnosis is 45 years. Patients are often asymptomatic with struma ovarii being an incidental finding on ultrasonography (US) or may present with lower abdominal pain, palpable lower abdominal mass, or abnormal vaginal bleeding (44, 46). Malignant transformation is relatively uncommon, reported in about 15% of patients (44). Thyroid hyperfunction develops in 5–15% of patients (45, 47). Struma ovarii-related thyrotoxicosis has been reported even after treatment of a thyroid toxic adenoma (45). Papillary carcinoma has also been described either as an incidental finding (48) or with metastases to the lungs and pleura (49).
Five cases of intra-adrenal thyroid gland tissue have been reported in the literature, in women of middle age. The patients were euthyroid and ectopic gland was diagnosed on histological examination after adrenalectomy. Enlarged adrenals, sometimes with a cystic compartment, were detected either incidentally or after investigation for secondary hypertension (10, 50–53).

Ectopic thyroid within or adjacent to the gallbladder as well as in the pancreas and duodenum is usually an incidental finding on histological examination after cholecystectomy for acute or chronic cholecystitis (9, 54) or during abdominal operations, such as vagotomy and pyloroplasty (55, 56). However, intra-abdominal thyroid may be large enough to cause abdominal and low back pain, diarrhea, and generalized weakness, presenting as a porta hepatis mass (57). In all these cases, no sings and symptoms of thyroid tumor were evident. However, in a case of intra-abdominal thyroid, the mass was located around the mesentery of the small intestine and presented with hyperthyroidism, even after the patient had undergone total resection of the normal thyroid (58). In all the above cases of subdiaphragmatic locations of thyroid gland, either aberrant migration or heterotropic differentiation of uncommitted endodermal cells could be hypothesized (7). Orthotopic thyroid gland usually coexists (45, 48, 58). In any case, the possibility of a metastatic origin for the ectopic follicles from an occult thyroid carcinoma should always be excluded. Finally, unique cases of ectopic thyroid include pituitary fossa, sphenoid sinus (61–64). It is of note that Graves’ disease in one of the two foci of dual ectopic tissue (72).

Primary carcinoma in ectopic thyroid has been described in cases where an orthotopic thyroid exists. The differentiation between carcinoma arising in ectopic thyroid tissue and a metastatic carcinoma is difficult. The diagnosis can be made indirectly by taking some features into account, such as separate blood supply of the ectopic gland from extra-cervical vessels, no personal history of malignancy, and normal or absent orthotopic thyroid with no history of surgery (34). Metastasis from ectopic thyroid carcinoma should also be considered.

Diagnosis

Scintigraphy, using Tc-99m, I-131, or I-123, is the most important diagnostic tool to detect ectopic thyroid tissue and shows the absence or presence of thyroid in its normal location. Thyroid scan can also unmask additional sites of thyroid tissue. It is both sensitive and specific for differentiation of an ectopic thyroid from other causes of midline neck masses (4, 16, 20, 61). However, the possibility of false positive diagnostic iodine scans must be taken into account, as a result of either normal or abnormal uptake in the head and neck. Physiological uptake includes the nasal mucosa, salivary glands, intestine, liver, and urinary bladder, while causes of pathological uptake may be meningiomas, dacyrocystitis, sinusitis, prostatic eye, and dental disease (12).

Radiological imaging modalities, such as grayscale or color Doppler US, computed tomography (CT), and magnetic resonance imaging (MRI), may help in designating the extension and location of ectopic tissue, thus contributing to a better pre-surgical evaluation of these cases (4, 16, 20, 61, 73, 74). Sometimes, chest radiography may also be useful in revealing some cases of intrathoracic goiter (34). Some authors, in cases such as thyroglossal duct cysts, recommend against routine use of scintigraphy due to the very low frequency of detecting ectopic tissue (29). They regard that US provides adequate information about the cyst and
scintigraphy is of value only in cases of hypothyroidism or if a normal thyroid gland is not visualized on US (29). Remarkably, a study assessing the ability of color Doppler US to detect the presence of ectopic thyroid in patients with congenital hypothyroidism showed a sensitivity of 90% compared with that of 70% of grayscale US or MRI (73). In this study, peripheral or internal color signal corresponded precisely to the focal concentration as indicated by radionuclide imaging. In most cases, ectopic thyroid was lingual (73). It appears to be either hypoechoic or hyperechoic compared with the surrounding tissue (73–75).

CT and MRI are valuable tools in identifying the site of ectopy, especially when it is distant from the descending pathway of thyroid. In cases of cervical lymphadenopathy or intratracheal invasion by the tumor, CT and MRI may assist as the suspicion for malignancy is increased (17, 34, 73, 76). Regarding CT imaging, thyroid tissue displays higher density on plain CT than the surrounding soft tissues, although enhanced images identify thyroid tissue more clearly than plain ones (17, 76). In MRI, ectopic thyroid appears as a rounded mass with higher signal intensity than that of the surrounding tissue in both the T1- and T2-weighed images (73). CT and MRI are also useful modalities in cases when radionuclide uptake by normal thyroid gland masks the uptake of the ectopic thyroid tissue, especially in the midline (33). In some ectopies, other diagnostic tools, such as the endoscopic evaluation of intratracheal thyroid, are valuable. In these cases, ectopic thyroid usually presents as a smooth reddish-brown submucosal mass in a subglottic posterolateral position (32, 76).

Last but not least, fine needle aspiration cytology (FNAC) provides considerable assistance in confirming the diagnosis of ectopic thyroid. It is the only modality to differentiate between a benign and a malignant lesion (3, 4, 17, 68, 74). The most useful immunohistological marker is Tg, as well as mRNA in needle wash out. However, FNAC results may sometimes be misleading or non-diagnostic, especially in cystic masses (17, 68).

**Differential diagnosis**

Thyroid cancer metastases should always be excluded, as they can manifest as ectopic thyroid tissue (12). In general, differential diagnosis depends on the location. Lingual and submandibular thyroid must be differentiated from adenomas and cysts in the midline, including angiomas, fibromas, lymphangiomas, lipo-mas, salivary gland tumors, thyroglossal duct cysts, midline branchial cysts, and epidermal or sebaceous cysts, as well as solitary fibrous tumor of the perithyroidal soft tissue (1, 16, 61). Lingual thyroid must also be differentiated from other swellings at the base of the tongue, such as hypertropic lingual tonsil, vallecular cyst, and mucous retention cyst (61). Differential diagnosis of intratracheal ectopic thyroid includes other benign conditions, such as papilloma, enchondroma, osteoma, and amyloid deposits, as well as malignant diseases other than thyroid carcinoma, such as chondrosarcoma, squamous cell carcinoma, or lymphoma (32, 77). Differential diagnosis for mediastinal thyroid includes germ cell tumors, neurogenic tumors, lymphomas, and thymic and mesenchymal tumors (36). Struma ovarii must be distinguished from primary ovarian tumors, such as granulosa cell tumors, Brenner tumors, papillary serous cystadenomas or cystadenocarcinomas, struma carcinoid, or rare cases of differentiated thyroid carcinoma metastatic to the ovary (78, 79). The other intra-abdominal ectopies are usually incidental findings and diagnosis is based on histological examination.

**Management**

There is no consensus about the optimal therapeutic strategy, perhaps due to the rarity of this clinical entity. Most authors agree that surgical treatment of ectopic thyroid in the neck (mainly lingual, sublingual, submandibular, and lateral cervical) depends on size and local symptoms (airway obstruction, dysphagia, and dysphonia), as well as on other parameters, such as patient’s age, functional thyroid status, and complications of the mass (ulceration, bleeding, cystic degeneration, or malignancy) (4, 16, 17, 21, 61, 80). Some recommend complete surgical resection, considering the potential of malignant transformation (34). For cases completely asymptomatic and euthyroid, regular follow-up is recommended in order to detect mass enlargement or development of complications (4, 16, 21, 61, 81). For mild symptoms and hypothyroid states, levothyroxine replacement therapy may be effective, leading to considerable mass reduction (4, 16, 21, 61, 82).

Several surgical approaches for lingual thyroid have been described, such as the transoral route and the transhyoid, suprahyoid, or lateral pharyngotomy. The former is usually preferred for small lesions since it does not affect deeper structures; thus, complications, such as lingual nerve injury and deep cervical infections, are avoided. The latter approach with or without preoperative tracheotomy is chosen for larger masses providing better control of bleeding (8, 16, 17, 21, 82, 83). For the transoral approach, more successful outcomes may be achieved by using monopolar coagulation, the CO2 laser, or laser diode (16, 17, 84, 85). In cases when ectopic is the only functional thyroid gland, some authors recommend transplantation of the resected tissue in order to avoid permanent hypothyroidism (8, 16). In rare cases of calcified masses of the lateral neck, modified radical neck dissection is recommended, considering the high possibility of malignancy (86).

With very few cases reported, it is difficult to assess the value of non-surgical management. Nonetheless,
in cases when a surgical approach cannot be applied, suppressive hormone therapy with levothyroxine in order to avoid ectopic thyroid tissue growth and I-131 therapy for decreasing tumor’s size can be proposed (17, 87). Iodine ablation of lingual thyroid appears to be a safe and effective strategy resulting in complete resolution of symptoms, 2 months after treatment and without disease recurrence during follow-up (87, 88). It is of note that much higher doses of radioiodine may be required for size reduction than those required to ablate the thyroid bed tissue (13). Ablative radioiodine should be avoided in children and young adults, due to potential deleterious effects on the gonads and other organs (16, 89).

Regarding symptomatic intrathoracic goiter, it is managed surgically. Its removal usually necessitates thoracotomy or sternotomy (35). For intracardial thyroid causing cardiac compression and related symptoms, surgery is also the treatment of choice. This disorder seems to be curable if complete resection is performed (42).

With respect to struma ovarii, surgical approach is indicated for benign lesions. Either resection of the tumor or salpingo-oophorectomy with or without hysterectomy is proposed. Disease recurrence during follow-up is uncommon. Regarding malignant struma ovarii, optimal management depends on the tumor size, patient’s age, and her decision for childbearing. For younger women desiring to preserve fertility, unilateral salpingo-oophorectomy is an option in the absence of extra-ovarian disease. For these low-risk cases (tumor size <2 cm), levothyroxine therapy, pelvic imaging, and periodic Tg assessment are recommended (44, 78, 90). For high-risk patients, such as those with larger carcinomas, extra-ovarian disease, or more aggressive histological features, surgical resection along with radioactive iodine ablation is indicated. After iodine ablation, any detectable serum Tg is a marker of persistent or recurrent disease (44, 78, 90). For residual or metastatic/recurrent disease, radiiodine therapy may have favorable outcome. In more refractory cases, such as those with multiple metastatic lesions or those who absorb radiiodine poorly, external beam radiation is a reasonable approach (44, 91).

Conclusions

In conclusion, developmental defects occurring at an early stage of embryogenesis generate ectopic thyroid tissue, residing anywhere along the gland’s embryological descending pathway, as well as in distant areas. The majority of cases are asymptomatic, but symptoms related to tumor size and location may develop, as well as primary thyroid malignancy. Thyroid scintigraphy plays an important role in establishing diagnosis, although other imaging modalities, mainly US, may contribute. Surgery is the treatment of choice in symptomatic cases, with a role for radiiodine ablation in recurrent disease. The clinician should always take into account the potential of this rare entity and differentiate it from other masses in the neck and distant sites.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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