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Review

Ectopic thyroid: etiology, pathology and management

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INTRODUCTION

Ectopic thyroid refers to the presence of thyroid tissue in locations other than the normal anterior neck region between the second and fourth tracheal cartilages. It is the most frequent form of thyroid dysgenesis, accounting for 48-61% of the cases.[1] Prevalence of this condition is reported to be between 1 per 100,000-300,000 persons and occur one in 4,000-8,000 patients with thyroid disease.[2] To date, about 500 cases have been reported in the English literature mainly from Europe, Asia and America, with a small number of reports coming from Africa. Sixty-five to eighty percent of cases occurred in females.[2] Although it is difficult to detect asymptomatic thyroid ectopy, post-mortem studies have suggested that 7-10% of adults may harbor asymptomatic thyroid tissue along the path of the thyroglossal duct.[3] Ectopic thyroid tissue co-existing with a eutopic thyroid may be equal to that without a normally located gland.[4]

Key words: Aetiology, Diagnosis, Ectopic goitre, Ectopic thyroid, Hypothyroidism, Treatment

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Lingual thyroid is the most common type accounting for 90% of cases, while sublingual types are less frequently encountered. The sublingual types may be suprahyoid, infrahyoid or at the level of the hyoid bone.[5] In 1869, Hickman reported the first case of ectopic thyroid tumour of the base of the tongue, pressing down the epiglottis on the larynx and causing death by suffocation sixteen hours after birth.[6] Other locations in the head and neck regions where ectopic thyroid tissue may be found include the trachea,[7] submandibular,[8] lateral cervical regions,[9] axilla,[10] palatine tonsils,[11] carotid bifurcation,[12] iris of the eye[13] and pituitary gland.[14] Furthermore, the presence of ectopic thyroid tissue in other places distant from the neck region has also been documented. These sites include the heart,[15] ascending aorta,[16] thymus,[17] oesophagus,[18] duodenum,[19] gallbladder,[20] stomach bed,[21] pancreas,[22] mesentry of the small intestine,[23] Porta Hepatis,[24] adrenal gland,[25] ovary,[26] fallopian tube,[27] uterus[28] and vagina.[29]

Existence of ectopic thyroid glands at two different locations is very rare. Only 27 cases of such dual ectopia have been reported in the English literature. Huang et al[30] described the second case of dual ectopia with a normally located pretracheal thyroid gland. Two cases of triple ectopia have been reported, one of these by Ibrahim et al,[31] where three separate ectopic thyroid masses were present in the lateral neck region with a co-existing eutopic goitre. The aim of this review is to highlight current knowledge about the aetiology, pathology and management of this condition.

EMBRYOLOGY AND AETIOLOGY

The thyroid gland is located in the neck region in mammals. In humans it lies in the anterior neck region between the 2nd and 5th tracheal rings. It is the first of the body's endocrine glands to develop, on approximately the 24th day of gestation. The gland has two diverse cell types, the thyroid follicular cells (TFCs) which produce thyroid hormones and the parafollicular or C cells which produce calcitonin. The cells originate from two different embryological structures: the thyroid anlage and the ultimobranchial bodies which are the sites of origin of the TFCs and C cells, respectively. The gland originates as a proliferation of endodermal epithelial cells on the median surface of the developing pharyngeal gut between the 1st and 2nd pharyngeal pouches. It lies between the tuberculum impar and the copula, at a point later indicated by the foramen caecum. The thyroid premordium penetrates the underlying mesoderm and descends, anterior to the pharyngeal gut, as a bilobed diverticulum. During the process of migration, the gland remains connected to the floor of the pharyngeal gut by the thyroglossal duct. It descends in front of the hyoid bone and the laryngeal cartilages to reach the final position in front of the trachea in the 7th week of gestation.

Although the molecular mechanisms involved in thyroid dysgenesis are not fully known, studies have shown that mutations in regulatory genes expressed in the developing thyroid could be responsible.[1] Genetic research has shown that the gene transcription factors TITF-1(Nkx2-1), *Foxe1*(TITF-2) and PAX-8 are essential for thyroid morphogenesis and differentiation. Mutation in these genes may be involved in abnormal migration of the thyroid.[1,32] Animal studies have shown that the essential functions that TITF-1 play at later stages of thyroid development, when follicular cells reorganize themselves into follicles, require phosphorylation of the protein.[33] It has also been shown in gene-targeting experiments that *Foxe1* is required for thyroid migration and that mice homozygous for *Foxe1* mutations show a sublingual thyroid.[1] Furthermore, the presence of a thyroid-specific regulatory element in the 5' upstream region of the PAX-8 gene has been reported. The identification of this regulatory element is believed to represent the first step in the investigation of upstream regulatory mechanisms that control *Pax8* transcription during thyroid differentiation.[34] In humans, more than 50% of thyroid dysgenesis cases are associated with an ectopic thyroid. However, no mutation in known genes has so far been associated with the human ectopic thyroid.[1] Cases of familial thyroid ectopy where aberrant thyroid tissues were present in two members of the same family have been described.[35]

The majority of thyroid ectopias are located in the midline along the tract of the thyroglossal duct due to arrest of migration along the line of descent. It is assummed by some authors that TFCs derive from both a median thyroid and a lateral thyroid bud (the ultimobranchial body). It is hypothesized that aberrant thyroid tissues found in the submandibular and lateral neck regions originate from a defective lateral thyroid component that cannot migrate and fuse with the median thyroid anlage.[1] Studies in animals also showed a possible link between development of major cervical arteries and relocalization of the thyroid gland.[36] The dependence of thyroid morphogenesis on the development of adjacent arteries is believed to be a conserved mechanism that might have evolved to ensure efficient hormone release into circulation. Variability in the architecture of cervical vessels and branching of carotid arteries from the aortic arch might influence thyroid morphogenesis and account for some cases of ectopic thyroid tissues.[36] Congenital defects of the cardiovascular system have been associated with congenital thyroid abnormalities.[37] Presence of ectopic thyroid tissues in distant locations could come about as a result of aberrant migration or heterotopic differentiation of uncommitted endodermal cells.[24] An overdescent of thyroglossal duct remnants has been suggested as the cause of ectopic thyroid tissue in the mediastinum and in mid-subdiaphragmatic locations, while their presence in the genital tract could be explained through a possible mechanism of parthenogenetic development of germ cells into thyroid tissue after failure of all germ cells to migrate to the genital crest in early embryological development.[38] More research is required to determine the actual cause of thyroid ectopy. Detection of the gene responsible for this condition in humans will assist early or prenatal diagnosis and better management of the disease.

PATHOLOGY

Ectopic thyroid may become goitrous[31] and may also be associated with clinically evident thyroid dysfunction, which could be either hypofunction[39] or hyperfunction.[40] Rarely, benign[41] or malignant[7,26] neoplastic changes can occur in ectopic thyroid tissue. Thyroiditis occurring in ectopic thyroid tissue has also been reported.[42] Ectopic thyroid is commonly detected during periods of increased demand for thyroid hormones, e.g. puberty and pregnancy. Increased levels of thyrotropin at these periods causes enlargement of the ectopic thyroid tissue, thereby making it clinically detectable as a mass, or following pressure symptoms. Thirty-three percent of patients diagnosed with ectopic goitre in Korea were between the ages of 10 and 20 years.[2] Dossing et al[43] described a case of recurrent pregnancy-related intra-tracheal thyroid growth stimulation causing upper respiratory obstructive symptoms. This was believed to be a result of the combination of increasing human chorionic gonadotropin (hCG) stimulation and borderline iodine deficiency. During pregnancy, thyroid gland size increases by an average of 30% in borderline iodine deficient regions.[44] It has been speculated that epidermal growth factor could also stimulate thyroid growth.[43] Administration of lithium, a drug used in the treatment bipolar disorder, was reported to be the cause of enlargement of an ectopic lingual thyroid in a patient.[45] Lithium inhibits thyroid function, leading to hypothyroidism and goitre.

Ectopic thyroid is the most common cause of congenital hypothyroidism in infants.[2] In addition hypothyroidism occurs in about 33% of patients with thyroid ectopy.[39] Seventy percent of patients with ectopic lingual thyroid without a co-existing eutopic thyroid tissue will develop sub-clinical hypothyroidism. This often progresses to become clinically manifest during periods of physiological stress.[46] Aberration in the migratory pathways of the rudimentary thyroid that may lead to ectopy almost certainly results in inadequate blood supply to support normal thyroid function.[47] While some amount of normal thyroid hormone is secreted by the ectopic gland, this may not be sufficient for higher physiological demands during puberty, pregnancy, infections and trauma.[48] Studies have also suggested that iodine organification defect which is associated with thyroid ectopy could be responsible for hypothyroidism in this condition.[49] It is rare for patients with ectopic thyroid to present with hypothyroidism during adulthood.[50] Shakir reported the case of a 43-year old female with lingual thyroid associated with hypothyroidism and lympomatous thyroiditis.[51] Hypothyroidism was believed to have followed thyroiditis, transforming lingual thyroid into a fibrous tissue which was not sensitive to the trophic action of TSH.

Hyperthyroidism arising from ectopic thyroid tissue is less common than hypothyroidism. However, an ectopic thyroid gland with histological features of Graves' disease has been found in different locations like the base of the tongue,[52] mediastinum,[53] submandibular region,[40] lateral neck [54] and the mesentry of the small intestine. [23] Some of these cases were found in patients who have had sub-total or total thyroidectomy for thyrotoxicosis.[23,53] Thyrotoxicosis arising from a recurrent ectopic mediastinal thyroid was reported by Basaria et al.[53] This was thought to have followed stimulation of thyroid remnant tissue by thyroid-stimulating immunoglobulins (TSI). It should be noted that ophthalmopathy can be associated with thyrotoxicosis in ectopic thyroid.[52]

Primary malignant transformation can occur in ectopic thyroid tissues in different locations. Papillary, follicular, mixed follicular and papillary, hurthle cell tumour and medullary carcinomas have been reported.[55-59] Frequency of carcinoma in lingual thyroid is estimated to be approximately one in 100 cases with a female to male ratio ranging from 3:1 to 8: 1. The majority of these tumours are described as being of the follicular type, while papillary forms comprise 23%. This is in contrast to normal thyroid gland neoplasms, of which papillary tumours form the predominant form. Other variants are less frequent.[57,60] Several rare tumours arising from ectopic thyroid tissues are single cases of teratoma[61] and primary B cell lymphoma.[62] Both cases occurred in a mediastinal ectopic thyroid. Rarely, malignant ectopic tumours can present with metastasis to lymph nodes.[55] Ectopic thyroid tissue located laterally in the neck was referred to in the past as 'lateral aberrant thyroid tumours' because they were thought to represent metastasis from thyroid carcinoma. However, several cases of laterally situated benign ectopic thyroid in the neck have been documented.[9,12,31]

CLINICAL FEATURES

The majority of patients with ectopic thyroid are asymptomatic, while some cases are detected incidentally. Symptoms are usually related to size and location of the ectopic gland as well as associated endocrine dysfunction. In lingual thyroid, clinical manifestations peak at a mean age of 40 years with two statistical peaks at the ages of 12.5 and 50 years.[63] Common symptoms include cough, pain, dysphagia, dysphonia, dyspnoea and haemorrhage.[2,43,63] Large masses can present with airway obstruction and stridor in children, while a third of patients have evidence of hypothyroidism.[63] Sleep apnoea and respiratory obstruction in adult patients with lingual thyroid have been reported.[64,65] A common finding on examination is enlargement of the posterior base of the tongue by a firm, midline mass. The colour can range from light pink to bright red, while the surface may be smooth or irregular. Haemorrhage or ulcerative changes may appear on laryngoscopy as a white or pink vascular mass.[63,64] Sublingual or pre-laryngeal ectopic thyroid commonly presents as an anterior neck mass above, below or at the level of the hyoid bone. It is usually painless, gradually increasing in size, and may move with swallowing. Characteristically, the mass has smooth margins and is soft in consistency, mobile and non-tender. It should be differentiated from thyroglossal duct cyst, epidermal cyst, lymphadenopathy, lipoma, lymphangioma, sebaceous cyst, cystic hygroma, dermoid cyst, midline branchial cyst and neoplasms.[66] Laterally placed ectopic thyroid in the neck region could present as a submandibular or lateral cervical mass. This must be differentiated from salivary gland tumours, lymphadenopathy and other subcutaneous swellings.

Intratracheal ectopic thyroid commonly present with progressive dyspnea, stridor, cough, difficulty swallowing and haemoptysis. Dyspnea in this condition may be mistaken for asthma and it might be difficult to differentiate stridor from the wheezing of asthma on physical examination.[67] Intra-tracheal ectopic thyroid is visualized during direct laryngoscopy as a sub-glottic or upper tracheal wall mass covered with normal mucosa.[67] Intra-thoracic ectopic thyroid is usually asymptomatic and is discovered incidentally. However, it may present with cough, dyspnoea, haemoptysis and rarely with dysphagia and superior vena cava syndrome.[68] Clinical presentation of intra-cardiac ectopic thyroid is commonly non-specific and cases are diagnosed during investigations for arrhythmias, embolism and obstructive symptoms.[15] In other rare locations symptoms may be related to the organ involved. Adrenal ectopic thyroid could present with hypertension,[25] while that in the gallbladder may present with right upper quadrant abdominal pain.[20]

Presentation with features of hypothyroidism occurs mainly in children. Thyroid ectopy is present in 24% of children with primary non-goitrous hypothyroidism.[63] Ectopic thyroid glands in infants and young children who suffer from failure to thrive and mental retardation is often detected during routine screening and work-up for hypothyroidism.[63] On the other hand, presentation with clinical features of hyperthyroidism is less common and the few reported cases were in adult and elderly patients.[23,40,52-54]

INVESTIGATION

Radionuclide thyroid imaging employing technetium-99m pertechnetate, iodine-131 or iodine 123 is useful in the evaluation for ectopic thyroid. Thyroid tissue takes up the radioisotope and this helps in localizing the ectopic thyroid and at the same time in determining the presence of a eutopic thyroid gland. This is crucial to know before surgical removal of the ectopic tissue since in more than half of the patients with thyroid ectopy, no other functioning thyroid tissue exists.[2] Technetium-99 pertechnetate yields better quality imaging and at the same time delivers a lower radiation burden to the body compared to iodine-131. In addition, it is widely available, waiting time is shorter following the administration of the tracer and it can be used safely in children. However, it accumulates in the background of the ectopic thyroid, including the salivary gland, making it difficult to distinguish small masses.[2,69,70] Iodine-123 is also widely used, especially in the evaluation of children, although the cost is high and its shorter half-life makes its availability more difficult.[2]

High resolution ultrasound scanning is generally favoured in the initial assessment, especially in patients presenting with neck masses. It is non-invasive, cost-effective and does not expose patients to ionizing radiation. At the same time it can be used to determine

the presence of a eutopic thyroid. The sensitivity of detection of an ectopic thyroid is enhanced by the use of colour Doppler technique by demonstrating peripheral or internal colour flow signals that are reflective of hypervascularity.[71] A normally located thyroid gland with normal echogenicity, contour and size confirmed on ultrasound is highly likely to be functional, this suggesting that an abnormal neck mass may be removed without the risk of postoperative hypothyroidism.[72] This may obviate the need for thyroid scintigraphy to confirm the presence of a functional thyroid tissue before surgical removal of the ectopic gland. Facilities for thyroid scintigraphy may not be readily available in some resource-poor countries and ultra-sonography may be the only available imaging modality for investigating these patients.

CT scan and MRI are valuable imaging tools in the investigation of patients with ectopic thyroid. They are especially useful when a eutopic thyroid gland is not identified by ultrasound. Ectopic thyroid tissue has a characteristic uniform high attenuation on non-contrast CT, while on MRI it shows an elevated signal on T1- and T2-weighted images compared with the surrounding musculature.[73] MRI is particularly useful in lingual thyroid when there is difficulty in differentiating thyroid tissue from tongue muscle. It offers less radiation exposure than CT scan. However, the cost of the procedure is higher, it requires longer imaging time and it may necessitate the use of anaesthesia in the paediatric group because of the confining nature of the imaging machine.[73] Angiography has been used in the past to determine patterns of vascularization of lingual thyroid and this can help in planning surgical intervention. It can also allow the use of embolization preoperatively to decrease the risk of intraoperative haemorrhage or serve as the primary treatment modality in patients who are treated nonoperatively.[63]

Tissue biopsy for histology or fine needle aspiration cytology (FNAC) is especially important when malignancy is suspected. Biopsy could be taken through the endoscope in lingual and intra-tracheal ectopic glands. FNAC is one of the most accurate diagnostic methods for detection of neck masses and gives correct diagnosis in 95–97% of cases. It can assist in making a preoperative diagnosis of ectopic thyroid tissue and this helps the surgeon to decide on request about further radioisotope imaging to determine whether the mass is the only functioning thyroid tissue.[73]

Thyroid function tests that assess the serum levels of T3, T4, TSH and thyroglobulin are carried out in suspected cases of ectopic thyroid. Test results indicate hypothyroidism in the majority, while the rest are often euthyroid.[2] Cases of hyperthyroidism may be encountered on rare occasions.[23,40,53] Plasma thyroglobulin measurement is useful in establishing the specific type of thyroid dysgenesis in infants with congenital hypothyroidism. Absence of thyroid uptake on scintigraphy with detectable serum thyroglobuling levels will indicate presence of ectopic thyroid tissue.[74] Other investigations that may be required in patients with ectopic thyroid depend on the location of the gland. Echocardiography and coronary angiography may be necessary in intra-cardiac thyroid ectopy,[15] while barium swallow is important in some patients presenting dysphagia.[18]

TREATMENT

Asymptomatic euthyroid patients with ectopic thyroid do not usually require therapy but are kept under observation. For those with symptoms, treatment depends on size of the gland, nature of symptoms, thyroid function status and histological findings. In patients with lingual, sublingual, lateral neck or intra-tracheal thyroid with hypothyroidism, suppressive therapy is administered using exogenous thyroid hormone. This suppresses the TSH level and causes reduction in the size of the gland. Euthyroid patients with mild obstructive symptoms can also benefit from suppressive therapy. However, the rate of reduction in size of the gland is generally slow and a quick result should not be expected. In a series, all four patients seen received hormone therapy yet failed to achieve significant reduction in size of their lingual thyroid and eventually underwent surgical excision.[63] It has also been recommended that all asymptomatic euthyroid patients should be given exogenous thyroid hormone to prevent a state of hypothyroidism which eventually develops in most patients.[63] In addition, it prevents progressive growth of the mass and possible malignant transformation.[75]

Surgical intervention is indicated when severe obstructive symptoms, bleeding, ulceration, cystic

degeneration and malignancy occur.[2,45] It is important to determine the presence of a normally located thyroid gland before removal of the ectopic tissue to avoid hypothyroidism. Excision of a lingual thyroid is usually carried out by the trans-oral route. It is best for small lesions because of the limited exposure it provides. In bigger lesions, exposure can be improved by adopting the midline mandibulotomy and tongue splitting technique. The drawback of this technique is the residual scar in the lower lip and mental region. To avoid this, a lower lip de-gloving technique without lip incision has been recommended.[76] Control of bleeding is another challenge associated with the trans-oral approach. To address this, feeding vessels such as the bilateral lingual arteries may need to be identified and ligated prior to excision,[63] although risk of tongue necrosis is increased with this method. Excision of the gland endoscopically using CO_2 laser or harmonic scalpel has been done successfully with lesser bleeding and post-operative morbidity.[63,77,78] Terries et al reported the removal of an obstructive lingual thyroid using a minimally invasive trans-oral procedure that incorporates Harmonic technology and high resolution endoscopy without external incision on an out-patient basis.[78] Large swellings are often removed surgically through lateral pharyngotomy, suprahyoid or transhyoid approaches. These techniques offer good exposure and control of bleeding is easier. They are, however, associated with higher risk of injury to vital structures and fistula formation between neck skin and the oropharynx.[76]

The ectopic gland may be the only functional thyroid and complete excision is followed by life-long hormone replacement. Procedures described to retain some degree of thyroid function in the patients are the transposition of the ectopic thyroid with a vascular pedicle flap into the muscle space at the floor of the mouth[76] or the lateral pharyngeal wall,[79] auto-transplantation of thyroid tissue into the anterior rectus sheath or under the strap muscles[80] and partial trans-oral endoscopic excision in small and anterior lesions.[81] The transposition technique enables satisfactory long-term post-operative thyroid function, while 70% of patients will require exogenous thyroid hormone replacement following auto-transplantation.[76,63] Control of intra-operative bleeding is a challenge in partial trans-oral ablation and substitutive hormone treatment may be required to preserve euthyroid status and avoid recurrence of the mass following the procedure.[81]

Ectopic thyroid in the antero-medial and lateral neck regions may require surgical excision for cosmetic reasons or when the swelling is symptomatic and does not respond to replacement therapy. Surgery is also indicated if malignancy is suspected. Surgical excision of ectopic intra-tracheal thyroid is indicated if the size of the gland is large and causing pressure symptoms or in cases of histological malignancy. The gland can be removed via the open cricoid procedure or the endoscopic laser-assisted approach.[82] Symptomatic intra-thoracic ectopic goitres are usually excised surgically via thoracotomy or sternotomy. Thoracoscopic excision, including robotic resection, has also been reported.[68,83] Intra-cardiac thyroid mass is surgically excised under standard cardio-pulmonary by-pass,[15] while sub-diaphragmatic intra-abdominal ectopic thyroid swelling is resected via laparotomy. After surgical resection, the ectopic thyroid tissue is sent for histological diagnosis. When diagnosis of ectopic thyroid is made post-operatively, patients are further evaluated for the presence of eutopic or other ectopic thyroid tissue and thyroid function. Further treatment is determined by the outcome of the investigations.

Radioactive iodine 131 therapy is an alternative to surgical ablation. However, shrinkage of thyroid tissue is not consistent following this mode of treatment. It is indicated in patients who are not fit for surgery, in those who refused operation and where surgical resection is not feasible due to anatomical difficulties.[63,84] It is contraindicated in pregnant women and avoided in younger paediatric patients. Other disadvantages include slow response to medication, fibrosis, radiation-induced tracheitis and dependence on life-long thyroid hormone replacement.[45,63,67] Treatment of ectopic thyroid with features of hyperthyroidism can be achieved by anti-thyroid medication or surgical excision. Radioactive iodine therapy can be used as well, especially in patients who do not respond satisfactorily to anti-thyroid drugs.[40] Life-long replacement therapy following surgical excision or radioiodine ablation of thyroid tissue may not be readily acceptable or affordable in some developing countries where patients are relatively poor. It is important to bear this in mind

when treating patients in such communities. Surgical procedures like transposition of the ectopic thyroid tissue should be considered in patients who may not comply with life-long replacement medication.

CONCLUSION

Ectopic thyroid remains a rare disease. Although the cause is not fully known, genetic factors have been associated with thyroid gland morphogenesis and differentiation. So far, no mutation in known genes has been associated with human thyroid ectopy. Different pathological changes that affect normal eutopic thyroid can occur in the ectopic tissue. The majority are asymptomatic; however, symptoms may arise following enlargement of the gland during periods of stress. Patients may present insidiously or as an emergency. Radionuclide thyroid imaging, ultrasonography, CT scan, MRI, biopsy and thyroid function tests are the main diagnostic tools. Surgical excision is often required as treatment for this condition. Employing a minimally invasive technique has made it possible to excise lingual thyroid as a day procedure.

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