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Review

Morphological, diagnostic and surgical features of ectopic thyroid gland: A review of literature

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ABSTRACT

Ectopic thyroid tissue remains a rare developmental abnormality involving defective or aberrant embryogenesis of the thyroid gland during its passage from the floor of the primitive foregut to its usual final position in pre-tracheal region of the neck. Its specific prevalence accounts about 1 case per 100.000–300.000 persons and one in 4.000–8.000 patients with thyroid disease show this condition. The cause of this defect is not fully known. Despite genetic factors have been associated with thyroid gland morphogenesis and differentiation, just recently some mutation has been associated with human thyroid ectopy. Lingual region in the most common site of thyroid ectopy but ectopic thyroid tissue were found in other head and neck locations.

Nevertheless, aberrant ectopic thyroid tissue has been found in other places distant from the neck region. Ectopic tissue is affected by different pathological changes that occur in the normal eutopic thyroid. Patients may present insidiously or as an emergency. Diagnostic management of thyroid ectopy is performed by radionuclide thyroid imaging, ultrasonography, CT scan, MRI, biopsy and thyroid function tests. 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. Surgical excision is often required as treatment for this condition.

1. Introduction

Thyroid gland ectopia is an infrequently encountered clinically observed condition, resulting from a developmental abnormality during the migration of the thyroid anlage from the floor of the primitive foregut to its final position in the neck. It can be found along the way of thyroid descent, in the midline, or laterally in the neck or even in the mediastinum or under the diaphragm or in other different sites [1]. Clinically, the majority of patients with thyroid ectopia are asymptomatic, so that the true incidence is unknown, but obstructive symptoms as well as hypothyroidism have been observed related to ectopic thyroid size, to its relationships with surrounding organs or to diseases affecting the ectopic thyroid in the same way they involve orthotopic glands. Sometimes, a growing mass can lead to the clinical suspicion of a tumor disease. On the other hand, thyroid ectopy must be distinguished from metastasis of thyroid cancer [2]. Scintigraphy and ultrasonography are the main diagnostic means for evaluating ectopic thyroid tissue, whereas fine needle aspiration could be useful in the presence of a nodular ectopic gland or when the coexistence of an orthotopic thyroid can arise the suspicion of a metastasis from a thyroid cancer [1,2]. The treatment of ectopic thyroid depends on its location and size and on the presence of symptoms or complications. In cases of small and asymptomatic ectopic thyroid, the functioning thyroid should be kept under observation, while patients with suspected bleeding, malignancy and ulceration or recurrent pathology should be treated with radioiodine therapy or surgical removal [1,2]. The aim of this review

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is to highlight current knowledge about the embryology, etiology, molecular pathogenesis, and clinical or surgical management of this condition.

2. Embriology and anatomical sites

The thyroid gland is normally located in the anterior neck region between the 2nd and 5th tracheal rings in humans. It is develop on approximately the 24th day of gestation. The thyroid primordium originates as a proliferation of endodermal epithelial cells in the floor of the primitive pharynx at the foramen cecum located in the midline at the junction of the anterior two thirds of the tongue (first branchial arch derivative) and posterior one third (third branchial arch derivative) during the fourth week of the embryonic development. Subsequently, between 5 and 7 weeks of gestation, the gland anlage penetrates the underlying mesoderm and descends, anterior to the pharyngeal gut, as a bilobed diverticulum through the tongue into the neck, passing anterior but can also be posterior to the hyoid bone and thyroid cartilage to reach its final position anterolateral to the superior part of the trachea in the seventh week of embryonic development. During its migration, the thyroid gland is attached to the foramen cecum by a narrow tube, the thyroglossal duct. This duct is normally obliterated and finally disappears. It is substantially clear that two anlagen, one for each lobe, are involved in the morphogenesis of the thyroid gland. These lateral thyroid anlagen should derive from the ultimo-branchial body, a descending diverticulum of the fourth pharyngeal pouch. They should become incorporated into the median thyroid anlage to contribute a small proportion of the final thyroid parenchyma. However, the existence of the lateral thyroid anlagen is controversial and it seems unlikely on the grounds of comparative embryology. In mammals it rapidly disappears. In birds it persists and shows a follicular structure similar to the thyroid. It is proposed, if the thyroid follicular cells are thought to derive from the median primordium, a contribution derives from the endoderm of the pharyngeal pouches. Thus, the existence of the lateral thyroid anlage may explain the occurrence of non-midline ectopic thyroid tissue in the neck. In fact, an arrest of migration of one of the lateral thyroid anlagen could cause the failure of fusion with the median anlage. 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. Ectopic thyroid tissue, the presence of functioning thyroid tissue in a location other than its normal pretracheal location, can be found anywhere along the course of descent of the thyroid gland. According to autopsy studies, the prevalence of ectopic thyroid tissue varies between 7% and 10%. Most cases of ectopic thyroid are diagnosed during the first three decades of life, and they are more common in females. Ectopic thyroid tissue co-existing with a eutopic thyroid may be equal to that without a normally located gland [1–4].

2.1. Lingual and sublingual thyroid

Approximately 90% of ectopic thyroid tissue is found in the base of tongue as lingual thyroid. Lingual thyroid results from complete arrest of descent of the median thyroid anlage. In 75% of patients with lingual thyroid, it is the only thyroid tissue present and the sole source of thyroid hormone production. Seventy percent of cases present with hypothyroidism. Rarely, lingual thyroid can be present along with normal pretracheal thyroid, but only the lingual thyroid is functional. Hyperthyroidism from hyperfunctioning lingual thyroid has also been reported. Most patients with lingual thyroid are asymptomatic; however, some can enlarge sufficiently to cause symptoms. Common symptoms include cough, pain, dysphagia, dysphonia, dyspnea and hemorrhage. When the mass is too large can present with airway obstruction and stridor in children, while a third of patients have evidence of hypothyroidism. Sleep apnea and respiratory obstruction in adult patients with lingual thyroid have been reported. A common finding on examination is enlargement of the posterior base of the tongue by a firm, midline mass. Hypertrophy of the lingual thyroid occurs as a response to thyroid-stimulating hormone (TSH) stimulation from normal physiologic demands. Thyroid hormone production from lingual thyroid tissue often cannot meet the normal physiologic needs, which can result in enlargement of gland. Some authors recommended that patients with lingual thyroid, even when small, be placed on lifelong thyroxine replacement to prevent subsequent enlargement. Lingual thyroid is typically benign but rarely can harbor malignancy, usually papillary thyroid carcinoma. Despite calcitonin-producing cells are not expected to be present in lingual thyroids; recently C cells were found in lingual ectopic thyroid case. This case demonstrates that ultimobranchial bodies are not the only source of calcitonin-producing cells in humans. 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. Differential diagnosis should be performed from many clinical conditions such thyroglossal duct cyst, midline branchial cyst, epidermal cyst, lipoma, lymphangioma, lymphadenopathy, sebaceous cyst, cystic hygroma, dermoid cyst and neoplasms [4–8].

2.2. Tracheal thyroid

Some authors report cases of multinodular goiter arising in thyroid tissue within the trachea. Unlike lingual thyroid, 75% of intratracheal ectopic thyroids are associated with functioning thyroid gland in its normal location. Intratracheal ectopic thyroid commonly present clinical symptoms. Progressive dyspnea, stridor, cough, difficulty swallowing and hemoptysis were described. Differential diagnosis should be made between dyspnea observed in this and asthma. It is might be difficult to differentiate stridor from the wheezing of asthma on physical examination. Intra-tracheal ectopic thyroid is visualized during direct laryngoscopy as a sub-glottic or upper tracheal wall mass covered with normal mucosa [9,10].

2.3. Submandibular thyroid

Submandibular region sometimes showed ectopic thyroid mass. 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. Subjects affected by this abnormality usually present with a lateral, palpable, mobile, painless mass in the carotid triangle or the submandibular area. Submandibular thyroid tissue is more common in females and is located mainly on the right side of the neck. In most cases, orthotopic thyroid gland usually coexists and the patients are euthyroid. Nevertheless, it may also present as the only functional thyroid tissue. 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 [11].

2.4. Lateral cervical region thyroid

Cases of ectopic thyroid detected in the lateral cervical region were regarded as malignant (metastatic) lesions and were termed

"lateral aberrant thyroid". This must be differentiated from salivary gland tumors, lymphadenopathy and other subcutaneous swellings. Few cases with thyroid tissue presenting as an oropharyngeal mass in the presence of a normal functioning thyroid gland has been reported in the literature. In literature was reported a case of a patient with an ectopic thyroid gland located in the right parapharyngeal space (PPS). Although ectopic thyroid is extremely rare, it is worth bearing in mind as a possible developmental anomaly in the parapharyngeal space. Palatine tonsil was reported as another possible site for ectopic thyroid tissue [12,13].

2.5. Axillary thyroid

Axillary masses are uncommon alterations when detected as an isolated finding. In literature some thyroid ectopic tissues in axillary region were described. Histologically, the tissue usually was a reactive lymph node with adjacent thyroid follicular tissue. In this cases FNAC (Fine needle aspiration cytopathology) could be a gold standard for diagnosis. The differential diagnosis included benign ectopic thyroid versus metastatic well-differentiated follicular-derived thyroid carcinoma. Because of the possibility of carcinoma, the patient should underwent a diagnostic total thyroidectomy [14].

2.6. Carotid region thyroid

Animal models also showed a possible link between development of major cervical arteries and developmental localization of the thyroid gland. 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. In humans two cases were described about thyroid tissues around carotid bifurcation. In one of these cases authors did not find a proper functioning thyroid gland in its normal location [15,16].

2.7. Iris of eye thyroid

In literature a multinodular tumor arising from the peripheral iris and the anterior chamber angle was described. After iridocyclectomy surgical procedure, histopathological examination of the resected tumor showed well-differentiated thyroid follicular ectopic tissue in the iris. Immunohistochemistry demonstrated immunoreactivity for nuclear thyroid transcription factor 1 and thyroglobulin. Differential diagnosis with well differentiated follicular thyroid carcinoma was excluded by systemic examination and the absence of any evidence of other primary or secondary tumors after more than a year of surveillance. The intraocular thyroid tissue cannot be explained by embryogenesis. We hypothesize that heterotopic thyroid tissue in the iris might be the result of aberrant differentiation of local tissues by heteroplasia or metaplasia. Recently, mutations of the thyroid transcription factor1gene or of genes regulating thyroid transcription factor 1 expression were implicated in ectopic thyroid development. A somatic mutation in genes that suppress inappropriate thyroid differentiation in non thyroid embryonic tissues could explain this condition [17].

2.8. Pituitary region thyroid

A unique case of ectopic thyroid tissue within the pituitary fossa and sphenoid sinus, associated with a lingual thyroid gland was reported in literature. The etiology of this ectopic tissue is postulated to be ascent of primitive thyroid endoderm at the time of formation of Rathke's pouch [18].

2.9. Cardiac, aortic and pulmonary thyroid

Cardiac malformations represent the most frequent birth defects related to thyroid dysgenesis. 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. Intrathoracic ectopic thyroid 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 or on autopsy. In cases of mediastinal ectopic thyroid, orthotopic tissue usually coexists and the patients are euthyroid. Intracardial 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. Larger tumors, resulting in severe right ventricular outflow tract obstruction, as well as de novo development of follicular carcinoma in ectopic intracardial thyroid have been described. 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. The patient can also be completely asymptomatic and the mass may be found incidentally during cardiovascular operations. Ectopic intrapulmonary thyroid is reported to be very rare. Patients are usual of middle age and clinically showed dry cough, dyspnea, and hemoptysis. Based on the radioisotope diagnostic test, an ectopic thyroid inside the thoracic cavity could be suspected; after surgical treatment, histological examination revealed an intrapulmonary thyroid [19–22].

2.10. Oesophageal thyroid

Ectopic intrathyroidal thymus tissue that may be present as a thyroid nodule is rarely reported. Pathological examination showed an ectopic intrathyroidal thymus tissue. In childhood, ectopic intrathyroidal thymus tissue can present as an enlarging microcalcifie Patient thyroid nodule that may mimic thyroid cancer and may grow during follow-up [23].

2.11. Duodenal thyroid

An ectopic thyroid goiter was sometimes founded in duodenum. Patients in those cases presented abdominal and low back pain, diarrhea, and generalized weakness. Abdominal CT should be the best diagnostic tool. Histopathological examination show nodular arrangement of thyroid follicles and colloid lakes with focal hyperplastic and nodular goiter changes. In those cases epithelial cells and colloid-like substance were both immunostained for thyroglobulin but no cells stained for calcitonin [24].

2.12. Gallbladder thyroid

Ectopic thyroid in a gall bladder is rare with only few cases of ectopic thyroid tissue in the gall bladder were reported in

literature. Patient usually referred recurrent right upper quadrant pain. Abdominal sonography revealed ectopic thyroid tissue within the wall of double gall bladder. Rarely duplication of gall bladder can be observed in association with ectopic thyroid tissue [25].

2.13. Gastric thyroid

Ectopic foci of normal thyroid tissue were found in non-thyroidal physiological sites like gastric mucosa or other gastrointestinal tract. Clinically these patient were usually asymptomatic and only in few cases abdominal pain was referred. In these cases the only question in the differential diagnosis between normal thyroid tissue and metastatic thyroid cancer inside stomach [26].

2.14. Pancreatic thyroid

Ectopic thyroid tissue can be seen anywhere along the path of the descending glands, but it is rarely seen in the abdominal cavity. A case of ectopic thyroid was discovered incidentally in the pancreas of a 50-year-old woman who underwent a bilateral truncal vagotomy and pyloroplasty for a duodenal ulcer. There were no signs or symptoms of a thyroid tumor [27].

2.15. Mesenteric thyroid

Ectopic thyroid tissue has been found in the developmental pathway of the thyroid gland and has also been reported in the abdominal cavity. Intra-abdominal thyroid tissue was totally resected around the mesentery of the small intestine in a 56-year-old woman. She had hyperthyroidism preoperatively and had also undergone a bilateral subtotal thyroidectomy 10 years earlier. No signs or symptoms of a thyroid tumor were present [28].

2.16. Porta hepatis thyroid

Discovery of ectopic thyroid tissue should raise suspicion of other ectopic thyroid tissues along the path of embryologic migration from its origin to the porta hepatis. This may necessitate assessment of radionuclide uptake and imaging of numerous areas. An ectopic thyroid extending from the duodenum to the porta hepatis was reported. A solitary inhomogeneous, hypoechogenic and hyperechogenic mass in the porta hepatis was accidentally discovered by ultrasonography. Subsequent computed tomography demonstrated a heterogeneous, well-defined tumor with small calcifications without signs of environmental invasion. Fine-needle aspiration cytology revealed normal thyroid tissue. (123)I-scintigraphy confirmed the presence of ectopic dual thyroid tissue in the hepatic porta [29].

2.17. Adrenal gland thyroid

Ectopic thyroid tissue is usually found anywhere along the embryonic descent pathway of the medial thyroid anlage from the tongue to the trachea (Wölfler area). However, ectopic thyroid tissue in the adrenal gland (ETTAG) is not easy to understand on the basis of thyroid embryology; because it is so rare, the possibility of metastasis should first be considered. ETTAG is a rare finding, with only seven cases reported; women are much more frequently affected than men (8:1), and it usually presents in the fifth decade (mean age 54, range 38–67) as a cystic adrenal mass incidentally discovered on abdominal ultrasonography and/or in computed tomography images. ETTAG is composed of normal follicular cells without C cells. The expression of some transcription factors (TTF-1, paired box gene 8, and FOXE1) involved in development and/or migration of the medial thyroid anlage is preserved. Although ETTAG pathogenesis remains unknown, the lack of C cells together with the coexistence of a congenital defect of the anterior diaphragm (hernia of Morgagni) in one of our patients could suggest an overdescent of medial thyroid anlage-derived cells in the origin of this heterotopia [30].

2.18. Ovaric, tubaric, uterine and vaginal thyroid

Thyroid tissue in the ovarian structures called “struma ovarii” is a rare form of thyroid gland ectopia. It usually presents with a benign course, although in some cases carcinoma or other malignant tumors can be found in the context of the ectopic tissue. The tumor was cystic and multilocular filled with colloid material. Histological examination revealed follicles of thyroid type, and stromal clusters of fusiform or polygonal cells were found in the stroma. Usually an extensive decidual reaction was observed. 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. Thyrotoxicosis develops in about 15% of cases and same percentage of malignant transformation was observed. Other ectopic thyroid sites in genital tract are Fallopian tube, Uterus and Vagina. Morphological and clinical features are the same that ovarian localization [31–34].

2.19. Other sites or conditions

Few cases of dual, triple and multiple ectopias with or without normal eutopic thyroid. These cases clinically show midline neck swelling or are completely asymptomatic. Mean age of presentation was about 20 years. Functionally euthyroid or hypothyroid masses were described [35,36].

3. Aethiopathology and molecular features

Molecular mechanisms involved in thyroid dysgenesis are not fully known but several studies have shown mutations in regulatory genes expressed in the developing thyroid [37]. Genetic researchs have described that candidate gene of transcription factors TITF-1(Nkx2-1), *Foxe1*(TITF-2) and PAX-8 are essential for thyroid morphogenesis and differentiation [37,38]. Mutation in these genes may be involved in abnormal migration of the thyroid [38]. TITF-1 play at later stages of thyroid development, when follicular cells reorganize themselves into follicles, require phosphorylation of the protein [39]. *Foxe1* is required for thyroid migration, although homozygous mutations for this gene show a sublingual thyroid in murine model [3]. Thyroid-specific regulatory element in the 5′ upstream region of the PAX-8 gene during thyroid differentiation has been reported. In humans, more than 50% of thyroid dysgenesis cases are associated with an ectopic thyroid but no mutation in known genes has so far been associated with the human ectopic thyroid [40]. 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. Some authors suppose that TFCs derive from both a median thyroid and a lateral thyroid bud (the ultimobranchial body). Aberrant thyroid tissues found in the submandibular and lateral neck regions could originate from a defective lateral thyroid component that cannot migrate and fuse with the median thyroid anlage [41]. This failure could be due to the ectopia of the lateral anlage in such an unusual site as the parapharyngeal space. Some Authors suggest that thyroid morphogenesis is strictly related with the development of adjacent arteries like carotids [42]. It is believed that this mechanism might have evolved to ensure efficient hormone release into circulation. Congenital defects of the cardiovascular system and variability in

the architecture of carotid from aortic arch have been associated with congenital thyroid abnormalities [43]. Aberrant migration or heterotopic differentiation of uncommitted endodermal cells could explain the presence of ectopic thyroid tissues in distant locations. 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 [44]. Further consideration regards the negative reaction to calcitonin at immunohistochemistry, indicating a failure of colonization of the ectopic thyroid tissue by C-parafollicular cells coming from the neural crest. More studies are necessary to determine all causes of thyroid ectopy. Prenatal diagnosis and better management of the disease will be performed easily when all molecular and genetic mechanisms will be clarified [3,44].

4. Hormonal status and pathology

Ectopic thyroid may be associated with clinically evident thyroid dysfunction or may develop a goiter [36]. Hypofunction or hyperfunction could be developed [45,46]. Benign or malignant neoplastic changes were sometimes described in ectopic thyroid tissue [47]. Some cases of thyroiditis occurring in ectopic thyroid tissue has also been mentioned [48]. Puberty and pregnancy are physiological conditions in which increases demand for thyroid hormones. During these periods ectopic thyroid is commonly detected. Thyrotropin increased levels usually observed at these periods causes enlargement of the ectopic thyroid tissue. This morphological change results clinically detectable as a mass, or following pressure symptoms. Dossing et al. described a case of recurrent pregnancy-related intra-tracheal thyroid growth stimulation causing upper respiratory obstructive symptoms [49]. Authors believed that increased human chorionic gonadotropin (hCG) stimulation and borderline iodine deficiency develop these symptoms. During pregnancy, thyroid gland size increases by an average of 30% in borderline iodine deficient regions. It has been speculated that epidermal growth factor could also stimulate thyroid growth [50]. Treatment of bipolar disorder by administration of lithium, was reported to be the cause of enlargement of an ectopic lingual thyroid in a patient. Lithium inhibits thyroid function, leading to hypothyroidism and goiter [51]. Hypothyroidism occurs in about 33% of patients with thyroid ectopy that is the first cause of congenital hypothyroidism in pediatric age [45]. A large percentage of patients with ectopic lingual thyroid without a co-existing eutopic thyroid tissue will develop sub-clinical hypothyroidism that become clinically manifest during periods of physiological stress [1,2,52–54]. Aberration in the migratory pathways of the rudimentary thyroid that may lead to ectopy often results in inadequate blood supply to support normal thyroid function. Normal thyroid hormone is secreted by the ectopic gland may not be sufficient for higher physiological demands during puberty, pregnancy, infections and trauma. Studies have also suggested that iodine organification defect which is associated with thyroid ectopy could be responsible for hypothyroidism in this condition [55]. It is rare for patients with ectopic thyroid to present with hypothyroidism during adulthood [56]. Shakir reported the case of a 43-year old female with lingual thyroid associated with hypothyroidism and lympomatous thyroiditis [57]. Hypothyroidism was believed to have followed thyroiditis, transforming lingual thyroid into a fibrous tissue which was not sensitive to the trophic action of TSH [57]. 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, mediastinum, submandibular region, lateral neck and the mesentery of the small intestine [58]. Some of these cases were found in patients who have had sub-total or total thyroidectomy for thyrotoxicosis. Thyrotoxicosis arising from a recurrent ectopic mediastinal thyroid was reported by Basaria et al. 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 [59]. Some available literature reports show a complex relationship between TH levels and oxidative stress, but the general principle is that elevated TH levels (hyperthyroidism) induce oxidative stress, whereas reduced THs levels (hypothyroidism) result in non-detectable to mild oxidative stress [60]. Nevertheless, an impaired control of oxidative stress mechanisms is associated with thyrocytes apoptosis and suggest a contributing factor for the development of immune thyroiditis [61]. Oxidative stress and elevated ROS (Reactive oxygen species) has been implicated in the mechanisms of cancer, diabetes, neurodegenerative, cardiovascular and other diseases [62,63]. Overproduction of oxidant molecules is due to several stress agents such chemicals, drugs, pollutants, high-caloric diets and exercise [64]. Malignant transformation can occur in ectopic thyroid tissues in different locations. Primary papillary, follicular, mixed follicular and papillary, hurthle cell tumor and medullary carcinomas have been reported [65–70]. 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 tumors 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 tumors form the predominant form while different variants are less frequent [68,71]. Several rare tumors arising from ectopic thyroid tissues are single cases of teratoma and primary B cell lymphoma [72,73]. Both cases occurred in a mediastinal ectopic thyroid. Rarely, malignant ectopic tumors can present with metastasis to lymph nodes. 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 [36].

5. Diagnosis

To discover and study an ectopic gland our imaging methods employ technetium-99 m pertechnetate, iodine-131 or iodine 123. This technique is based on typical characteristics of thyroid tissues, which takes up radioisotope so we can discover eventual ectopic gland and evaluate the presence, or not of the orthotropic thyroid. This diagnostic time is a main step for a good therapy because the localization of the gland and the absence of a eutopic thyroid can change radically therapeutic choices [1,2]. Technetium-99 pertechnetate differs to other isotopes because of the better quality of imaging and the less radiation dose, so it might be used in children. It is characterized also by a long life time. Despite this advantages it accumulates in the background of the ectopic thyroid, including the salivary gland making problems in the study of small masses [74,75]. Children can be also evaluated with Iodine-123, which is a largely used marker, but its use is reduced by expensive cost and its short half-life time [1,2]. High resolution ultrasound are a useful strategy to don't expose patients to radiations, ultrasounds are also excellent for the first approach to the patient. They are non-invasive, cheap, and detect also the presence of a eutopic thyroid. Moreover we can increase sensibility of ultrasound imaging using color-power-doppler technique by demonstrating peripheral or

internal color flow signals that are reflective of hypervascularity [76]. We can affirm that, if ultrasounds suggest the presence of a normal thyroid, without sign of inflammation or nodules we can perform a removal of the ectopic gland, free of risk of hypothyroidism [77]. B-flow imaging (BFI) is an exciting new imaging technology. It can be described as a non-Doppler technology for blood flow imaging. The main advantage of this technology lies in the direct visualization of blood reflectors without the limitations of conventional Doppler technology; this is extremely useful in the assessment of complex hemodynamics. It is actually clear that BFI technique is a useful method to characterize different twinkling sign patterns for accurate evaluation of thyroid nodules [78–81]. Ultrasounds might allow to avoid the need of scintigraphy to perform a pre-operative study of the orthotropic thyroid gland. This may obviate the need for thyroid scintigraphy to confirm the presence of a functional thyroid tissue before surgical removal of the ectopic gland [77]. CT scan and MRI are useful imaging tools when a eutopic thyroid gland is not identified by ultrasound. CT scan without contrast of ectopic thyroid tissue has a characteristic uniform high attenuation [82]. Ectopic thyroid tissue appears on MRI as a rounded mass with higher signal intensity than that of the surrounding tissue like neck muscles in both the T1- and T2-weighed images. MRI is particularly useful in lingual thyroid when there is difficulty in differentiating thyroid tissue from tongue muscle [82]. CT and MRI are also useful modalities in cases when radioiodine uptake by normal thyroid gland masks the uptake of the ectopic thyroid tissue, especially in the midline. The cost of the MRI procedure is higher than CT scan. It requires longer imaging time and it may necessitate the use of anesthesia in the pediatric group but offers less radiation exposure than CT scan. Patterns of vascularization of lingual thyroid to help planning of surgical intervention were studied by angiography in the past. This diagnostic tool should be allow the use of embolization preoperatively to decrease the risk of intraoperative hemorrhage [82]. Nevertheless, it is used as the primary treatment modality in patients who are treated nonoperatively. Fine needle aspiration cytology (FNAC) provides considerable assistance in confirming the diagnosis of ectopic thyroid. It is the best modality to differentiate between a benign and a malignant lesion. FNAC is one of the most accurate diagnostic methods for detection of neck masses and gives correct diagnosis in 95–97% of cases. However, FNAC results may sometimes be misleading or non-diagnostic, especially in cystic masses. It can help in making a preoperative diagnosis of ectopic thyroid tissue and this assists the surgeon decision on request about further radioisotope imaging to manage whether the mass is the only functioning thyroid tissue [1,2,82]. Thyroid function tests that assess the serum levels of T3, T4, TSH and thyroglobulin are carried to assess functional status of ectopic thyroid. 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 thyroglobulin levels will indicate presence of ectopic thyroid tissue [83]. Other investigations that may be required in patients with ectopic thyroid depend on the location of the gland. For instance echocardiography and coronary angiography may be necessary in intra-cardiac thyroid ectopy, while barium swallow is important in some patients presenting dysphagia [1,2].

6. Treatment

As shown by the most part of Authors the best treatment strategy for ectopic thyroid is linked to patient's age, localization, local symptoms, malignancy, surgical and anesthesiological risk management, and last but not the least thyroid functional status [1,2]. For patient without symptoms it might be proposed a strict follow-up to discover as soon as possible the presence of malignancy or development of other complications (enlargement of the mass, hormonal imbalances, etc.) In order to this considerations patients who are symptomatic need different therapeutic approaches depending on localization of the gland, type of symptoms, malignancy of symptoms, and functional status [2]. If the main problem is related to ectopic gland size is suitable to perform a suppressive drug therapy based on suppressive dose of levothyroxine. This kind of approach is a good option for patients who are not suitable for surgery and have only obstructive symptoms or patients who have a slow and progressive enlargement of the mass where surgery could be considered only few years later. Drug therapy based on levothyroxine is suggested also to prevent malignant transformation of the ectopic gland and to prevent developing hypothyroidism [84]. A Surgical approach to this pathology is suggested when obstructive symptoms are not even more tolerated, or when bleeding or malignancy occur. Before surgery is mandatory to search the presence of the thyroid gland in his orthotopic site to avoid hypothyroidism. Lingual thyroid is often removed by the trans-oral route. This way is the most suitable for small lesions because the small exposure it provides. Big lesions are approached by midline mandibulotomy and tongue splitting technique. Despite this technique is more convenient for surgical reasons, it left a ugly scar in mental region and in the lower lip, for this reason it might be performed an alternative technique without lip incision. An other problem of this technique is linked to the high bleeding risk [85]. Some authors suggest to tie vessels before excision. The improvements of technologies solve in part this problem, in fact the excision of the mass using a mini-invasive approach is considered safe and more convenient in terms of bleeding and post-operative morbidity. Moreover mini-invasive surgery avoid the risk of ugly scar for the patient [86,87]. Excision of the gland endoscopically using CO2 laser has been done successfully with lesser bleeding and post-operative morbidity as well as other otolaryngology surgical approaches [88,89]. Transoral robotic surgery (TORS) is the last innovation in this way and gives some benefits like better view of the surgical field, four-handed surgery, six degrees of motion [90]. A less wide view of structures in minivasive surgery versus open surgery expose surgeon to a higher risk of complications in management of vital structures and fistula formation. Those consideration are suitable if the ectopic thyroid is not the main gland of the organism [86,87]. If the ectopic gland is the only functional thyroid in the body a complete excision must be followed by an hormone replacement. It could be proposed a transposition of the gland with a vascular pedicle flap in the mouth floor or in the lateral pharyngeal wall. However this transposition in the 70% of cases ends in few years in drug replacements. The target of trans-oral ablation is bleeding control; substitutive hormone treatment is useful to maintain euthyroid status and to prevent recurrence of pathology [91]. Patients who are affected by neck locations of the ectopic gland might be indicated to surgery for esthetic reasons or for an unresponsive replacement treatment [92]. In tracheal localization surgical indication are linked to compressive symptoms, blooding and malignancy suspicion [93]. The gland can be removed via the open cricoid procedure or the endoscopic laser-assisted approach. Intra-thoracic ectopic glands are treated by open surgery (thoracotomy, sternotomy) or using mini-invasive approaches like thoracoscopy and robotic assisted surgery [90,94]. Intra-cardiac thyroid mass is surgically excised under standard cardio-pulmonary by-pass, intra-abdominal masses are approached using classical techniques of the digestive surgery. As usually after operation tissues are sent to pathological anatomy for histological diagnosis. If diagnosis is made after surgery is reasonable to start with further investigations. Obviously patients will be treated in relation to the outcome of investigations

[1,2,90,93]. Radioactive treatment using iodine 131 could be considered a possible treatment, this method should be not indicated for patients who are suitable to operation, but it might be a salvage therapy in patient not suitable for surgery or patient who refuse operation. It is quite clear that young people or pregnant women are not indicated be exposed to radiation [95]. Radioactive iodine therapy can be used, also, in patients who do not respond satisfactorily to anti-thyroid drugs. A life-long drug replacement therapy after surgery can be placed only in countries where economic conditions allow a chronic subministration of levothyroxine. In poor countries where it is quite difficult to have a long-life drug subministration a transposition of the gland must be the first time approach [95]. Standard chemotherapies have systemic toxicities and limited efficacy in the case of ectopic derived thyroid cancer as well as of other more common solid tumor [96–98]. Actually in thyroid cancer, there is no hint of a remodeling of the Ca^{2+} toolkit, that has been observed in other malignancies, including renal cellular carcinoma [99–101], and prostate cancer [102], mielofibrosis [103], and has been put forward as alternative target for selective molecular therapies [98].

7. Conclusions

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. 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 isasymptomatic; however, symptoms related to tumor size and location may develop. Different pathological changes that affect normal eutopic thyroid can occur in the ectopic tissue as well as primary thyroid malignancy. Thyroid scintigraphy, ultrasonography, CT scan, MRI, biopsy and thyroid function tests are the main diagnostic tools. Surgery is the treatment of choice in symptomatic cases, with a role for radioiodine 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.

Ethical approval

Ethical approval was requested and obtained from the "University of Molise" ethical committee.

Author contribution

Germano Guerra: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Mariapia Cinelli: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Massimo Mesolella: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Domenico Tafuri: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Aldo Rocca: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Bruno Amato: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Stefania Montagnani: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Domenico Testa: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

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