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SHORT REVIEW

Thyroid cancer in lingual thyroid and thyroglossal duct cyst

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Abstract Ectopy is the most common embryogenetic defect of the thyroid gland, representing between 48 and 61% of all thyroid dysgeneses. Persistence of thyroid tissue in the context of a thyroglossal duct remnant and lingual thyroid tissue are the most common defects. Although most cases of ectopic thyroid are asymptomatic, any disease affecting the thyroid may potentially involve the ectopic tissue, including malignancies. The prevalence of differentiated thyroid carcinoma in lingual thyroid and thyroglossal duct cyst is around 1% of patients affected with the above thyroid ectopies. We here review the current literature concerning primary thyroid carcinomas originating from thyroid tissue on thyroglossal duct cysts and lingual thyroid.

PALABRAS CLAVE
Defectos embrionarios del tiroides;
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Tiroides lingual;
Tiroides ectópico;
Cáncer diferenciado de tiroides

Cáncer de tiroides en tiroides lingual y quiste del conducto tirogloso

Resumen La ectopia es el defecto embriogenético más frecuente de la glándula tiroides, responsable de entre el 48 y el 61% de todas las disgenesias tiroideas. La persistencia de tejido tiroideo en el contexto de un resto de conducto tirogloso y el tejido tiroideo lingual son los defectos más comunes. Aunque la mayoría de los casos de tiroides ectópico son asintomáticos, cualquier proceso que afecte al tiroides puede afectar potencialmente al tejido ectópico, incluidos los tumores malignos. La prevalencia de carcinoma tiroideo diferenciado en tiroides lingual y quiste del conducto tirogloso es de alrededor del 1% en los pacientes con las ectopias tiroideas antes citadas. Revisamos aquí la bibliografía actual sobre los carcinomas tiroideos primarios originados a partir de tejido tiroideo de quistes del conducto tirogloso y tiroides lingual.

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Introduction

Thyroid embryogenesis begins by about day 24, from a median endodermal thickening forming the *thyroid diverticulum*. This primordial structure migrates from the floor of the primitive pharynx and by week 7 of embryonic development it reaches its definitive location in front of the trachea. A failure of the thyroid anlage to descend throughout the normal pathway results in abnormalities in thyroid organogenesis, including an incomplete (thyroid hypoplasia) or absent (thyroid agenesis) development of the thyroid gland, or in an aberrant location of the gland along the midline, from the base of the tongue to the mediastinum (thyroid ectopy). All these conditions, overall covering 80–85% of the cases of congenital hypothyroidism, are usually indicated as ''thyroid dysgenesis'' (TD).[1]

Molecular studies suggest that the co-expression of the transcription factors TITF1/NKX2-1, FOXE1, PAX8, and HHEX in the thyroid anlage is essential for regular organogenesis. In particular, mice homozygous for Foxe1 mutations show sublingual thyroid,[2] an evidence that indicates that this transcription factor is required for thyroid migration. However, to date no mutation in the above-mentioned transcription factors has been found in patients with ectopic thyroid.

Among ectopic thyroid locations, the most common is the tongue, which accounts for 90% of reported cases. Less frequently, ectopic thyroid tissue may be found in the submandibular area, larynx, trachea, esophagus, mediastinum, diaphragm, and heart.[3] In addition, a failure of obliteration of the mid portion of the thyroglossal duct may result in the persistence of epithelial tissue along the path of the descent of the thyroid gland. This embryological remnant may remain clinically quiescent, or presents itself as a cyst (thyroglossal duct cyst, TGDC) located in most cases between the hyoid bone and the thyroid cartilage.

Although most cases of ectopic thyroid are asymptomatic, any disease affecting the thyroid may potentially involve the ectopic tissue, including malignancies.[4–7] We here review current literature concerning primary thyroid carcinomas originating from thyroglossal duct cysts and lingual thyroid, which are the most common ectopic thyroid malignancies.

Data acquisition

We used the keywords ''lingual thyroid'' and ''thyroglossal duct cyst'', both separately and in conjunction with the terms ''thyroid cancer'' and ''ectopic thyroid cancer'' to search MEDLINE for clinical case series and/or case reports and review articles published between 1990 and December 2015, and focused on thyroid cancer originating from the above thyroid ectopies. After exclusion of articles with no abstract available and those in languages other than English, 70 articles were selected and analyzed. For the purposes of this brief review, only case series and review articles were quoted.

Thyroglossal duct cyst carcinoma (TGDCC)

TGDC is usually referred to as the most common congenital neck mass.[7] The development of a carcinoma on a TGDC is rather unusual, with a reported prevalence ranging from 0.7 to 1% of patients with TGDC.[7–9] However, the estimated prevalence of TGDCC in surgical series, likely comprising patients with suspicious clinical and/or imaging features, is as high as 13–14%.[10,11]

Since Brentano first described one case in 1911,[12] only about 250 cases of TGDCC have been reported in the literature.[8] TGDCC originate from both thyroid and squamous cells.[10] Papillary thyroid cancer (PTC) is the most common histological type (80%), followed by the follicular variant of PTC (8%), by squamous cell carcinoma (6%), and by follicular thyroid carcinoma (FTC), Hürthle cell, C-cell and anaplastic carcinoma in the remaining 6%.[9,13] TGDCC has been reported to occur as an isolated lesion, with no coexisting malignancies within the orthotopic thyroid tissue.[14,15] However, the simultaneous occurrence of a TGDCC and a thyroid carcinoma has been reported in 11–62% of all cases of TGDCC,[9,16,17] likely suggesting the lesion to be either a multifocal thyroid neoplasia, or a metastasis of a primary thyroid carcinoma that has spread through the thyroglossal duct. Alternatively, it has been suggested that the cancer originated in the thyroglossal duct cyst may represent the primary tumor, being the thyroid gland a secondary localization.[17,18]

The majority of TGDCCs are located in small cysts and capsular invasion is sometimes reported. Lymph node metastases are found in between 7% and 15% of cases and distant metastases are uncommon.[18,19] Diagnosis is usually postoperative, due to the fact that many clinical features are common to both malignant and benign lesions.[20] Fine needle aspiration cytology can facilitate preoperative diagnosis and should therefore be routinely prescribed for all adult patients with a clinical diagnosis of TGDC.[9]

There is generally unanimous agreement that the surgical treatment of TGDCC should employ the Sistrunk technique, which involves excision of the cyst, the central portion of the body of the hyoid bone, and a core of tissue around the thyroglossal tract extending up to the foramen caecum.[21] Conversely, the need of performing thyroidectomy in the management of TGDCCs is debated.[16] In agreement with some authors,[9,15,17,19] we believe that thyroidectomy should be performed on all TGDCC patients. Although this opinion is in apparent conflict with current 2015 ATA guidelines,[22] we personally believe that it might be considered for at least two reasons. First, these neoplasias may be metastases of occult thyroid carcinomas, and therefore thyroidectomy would form the basis of a definitive treatment. Second, thyroidectomy allows optimal staging, radiometabolic therapy, if required, and long-term follow-up with thyroglobulin assays.[7,10,17,23]

Radiometabolic treatment in such patients should be performed in those classified as high risk (being of advanced age, having metastatic or invasive tumors, or histological features indicating a poor prognosis, or a coexisting thyroid carcinoma).[18,22] The prognosis for differentiated thyroid cancer (DTC) originating from TGDC is as good as that reported for primary DTC in orthotopic glands, with distant metastatic disease occurring in less than 2% of cases.[18]

Lingual thyroid cancer (LTC)

Lingual thyroid (LT) is a rare condition, with an estimated prevalence ranging between 1:100,000 and 1:300,000.

Females are more often affected with this TD, and the female/male ratio is of 3:1–8:1. Carcinoma arising from lingual thyroid is even rarer. The prevalence is estimated in about 1% of patients with LT, with a female/male ratio of approximately 2:1, and a higher prevalence in the third decade of life.[7,24,25]

At variance with DTC arising from orthotopic thyroid, FTC is usually reported as being the predominating histopathology in lingual thyroid.[24,26–28] The reasons for the higher occurrence of more aggressive cancers in LT are not clear. It has been suggested that this event may be related to the long-term condition of hypothyroidism due to the absence of the orthotopic gland, which, in turn may induce a thyotropin-mediated compensatory hyperplasia,[28] like that observed in conditions of long-term iodine deficiency.[29,30] The possibility of histological misclassifications in early reports should also be taken into account, since follicular variants of papillary thyroid carcinoma were previously classified as follicular lesions.[28] In accordance with this speculation is the observation that a review of LTC cases diagnosed following the release of standardized criteria of histological typing,[31] PTC accounted for about 65% of the reported cases, thus representing the prevailing histotype of LTC.[25] However, even when only cases described in more recent years were considered, the PTC/FTC ratio in lingual thyroid was approximately 2:1,[25] thus definitely higher than that observed in DTC arising from eutopic thyroid.[32] Peculiar among the cases reported are one case of medullary carcinoma[33] and the coexistence of a PTC with a squamous cell carcinoma of the tongue.[34]

Owing to the rarity of LTC, the natural history of this condition is poorly known. In most of the cases reported, the neoplasia was confined to the tongue, with loco-regional and distant metastases accounting for 20% and 14% of cases, respectively.[7,24,25] Presently available data indicate that, similarly to DTC arising from orthotopic thyroid tissue, lingual PTC shows a tendency to lymphatic diffusion,[3,7,25] whereas hematogenous metastases are more common in follicular carcinoma.

As far as LTC diagnosis is concerned, clinical signs include the evidence of an oral mass with or without aspecific symptoms (hoarseness, dyspnea, the perception that a foreign body is present, dysphagia and/or hemoptysis). The differential diagnosis includes all lesions potentially arising in the region[3] (lingual tonsil hypertrophy, mucous and dermoid cysts, squamous cell carcinoma and lymphoma, among others), and ^{99}Tc or ^{123}I scintiscan may be helpful to assess the thyroid origin of the tissue, although some false negative cases were reported.[35]

Although there are several limitations due to the fact that LT tissue characteristically has an incomplete or poorly defined capsule, biopsy of the lesion can be helpful for distinguishing LTC from normal LT tissue.[7,24]

Concerning LTC management, preoperative neck ultrasound and ultrasound-guided fine-needle aspiration of sonographically suspicious lymph nodes, if any, should be performed in order to plan the most appropriate therapeutic approach. Routine preoperative use of computed tomography (CT) and especially magnetic resonance (MR) is also recommended, as they are helpful in differentiating thyroid tissue from tongue muscle.[24] When diagnosis is confirmed, the first approach may be surgical or by means of radioiodine treatment, the choice mostly depending on the extension of the lesion. Indeed, to be successful, the surgical approach should be performed with wide margins of excision and followed by complementary ^{131}I treatment. The latter may also be used as a first-line approach in cases of large cancers in which surgery would be highly invalidating. Finally, neck dissection is indicated in the presence of additional suspected lesions or metastatic disease.[7]

In conclusion, dysembryogenetic thyroid lesions, although rare, are at risk of harboring cancers, with a seemingly higher frequency than that observed in eutopic thyroids. Concerning thyroid cancer in the TGDCs, in most cases the diagnosis of these tumors is made when the disease is no longer limited to the thyroglossal duct cyst. In particular, the coexistence of thyroid cancer in the TGDC and in the thyroid has been reported with high frequency. This observation raises the question of whether the primary lesion originates in the ectopic rather than in the orthotopic thyroid tissue, with the other being a metastatic localization. In favor of a primary origin of tumors in the TGDC is the evidence of a usually larger size of tumor in the ectopic localization, the frequent involvement of the highest lymph node stations (I, II, III and IV) with the central compartment being less frequently involved, and finally the more frequent extension to adjacent soft tissue of TGDC cancer.[17] In this view, a close monitoring of TGDCs would be recommended, with a preventive surgical removal of the lesion to be seriously considered in patients with an increased risk of thyroid malignancies (family history of thyroid cancer or history of neck/chest radiation).

As far as lingual thyroid cancer is concerned, common diagnostic strategy also includes magentic resonance imaging in the preoperative work-up to define morphological features, and the therapeutic approach involves the use of ^{131}I to complete surgical excision, or as a first line treatment whenever the lesion is either unresectable or in patients refusing surgery.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

No informed consent is required.

Conflict of interest

The authors declare that they have no conflict of interest.

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