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LYMPHOEPITHELIAL CYST OF THE THYROID GLAND AS AN UNCOMMON CONDITION WITH CLINICAL SIGNIFICANCE: CASE REPORT AND BRIEF REVIEW OF THYROID CYSTIC LESIONS.

QUISTE LINFOEPITELIAL DE LA GLÁNDULA TIROIDES COMO UNA CONDICIÓN POCO COMÚN CON RELEVANCIA CLÍNICA: REPORTE DE CASO Y BREVE REVISIÓN DE LAS LESIONES QUÍSTICAS TIROIDEAS.

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RESUMEN
Los quistes linfoepiteliales de la tiroides (LEC-T) son lesiones tiroideas benignas poco frecuentes que representan un reto diagnóstico debido al amplio diagnóstico diferencial de los nódulos tiroideos quísticos. Histológicamente, se asemejan a un quiste del saco branquial, con un revestimiento de epitelio escamoso estratificado y, en ocasiones, áreas de metaplasia ciliada. Se han documentado pocos casos en la literatura, con frecuencia asociados a tiroiditis linfocítica crónica (tiroiditis de Hashimoto). En este artículo presentamos el caso de un LEC-T de gran tamaño en un paciente sin características de tiroiditis.

ABSTRACT
Lymphoepithelial cysts of the thyroid (LEC-T)are rare benign thyroid lesions that are diagnostically challenging due to the broad differential diagnosis of cystic thyroid nodules. Histologically, it resembles a branchial pouch cyst with a lining of stratified squamous epithelium, occasionally exhibiting areas of ciliated metaplasia. A limited number of cases have been documented in the literature, frequently in relation to chronic lymphocytic thyroiditis (Hashimoto's thyroiditis). In this article, we report a case of a large LEC-T in a patient without features of thyroiditis.

Keywords: Thyroid cyst, thyroid nodule, lymphoepithelial cyst, solid-cystic thyroid lesion, thyroid pathology.
Palabras clave: Quiste tiroideo, nódulo tiroideo, quiste linfoepitelial, lesión tiroidea sólido-quística, patología tiroidea.

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INTRODUCTION

The availability of advanced diagnostic imaging techniques has resulted in a rise in the diagnosis of thyroid nodules, the majority of which are identified incidentally and in healthy individuals[1].Thyroid nodules are benign in more than 90% of affected individuals,asymptomatic and more common among women with a female to male ratio of 4:1[2].By imaging, most thyroid nodules can be categorized as solid or solid-cystic nodules which usually carry a higher risk of malignancy or entirely cystic lesions which are usually benign[3].

A cyst is defined as a cavity lined by epithelium with fluid or semisolid material occupying the cyst cavity. Embryogenic defects, infections, tissue degeneration and neoplastic mechanisms are implicated in the formation of many cysts. Thyroid cysts are fluid-filled cavitary lesions that may vary in size, and can occasionally exhibit rapid growth [4]. Heterogeneous lesions comprising both solid and fluid components necessitate thorough evaluation by individuals skilled in imaging and cytopathology techniquesin order to determine potential indications for a fine-needle aspiration biopsy (FNAB), ideally in accordance with EU-TIRADS criteria. This is particularly important as lesions with a minimum of 50% solid component have shown a higher risk of malignancy compared to entirely solid lesions of equivalent size [5]. Malignancies arising in thyroid nodulesusually originate from the solid component of a solid-cystic nodule or concurrently with other solid thyroid nodules [6].

The main management of assymptomatic thyroid cysts measuring <3-4 cm includes observation and close clinical follow-up with imaging to monitor for any changes. Additionally, aspiration with sclerotherapy (ethanol instillation or other ablative techniques) yields better outcome as an effective method of management of simple thyroid cysts when compared with simple aspiration due tofrequent reaccumulation[7,8]. Thyroid surgery effectively excises thyroid cysts however it is usually reserved for specific clinically determined situationssuch as numerous large cysts that are visually conspicuous or symptomatic for the patient [9].

The differential diagnosis of a cystic lesion in the thyroid encompasses nodular thyroid disease (colloid goiter) with cystic degeneration, benign and malignant thyroid neoplasms exhibiting cystic changes (adenomas, carcinomas), intrathyroid parathyroid cysts, intrathyroid thyroglossal duct cysts, intrathyroid thymic cysts, epidermal inclusion cysts, parasitic cysts (particularly Echinococcus), thyroid metastasis, and lymphoepithelial thyroid cyst (LEC-T) as discussed in this article.

LEC-T is a benign cystic lesion of the thyroid, with a lining primarily composed of stratified squamous epithelium, which may be keratinizing or nonkeratinizing. Less frequently, respiratory epithelium forms the lining of these cysts. The cyst wall shows characteristic lymphoid aggregates, frequently with germinal centers [10]. The occurrence of LEC-T is rare. Since their initial description in 1989 [11], only a few dozen cases have been documented in the global medical literature. The rarity of LEC-T sometimes leads to delayed and missed diagnoses, therefore each new, well-documented case provides essential information, enhancing our understanding of its pathophysiology, clinical presentation, and appropriate care. In this article authors introduce a case report of patient with this rare condition.

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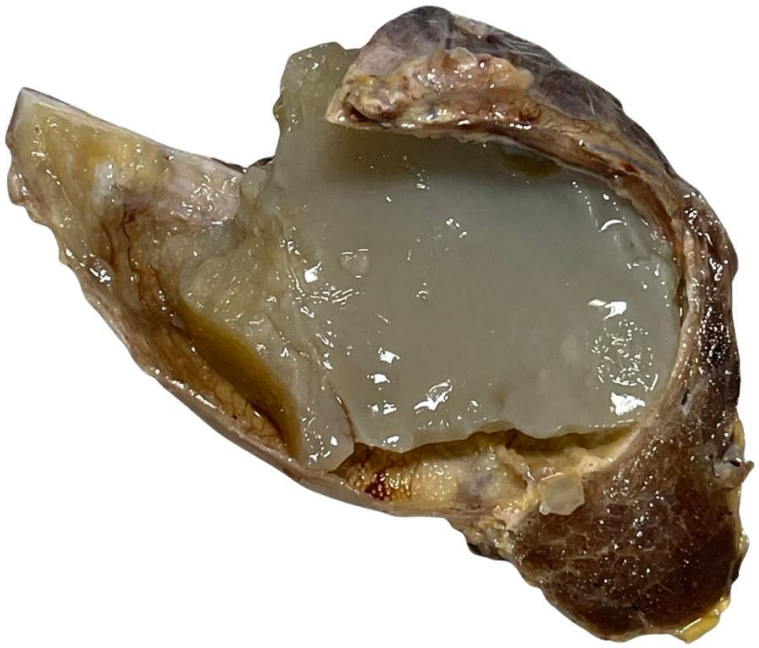
CASE REPORT

A 43-year-old man, a moderate smoker for 23 years, consulted his primary care physician after discovering a painless lump in his neck, without any accompanying symptoms. He stated that the lesion had enlarged over the past two months. An ultrasound of the neck identified a cystic lesion in the right thyroid lobe, measuring 4 cm at its largest dimension, with no accompanying calcifications (EU-TIRADS 2). The remaining thyroid gland exhibited no notable abnormalities, and lymphadenopathy was not detected. Following normal laboratory test results, the patient was scheduled for surgery – the patients underwent a right partial lobectomy with satisfactory postoperative recovery.

The submitted portion of the right lobe of the thyroid measured 5.0 × 3.0 × 2.0 cm and exhibited a deep brown, nodular capsular surface. Sectioning revealed unilocular cystic cavity measuring up to 4.5 cm in maximum diameter with a smooth inner lining. The cyst contained clear gelatinous fluid. Calcification was not observed in the walls of the cyst, and the residual tissue was firm and red-brown. Figure 1. illustrates the macroscopic appearance of the cyst.

Figure 1: Macroscopic findings of the thyroid lymphoepithelial cyst as received at the laboratory.



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Histological sections were prepared and stained with hematoxylin and eosin.

Microscopic examination revealed a benign stratified squamous epithelial lining overlying an extensive band of lymphoid cells in the cyst wall, with focal lymphoid aggregates containing well-defined germinal centers present **(Figure 2.)**.

The cyst cavity showed amorphous eosinophilic debris with some neutrophils and macrophages, **(Figure 2.a. to 3a.).**

Occasional anucleate squames are also seen in the lining epithelium and cyst debris. Entrapped atrophied thyroid follicles are seen on the exterior aspect of the cystic wall**(Figure 2c.)**.

Normal thyroid parenchyma is also seen proximal to the cyst **(Figure 2c.)**. p63 and p40, immunohistochemistry performed, showed strong positive staining in the lining epithelium confirming squamous cell origin **(Figure 3. b. & c.) -** a clear, positive nuclear reaction is seen in the cells of the stratified squamous epithelium that lines the cyst. TTF-1 nuclear staining was positive within both the lining epithelium and the entrapped thyroid follicles, adding supportive evidence of the origin of the cyst **(Figure 3. d.)**.

The cytological and immunohistochemical findings are specific and confirmatory for LEC-T, which was the definitive diagnosis provided.

Except for hormone replacement therapy with levothyroxine, the patient did not require any further treatment following the diagnosis.

A follow-up thyroid ultrasound revealed no new lesions in the remnant of the right lobe and the entire left lobe of the thyroid.

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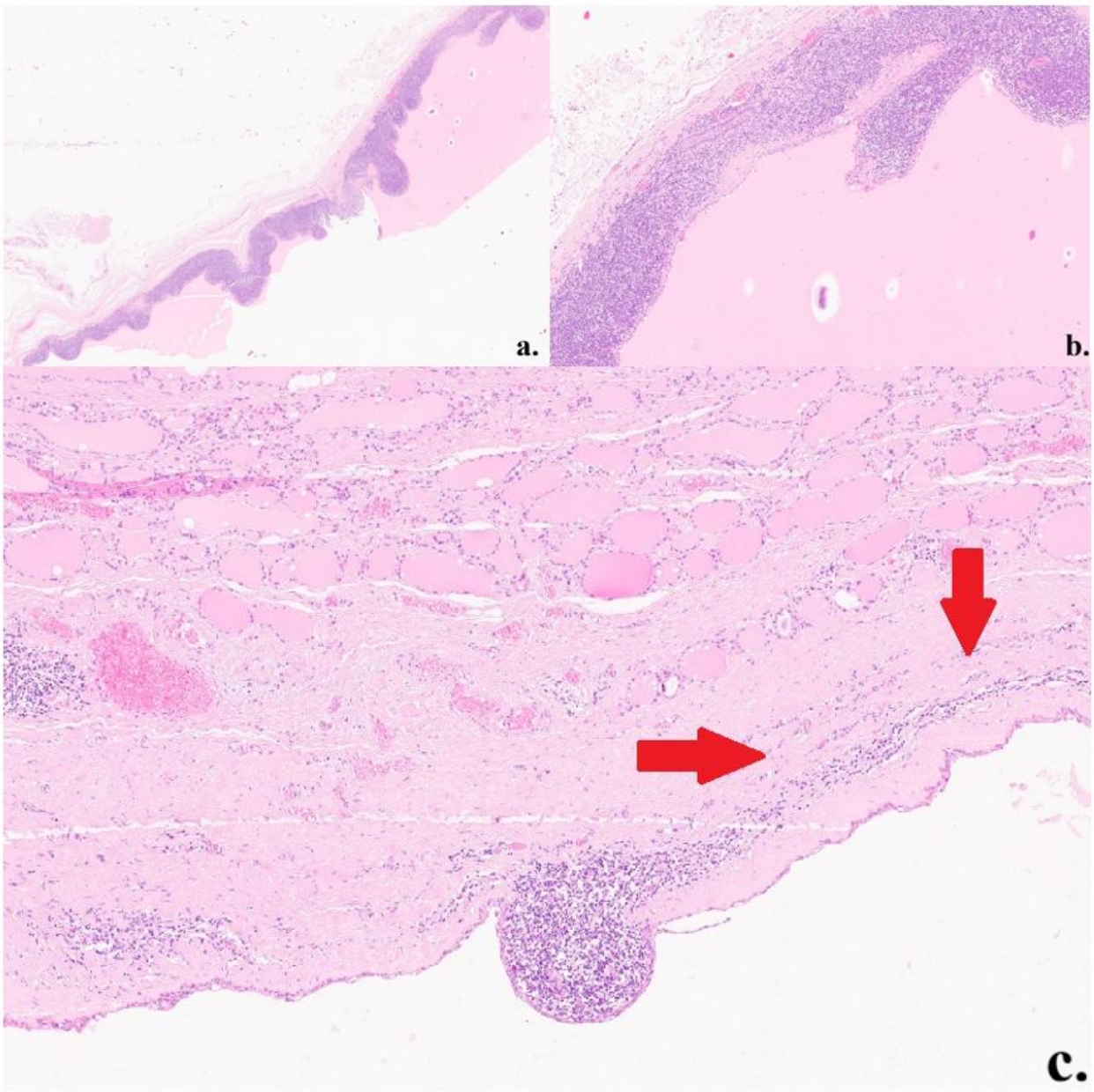

Figure 2. Low power view photomicrographs of benign stratified squamous epithelial lining and extensive lymphoid tissue within the fibrous cyst wall (images **a.** and **b.**). Image **c.** with entrapped thyroid follicles within the cyst wall (red arrows).

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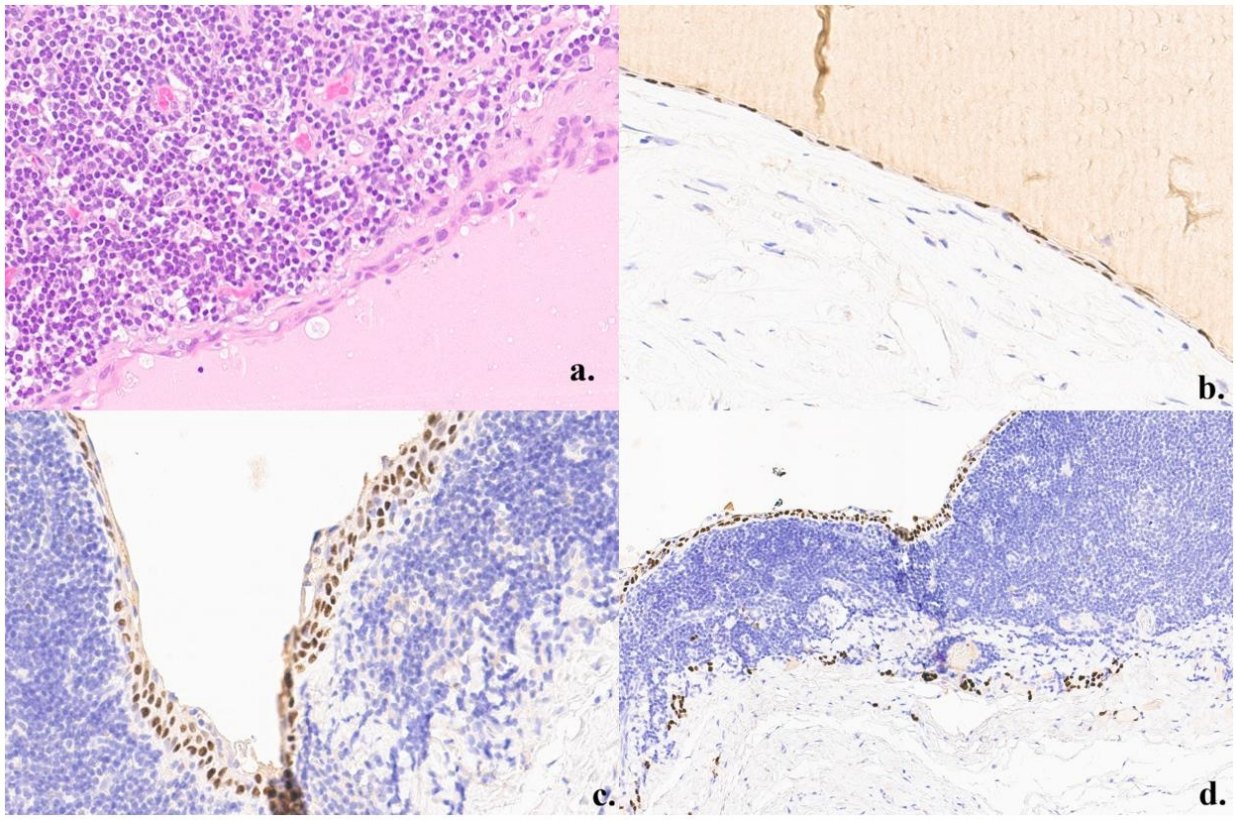

Figure 3. Higher power views of the cyst with proteinaceous content in the cyst cavity **(image a.)**. Immunohistochemistry; images **b.**p40, **c.**p63, **d.**TTF-1 highlighting entrapped follicles.

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Discussion.

An accurate preoperative diagnosis of LEC-T is often challenging owing to the fact that these cysts are rare and present with overlapping clinical and imaging features with other benign and neoplastic thyroid cysts/cystic nodules. This underscores the clinical significance of this benign entity. LEC-T usually manifests clinically as a vague, gradually enlarging, and asymptomatic thyroid nodule that cannot be differentiated by palpation from more prevalent diseases [10]. Imaging studies, particularly ultrasonography, which are crucial instruments in assessing thyroid nodules, may yield false positive findings for malignancy. On imaging, LEC-T presents as an anechoic cystic lesion, however it may occasionally manifest as a pseudo-solid lesion or a nodule with many hyperechoic foci exhibiting acoustic shadowing, which might be misinterpreted as calcifications and heighten the suspicion of malignancy [12,13]. Likewise FNAB, the gold-standard early screening modality which provides critical information regarding risk of malignancy, frequently yields Bethesda I (unsatisfactory) or III (atypia of undertermined significance) categories, further complicating clinical decision making. The presence of squamous cells and lymphocytes is not limited to this cyst and therefore careful macroscopic and microscopic evaluation of aspirates to exclude other diagnoses with similar cytology is paramount. The differential diagnosis on cytology includes and intrathyroidal thyroglossal duct cyst, branchial cleft cyst, cystic thymic remnant,primary or metastatic malignancies including squamous, anaplastic and uncommon subtypes of papillary thyroid carcinoma [11,14–16].

The etiopathogenesis of LET-C has been a focal point of intense scholarly discourse for years, resulting in the emergence of two conflicting ideas. Historically, the prevailing idea stated that LEC-T arises from ectopic remnants of the branchial apparatus, which were entrapped in the thyroid gland parenchyma during its descent in development. The justification for this theory was the histological resemblance of LEC-T to lateral neck cysts which arise within remnants of the third, fourth or fifth branchial pouch, from which solid cell nests develop in the thyroid gland. The existence of additional branchial-derived structures within the thyroid parenchyma, including ectopic thymus or parathyroid tissue, further strengthened this hypothesis [10,11,17,18]. However, more recent studies using advanced immunohistochemical techniques have cast serious doubt on this theory - revealing that the solid cell nests and epithelial cells of typical lateral neck cysts display a distinct immunohistochemical profile in contrast to LEC-T. The primary distinction is the absence of expression of immunomarkers in the epithelial cells of the branchial structures of other cysts which are typically expressed in thyroid tissue, including thyroglobulin, TTF-1 and PAX-8[16,19]. Variations in the topography of these lesions have been noted, with solid cell nests predominantly situated in the upper and central regions of the thyroid lobes, while LEC-T are more frequently found in the middle and lower regions. The strong clinical and histological connection between LEC-T and Hashimoto's thyroiditis offers more evidence. Research indicates that as much as 95.2% of LEC-T cases are accompanied with characteristics of chronic lymphocytic thyroiditis, with more than 85% of patients exhibiting serologically verified Hashimoto's thyroiditis [19]. It is crucial to acknowledge that this association clarifies the paradox presented by the branchiogenic theory. The metaplastic changes suggest that a cyst is not

an independent embryonic structure activated by inflammation, but is a direct consequence of this inflammatory process, which affects native thyroid cells [20]. Consequently, LEC-T should be regarded not as an embryogenic anomaly, but as an uncommon, acquired reactive lesion primarily resulting from severe autoimmune thyroiditis. In our patient's case however, features of autoimmune thyroiditis were absent in the portion of the right lobe submitted for histopathology evaluation.

While LEC-T typically presents as a standard simple cyst (characterized by an anechoic, well-defined lesion with a thin wall and posterior acoustic enhancement), it may also manifest as a hyperechoic, pseudo-solid lesion on ultrasound due to the dense, proteinaceous contents comprising exfoliated keratin, cellular debris, and cholesterol crystals. In exceptional instances, tightly packed keratin aggregates may reflect ultrasonic waves with such intensity that they obstruct further transmission, resulting in an acoustic shadow behind the lesion, characteristic of true calcification despite its absence. In both scenarios, the lesion will be classified as EU-TIRADS-3 rather than the standard EU-TIRADS-2 designation (or even an EU-TIRADS-5 designation), prompting clinicians to pursue more invasive diagnostics and heightening the patient's stress levels [5,12,13,21]. The dense and viscous nature of the cystic contents typically renders FNAB non-diagnostic (Bethesda category I) due to the poor diagnostic yield of cellular material for analysis [22,23]. Wherean adequate aspirate is available, cytological characteristics overlap with other disease entities which may also present with mature benign squamous epithelial cells, frequently anucleate (referred to as keratinous scales), abundant lymphocytic infiltrate, and a dense, granular, or amorphous background, consistent with aggregates of keratin [24]. The occurrence of squamous cells typically serves as a significant diagnostic clue, as this type of epithelium is not ordinarily found in the thyroid gland. Diagnosis involves meticulous algorithms and criteria which focus on distinguishing LEC-T from: primary differentiated carcinomas of the thyroid with squamous differentiation, metastases of squamous cell carcinoma to the thyroid, anaplastic carcinoma with squamous differentiation, mucoepidermoid carcinoma, Warthin-like subtype of papillary thyroid carcinoma, and other lesions aforementioned in the introduction of this article [16,25]. A working knowledge of the wide differential diagnosis of LEC-T on FNABavoids unnecessarily ascribingneoplastic Bethesda categories V or VI which invariably result in the recommendation for unwarranted aggressive surgical interventions[23].

Typically, cystic lesions of the thyroid gland are predominantly colloid nodules, which are benign proliferations of normal glandular tissue with brown cyst content macroscopically. The cystic transformation inside these nodules is a secondary occurrence arising from hemorrhagic events, necrosis, and liquefaction within the enlarged follicles. In contrast, the cyst content of LEC-T appears mucinous on gross examination of histology specimen. The pathognomonic ultrasound sign of a colloid nodule, strongly indicating its benign nature, is the presence of numerous, small, echogenic foci corresponding to thickened colloid, which generate a characteristic "comet tail" artifact [26,27]. Although colloid nodules are more prevalent, it is important to note that both adenomas and malignant thyroid cancers can also undergo cystic transformation implying that this particular macroscopic characteristic does not rule out malignancy [28,29]. A critical aspect of the

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diagnosis is ultrasound risk stratification, which aims to determine eligibility for FNAB by evaluating the morphology of any solid component, its margins, echogenicity, presence of microcalcifications, shape, and other characteristics [5,27,29]. About 5% of cystic nodules identified as thyroid cysts do not arise from the follicular epithelium but from the parathyroid glands; these cysts may be indicated by the color of the cystic fluid, which is typically, but not invariably, as transparent as water. The definitive diagnosis is established by identifying elevated levels of parathyroid hormone and low or undetectable levels of thyroglobulin in the aspirated fluid [30]. Another cyst with a potential extrathyroidal origin is the thyroglossal duct cyst, typically situated in the midline of the neck, remnants may infrequently become entrapped within the thyroid parenchyma. The ultrasonography characteristics are nonspecific and do not facilitate a dependable distinction from other thyroid cystic lesions. The cytological analysis of the aspirate may reveal benign squamous cells and inflammatory cells, indicative of the epithelial lining of the persistent duct [31]. Cysts of ectopic thymic tissue within the thyroid are also frequently observed in the pediatric demographic. Ectopic thymus is an ultrasound mimic of malignancy, characterized by multiple pinpoint internal echoes that may imply microcalcifications. The true origin of these internal echoes however are ultrasound wave reflections from adipose tissue interspersed with lymphoid tissue. The cytological morphology is characteristic due to the presence of Hassall's corpuscles, pathognomonic for thymic tissue [32,33]. Extremely rare benign lesions arising from the migration of ectodermal tissue into the thyroid gland may manifest as epidermal inclusion cysts. These cysts can result from trauma, surgical procedures, or the entrapment of embryonic remnants. Because of the variability in ultrasound imaging, they may occasionally mimic malignant lesions; however, the cytological analysis following FNAB typically reveals a distinctive profile, characterized by the presence of mature, superficial squamous cells, anucleate keratinous masses, and keratin debris in the background, particularly after the collection of purulent or bloody material [34]. Parasitic thyroid cysts and hydatid disorders are exceedingly rare, with just over 50 documented occurrences, primarily linked to Echinococcus granulosus, which can access the thyroid gland via the liver and lungs. FNAB is not advised due to the potential danger of distributing cyst fluid and inducing anaphylactic shock; however, this concern is based on a singular report in the literature documenting an allergic reaction following FNAB[35]. We must also consider the potential, although infrequent, cystic metastases of cancer to the thyroid - the most prevalent cancers that metastasize to the thyroid are renal cell carcinoma, breast cancer, lung cancer, and melanoma; however, it is challenging to confirm which of these most frequently induces cystic alterations [36].

The rapid expansion of these lesions and the frequent difficulty in ruling out malignancy at an early stage render surgical intervention the predominant treatment option. The prognosis for individuals with LEC-T is excellent. The lesion is benign, with no reported cases of malignant changes. Recurrence does not occur following full excision. It is crucial to acknowledge that these patients, frequently diagnosed with Hashimoto's disease, necessitate adequate endocrine surveillance [10]. The presence of autoimmune thyroiditis elevates the likelihood of further problems, including the onset of thyroid lymphoma [37]. Although this pertains to the

broader illness setting rather than LEC-T specifically, it underscores the necessity for ongoing patient surveillance.

Conclusions

LEC-T is an uncommon, benign clinicopathological condition whose pathophysiology, as indicated by recent investigations, is most likely associated with squamous metaplasia within thyroid follicular cells within the background of thyroiditis. It presents a considerable diagnostic problem due to its clinical and radiological features closely resembling malignancy, and the outcomes of fine-needle aspiration biopsy are frequently ambiguous, raising oncological apprehensions. It is also essential for every practicing clinician to be aware of the need for differential diagnosis of cystic lesions.

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