Case report
Prikaz bolesnice

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THYROID LYMPHOEPITHELIAL CYST NOT ASSOCIATED WITH HASHIMOTO'S THYROIDITIS – CASE REPORT

Intratireoidna limfoepitelna cista bez Hashimotovog tireoiditisa – prikaz bolesnice

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Summary

Introduction: Intrathyroidal lymphoepithelial cyst (TLEC) is an uncommon benign lesion of the thyroid gland, with less than 50 cases described in literature, often associated with chronic thyroiditis or other thyroid abnormalities. Two proposed hypotheses regarding its pathogenesis are branchial cleft origin and squamous metaplasia. Immunohistochemical analyses of the cyst epithelium serve as a valuable instrument for distinguishing the cell's origin, however, the exact pathogenesis of TLEC is still uncertain. In our case, we demonstrate that lymphoepithelial cysts can develop within the thyroid gland's healthy parenchyma, devoid of chronic inflammatory changes.
Case presentation: We present the case of a 45-year-old woman with a growing mass in the left lateral neck and signs of compression, dysphagia, dyspnea, and fatigue. Ultrasonography and computerized tomography revealed a large solitary cyst measuring 22 x 25 x 36 mm within the left thyroid lobe, with no other abnormalities noted in the thyroid structure. Left thyroid lobectomy was performed with an outstanding outcome and no observed complication. Histologically, the diagnosis of the intrathyroidal lymphoepithelial cyst was made with no signs of Hashimoto's thyroiditis or other thyroid pathology. After the definitive diagnosis, a detailed literature search was done by *PubMed* and *Google Scholar* to investigate such a rare disease.
Conclusion: Our case highlights the complexity of TLEC diagnosis. The im-

munohistochemical analysis suggesting a potential branchial cleft origin challenges the conventional association with chronic inflammation. Furthermore, our comprehensive literature review revealed a lack of well-conducted scientific research regarding its pathogenesis, highlighting the need for standardized protocols for immunohistochemical staining in suspected cases.

Sažetak

Uvod: Intratireoidna limfoepitelna cista (TLEC) rijetka je benigna lezija štitnjače, s manje od 50 opisanih slučajeva u literaturi. Obično se povezuje s kroničnim tireoiditisom ili drugim abnormalnostima štitnjače. Dvije vodeće hipoteze o patogenezi razvoja ove ciste uključuju branhijalno porijeklo i skvamoznu metaplaziju. Imunohistokemijske analize epitela ciste koriste se za razlučivanje podrijetla stanica, no točna patogeneza TLEC-a i dalje ostaje nejasna. U ovom radu prikazujemo da se limfoepitelne ciste mogu razviti unutar zdravog parenhima štitnjače, bez prisutnosti kroničnih upalnih promjena.
Prikaz bolesnice: Bolesnica stara 45 godina javila se na pregled s progresivno rastućom masom na lijevoj lateralnoj strani vrata, uz simptome kompresije, disfagijom, dispnejom i umorom. Ultrazvučni pregled i kompjutorizirana tomografija otkrili su solitarnu cistu dimenzija 22 x 25 x 36 mm unutar lijevog režnja štitnjače, bez drugih strukturnih abnormalnosti. Bolesnica je podvrgnuta lijevostranoj lobektomiji štitnjače, a operacija je prošla bez komplikacija. Histopatološkom analizom postavili smo definitivnu dijagnozu intratireoidne limfoepitelne ciste, bez znakova Hashimotovog tireoiditisa. Nakon postavljanja dijagnoze, proveli smo temeljitu pretragu literature putem baza podataka *PubMed* i *Google Scholar* u svrhu dubljeg razumijevanja ovog rijetkog entiteta..
Zaključak: Ovaj prikaz naglašava dijagnostičke izazove vezane uz TLEC. Imunohistokemijska analiza koja ukazuje na moguće porijeklo iz bronhijalnog luka dovodi u pitanje uobičajenu povezanost ove lezije s kroničnom upalom. Naša sveobuhvatna analiza literature otkrila je nedostatak kvalitetno provedenih istraživanja o patogenezi ove bolesti, ističući potrebu za standardiziranim protokolima imunohistokemijskog bojenja u dvojbenim slučajevima.

Ključne riječi:
štitnjača, ciste, branhiogeni tumori, imunohistokemija, prikaz bolesnice

INTRODUCTION

Disorders of the thyroid gland are very common, affecting millions of people worldwide. Partial and complete thyroidectomy belong to one of the most frequent procedures performed in the otorhinolaryngology departments. The most common indications for surgery are benign diseases such as goiter or hyperthyroidism and suspected malignant disease. Pathohistological examination usually matches the working diagnosis but sometimes it reveals something extraordinary, like an intrathyroidal lymphoepithelial cyst (TLEC). This rare entity is usually found incidentally after thyroid lobectomy or total thyroidectomy with less than 50 cases described in the literature. The literature search was done by *PubMed* and *Google Scholar* databases to identify published cases which were mostly case reports. The largest research conducted by Tsutsuura et al.[1] included 32 cases accumulated in 10 years. Due to its rarity and lack of original research, the pathophysiology of this disease remains unclear. Therefore, cases of TLECs should be adequately reported for a better understanding of this rare entity.

In our case, we demonstrate that lymphoepithelial cysts can develop within the thyroid gland's healthy parenchyma, devoid of chronic inflammatory changes.

CASE PRESENTATION

A 45-year-old woman presented with a 2-month history of painless left-sided neck mass with signs of compression, dysphagia, dyspnea, and fatigue. Except for psychotropic medication (zolpidem and diazepam), the past medical history of the patient was unremarkable as well as the family history. The patient was well motivated for further diagnostic testing and no challenges in the routine examinations were seen. Physical examination revealed a smooth 2 cm mass in the left lateral neck. Flexible fiberoptic laryngoscopy showed normal larynx and hypopharynx structures with no accumulation of saliva in the piriform sinuses and white, symmetrically movable vocal cords. Laboratory test results of thyroid hormones (triiodothyronine, thyroxine, and thyroid-stimulating hormone) were within normal limits. Neck ultrasonography revealed a cystic mass in the left thyroid lobe, with no differentiated cysts or nodules in the right thyroid lobe. Ultrasound-guided fine-needle aspiration was performed, and cytology findings reported 10 ml of transparent liquid content with scanty cellularity and no identifiable malignant cells. The computerized tomography scan of the neck described a large cyst in the lower pole of the left thyroid lobe measuring 22 × 25 × 36 mm (LR × AP × CC), extended caudally to the lower edge of the clavicle. It was in direct contact with the left common carotid artery

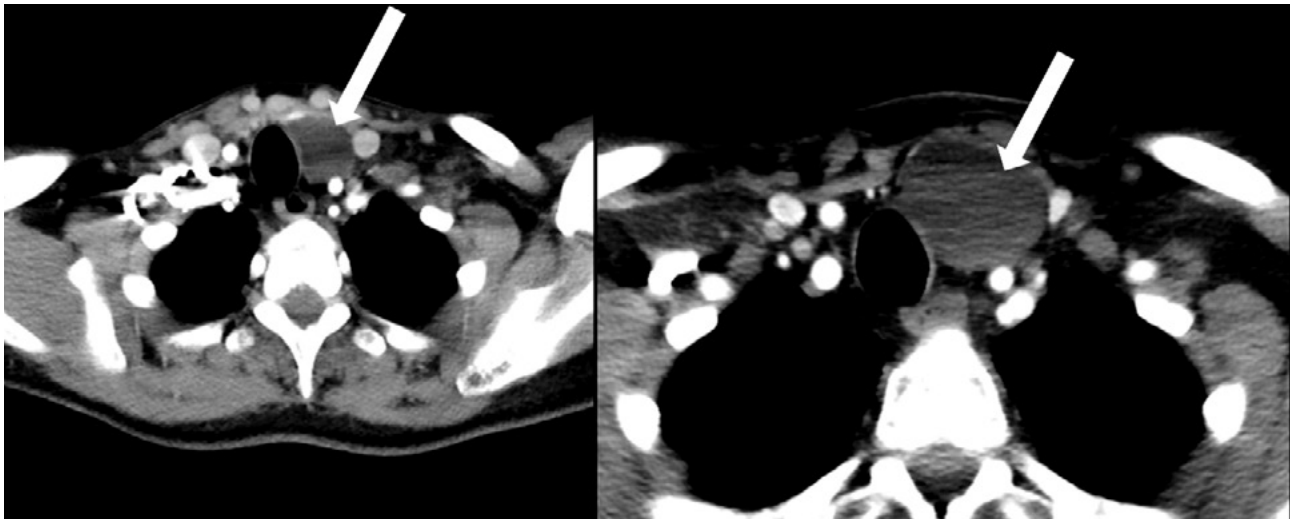


Figure 1 Computed tomography (CT) scan of the thyroid. A cystic lesion is marked with an arrow
Slika 1. *CT štitnjače. Cistična lezija označena je strelicom*

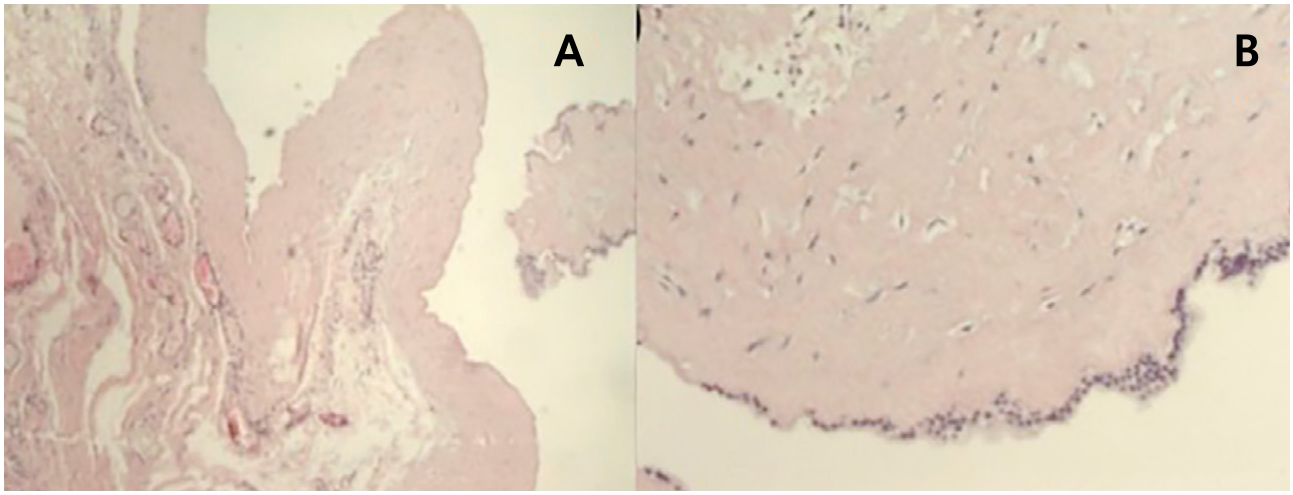


Figure 2 Histological findings of the cyst. (A) (HE, x4) (B) (HE, x20)
Slika 2. *Histološki prikaz ciste (A) (HE, x4) (B) (HE, x20)*

and compressing the trachea to the right. All the other structures in the neck were without abnormalities (Figure 1). The working diagnosis was a benign thyroid nodule, and the patient was informed about the possible therapeutic options and good prognosis. Even though there were no signs of malignancy, the patient chose the surgical approach for definitive treatment because of the compressive effect the lobe was making on the trachea. The left thyroid lobectomy was performed under general anesthesia. The horizontal incision of the skin and subcutaneous tissue of the neck was made, the infrahyoid musculature was dissected, and the enlarged left lobe of the thyroid gland was shown. The lobe was dissected, the upper and lower poles were ligated, and the left recurrent nerve and the left upper and lower parathyroid glands were identified and preserved. The lobe was entirely removed and sent to histopathological analysis. After achieving proper hemostasis, the wound was closed in layers. The postoperative recovery was satisfying, and no observed complications were seen. During the hospital stay, the patient received only analgetic therapy when needed. The level of thyroid hormones as well as calcium stayed within the limits and the patient was discharged from the hospital on the second postoperative day.

Grossly, the left thyroid lobe measured 50 × 25 × 20 mm. In the lower part of the lobe, a collapsed, hollow formation with a diameter of 18 mm and a grayish, smooth wall was recorded. Microscopically, the cyst wall consisted of hyalinized connective stroma, luminally lined with both squamous and respiratory epithelium. Lymphocyte infiltration is seen along the marginal wall (Figure 2). The remaining thyroid parenchyma showed cystically enlarged follicles lined with cubic thyrocytes with few resorption vacuoles filled with colloid. Focal lymphocyte infiltration and foaming macrophages are sparsely seen in the interstitium. Immunohistochemical analysis revealed cyst epithelium positive for pan-cytokeratin (PanCK) and luminal membrane positive for carcinoembryonic antigen (CEA) but negative for thyroglobulin, thyroid transcription factor 1 (Figure 3), chromogranin, and synaptophysin. Histologically, these findings justify intrathyroidal lymphoepithelial cyst diagnosis.

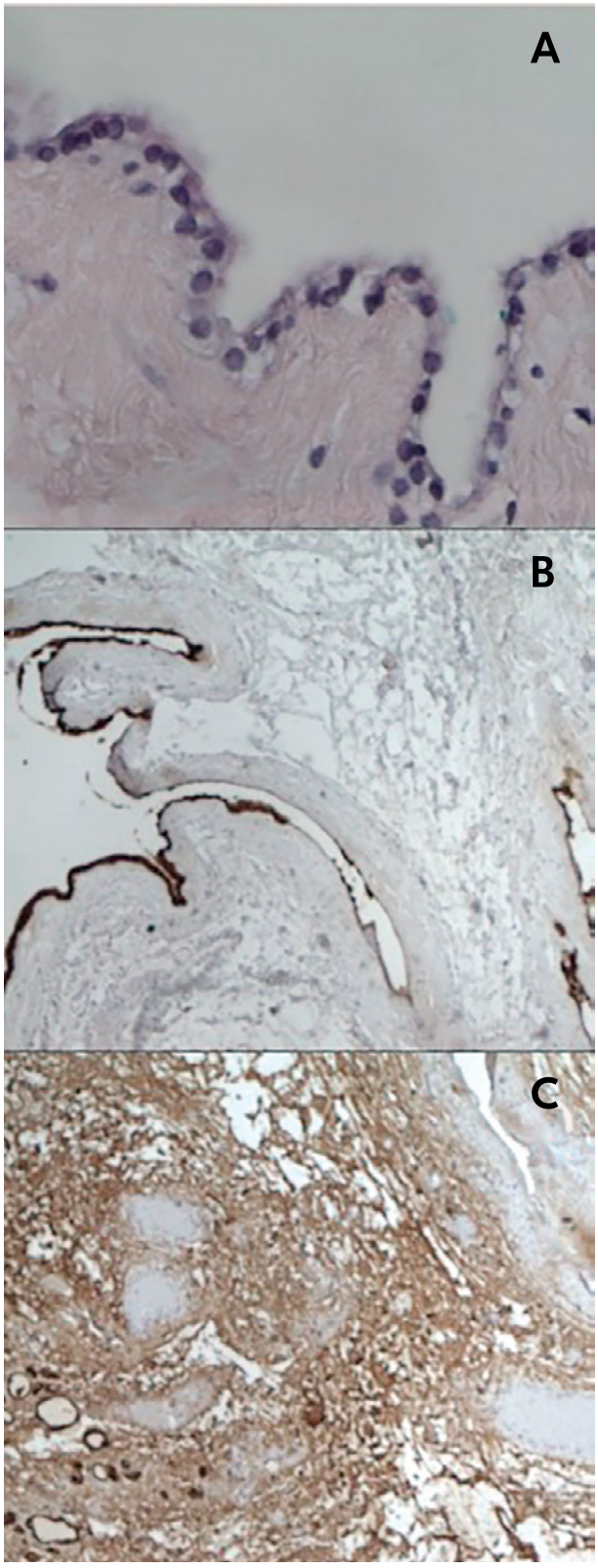


Figure 3 Immunohistochemical findings of the cyst. A) Thyroid transcription factor 1 negative. B) Pan-cytokeratin positive. C) thyroglobulin negative
Slika 3. *Imunohistokemijsko bojanje ciste. A) Negativan tireoidni transkripcijski faktor 1. B) Pozitivan pan-citokeratin. C) Negativan tireoglobulin*

The suture was removed on the 7th postoperative day. The hormone levels stayed within normal limits and no medications were prescribed. The patient had no signs of hoarseness, dysphagia, dyspnea, or fatigue on the follow-up examinations and was very well satisfied with the outcome. No adverse and unanticipated events were seen. The postoperative scarring was minimal, and the patient was thrilled with the entire diagnostic and therapeutic strategies we had performed in treating this benign thyroid diagnosis.

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. This study was approved by the Institutional Review Board of General Hospital "Dr. Josip Benčević" Slavonski Brod (Registration number, 04000000/22-51).

DISCUSSION

Thyroid lymphoepithelial cysts (TLECs) are rare entities first described in 1989 by Louis and al.[2] Histologically the cysts are coated by squamous and sometimes focally respiratory-type epithelium, surrounded by lymphoid tissue and a fibrous capsule.[2] Such cysts can be found at different sites, including the oral cavity[3,4], parotid and submandibular gland[5,6], pancreas[7,8], and thyroid.[1-2,9-27] Interestingly, one case reported multiple cysts originating simultaneously in the thyroid, thymus, and right parotid gland, with nearly the same histopathological features.[25]

Tsutsuura et al.[1] examined 32 ultrasonography reports of TLECs and concluded that almost 50% of the cases did not exhibit the typical sonographic features of simple thyroid cysts. They divided their ultrasonographic reports into four types: cystic, pseudo-calcified, mixed solid cystic, and pseudo-solid. Our patient's ultrasonography belongs to the most frequent cystic type. Because of the different variations of the ultrasonography reports, TLEC cannot be diagnosed with ultrasound. A certain diagnosis can be made after the pathohistological evaluation. Therefore, the definitive treatment is partial or total thyroidectomy, whichever is appropriate.

The exact pathogenesis of TLECs is still uncertain, with both congenital and acquired etiology proposed. The first hypothesis is that cysts are congenital branchial remnants and because of their histological resemblance with branchial cleft cysts of the lateral neck, they are sometimes called "branchial cleft-like cysts", thought to be derived from the ultimobranchial body and solid cell nests.[2,23] The second hypothesis claims the cysts result from squamous metaplasia of a cystic lesion that appeared due to degeneration of a normal follicle in goiter or autoimmune thyroiditis.[13,26,27] However, thyroiditis may also stimulate the growth of previously existing branchial cleft-like cysts.[2]

Consequently, immunohistochemistry is used as a helpful instrument in differentiating cell origin. Thyroid transcription factor 1 (TTF-1), paired box gene 8 (PAX8), and thyroglobulin serve as immunomarkers for thyroid tissue.[28] Markers against calcitonin are used to identify parafollicular cells of the thyroid and medullary thyroid carcinoma.[29] The most relevant neuroendocrine immunomarkers reactive to parathyroid tissue are chromogranin and synaptophysin.[30] CEA's positivity can normally be seen in healthy adults localized in the tongue, stomach, duodenum, colon, and trachea[31], but it's mainly used as the serum tumor marker for follow-up of relapses in gastrointestinal malignancies, as well as neuroendocrine tumors, like medullary thyroid carcinoma.[32] CEA immunoreactivity can also be seen in branchial cleft cysts.[33,34] A variety of cytokeratins are used for the recognition and classification of epithelial cells with the pan-cytokeratin antibodies applied for essentially all epithelial tissues and their neoplasms.[35]

When looking at the immunohistochemistry of previous case reports of TLECs (Table 1), the epithelial lining of the cyst is always negative for thyroglobulin and chromogranin but positive for cytokeratin. Most of the cases reported positivity for CEA (93%) and negativity for calcitonin (92%). Only four cases researched TTF-1 and the results were equally divided.

Suzuki et al.[27] tested 21 samples of thyroid lymphoepithelial cysts for PAX8, TTF-1, p63, and CEA (100%, 57.1%, 100%, 14.3%, respectively) and compared the results with squamous metaplasia, solid cell nests, and lateral cervical cysts.

Table 1 Reports of intrathyroidal lymphoepithelial cyst
Tablica 1. *Radovi objavljeni o intratiroidnoj limfoepitelnoj cisti*

Reference (year) *Rad (godina)*	Age/ Sex *Dob/spol*	Inspection *Inspekcijski pregled*			Pathology *Patološki nalaz*		Immunohistochemistry *Imunohistokemija*					
		Site (lobe) *Lokacija (režanj)*	Number of cysts *Broj cisti*	Size (cm) *Veličina (cm)*	Lining cells *Stanični zid*	Associated conditions *Povezana stanja*	Thyrogl	Calc	CEA	TTF-1	Chr	Cytok
Louis et al [2] (1989)	46/F	Bil	m	2.5	SC, RE	HaT	-	-	NT	NT	NT	NT
	47/F	Left	m	1.8	SC, RE	HaT	NT	NT	NT	NT	NT	NT
Carney[9] (1989)	54/F	Right	s	2.0	SC	NH	NT	NT	NT	NT	NT	NT
Delabie et al[10] (1990)	34/F	Bil	m	NA	SC	NH, T	NT	-	+	NT	NT	NT
Lim-Tio et al[11] (1992)	37/F	Left	s	1.4	SC	NH	-	-	NT	NT	-	+
Radhi[12] (1994)	43/F	Left	s	3.0	NA	HaT	NT	NT	NT	NT	NT	NT
Apel and Asa[13] (1994)	26/F	Left	s	0.5	SC, SCN	PC, CLT, HTT, HTP	-	NT	+	NT	NT	+
	39/M	Left	s	0.5	SC, SCN	MNG, PC, CLT	-	NT	+	NT	NT	+
	24/M	Left	s	0.7	SC, SCN	CLT	-	NT	+	NT	NT	+
	52/F	Right	s	0.3	SC, SCN	CLT	-	NT	+	NT	NT	+
	58/F	Left	s	3.0	SC, SCN	NH, PC, CLT	-	NT	+	NT	NT	+
	34/F	Right	m	2.2	SC	CLT	-	NT	+	NT	NT	+
Watanabe et al[14] (1995)	42/M	Left	m	1.7	SC, RE	T, PC	-	-	NT	NT	NT	+
Ryska et al[15]. (1997)	31/F	Left	m	2.0	SC, SCN	MNG	-	-	+	NT	-	+
	47/F	Right	s	1.9	SC	NH	-	-	+	NT	-	+
Ahuja et al[16] (2000)	64/M	Right	s	2.5	SC	CLT	NT	NT	NT	NT	NT	NT
Asanuma et al[17] (2000)	36/F	Bil	m	4.3	SC	HaT, MNG	-	NT	-	NT	NT	+
Haba et al[18] (2000)	71/M	Right	s	2.2	SC	CLT	NT	-	+	NT	-	+
Cassa-rino et al[19] (2003)	47/M	Bil	m	3.8	SC, SCN	MNG, CLT	NT	-	+	NT	NT	NT
Carter et al[20] (2003)	55/F	Bil	m	1.4	SC, RE, SCN	CLT, HTP	NT	+	+	NT	NT	+
Park et al[21] (2004)	7/F	Left	s	2.4	SC, RE, SCN	HSG	NT	-	+	-	NT	+
Kwak et al[22] (2006)	52/M	Left	m	2.0	SC, RE	NH	NT	NT	NT	NT	NT	NT
Michal et al[23] (2006)	65/M	Right	m	4.0	SC, SCN	HaT	-	-	NT	-	NT	NT
Choi et al[24] (2010)	49/M	Bil	m	3.0	SC, SCN	MNG, HaT	NT	NT	NT	NT	NT	+

Reference (year) *Rad (godina)*	Age/ Sex *Dob/spol*	Inspection *Inspekcijski pregled*			Pathology *Patološki nalaz*		Immunohistochemistry *Imunohistokemija*					
		Site (lobe) *Lokacija (režanj)*	Number of cysts *Broj cisti*	Size (cm) *Veličina (cm)*	Lining cells *Stanični zid*	Associated conditions *Povezana stanja*	Thyrogl	Calc	CEA	TTF-1	Chr	Cytok
Nakazawa et al[25] (2015)	41/M	Bil	m	7.0	SC	HaT, MLEC	-	-	NT	+	NT	NT
Miyazaki et al[26] (2016)	77/M	Left	m	4.5	SC, SCN	HaT	-	-	+	+	NT	+
Our case	45/F	Left	s	1.8	SC, RE	-	-	NT	+	-	-	+

F=female, M=male, Bil=bilateral, m=multiple, s=solitary, size=diameter of the biggest cyst, NA=not available data, SC=squamous cells, RE=respiratory-type epithelium, SCN=solid cell nests immediately adjacent to the cyst wall, HaT=Hashimoto's thyroiditis, NH=nodular hyperplasia, T=thyroiditis, PC=papillary carcinoma, CLT=chronic lymphocytic thyroiditis, HTT=heterotrophic intrathyroidal thymus, HTP=heterotrophic intrathyroidal parathyroid, MNG=multinodular goiter, HSG=heterotrophic salivary gland, adult fat and immature cartilage, MLEC=multiorgan lymphoepithelial cysts, Thyrogl=thyroglobulin, Calc=calcitonin, CEA=carcinoembryonic antigen, TTF-1=thyroid transcription factor 1, Chr=chromogranin, Cytok=cytokeratin, NT=not tested, -=negative, +=positive

F=žene, M=muškarci, Bil=obostrano, m=multipli, s=solitarni, size=radijus najveće ciste, NA=nedostupni podaci, SC=pločaste stanice, RE=respiratorni epitel, SCN=otočići stanica izravno priljubljeni uz stijenku ciste, HaT=Hashimotov tireoiditis, NH=nodularna hiperplazija, T=tireoiditis, PC=papilarni karcinom, CLT=kronični limfocitni tireoiditis, HTT=heterotopična timus unutar štitnjače, HTP=heterotopična paratireoidna žlijezda usred štitnjače, MNG= multinodalna struma, HSG=heterotopična žlijezda slinovnica, mast i hrskavica, MLEC=multiorgansko limfoepitelne ciste, Thyrogl=tireoglobulin, Calc=kalcitonin, CEA=karcinoembrionalni antigen, TTF-1=tireoidni transkripcijski faktor 1, Chr=kromogranin, Cytok=citokeratin, NT=nije testirano, -=negativno, +=pozitivno

Statistically significant was the absolute positivity for PAX8 in TLECs compared with high positivity in squamous metaplasia and low positivity in solid cell nests and lateral cervical cysts. Interestingly, when testing for CEA, only lateral cervical cysts were predominantly positive, while TLECs were positive in only 14.3% of cases. This result differs from the other known case reports (Table 1). Due to these pathological and immunohistochemical findings, they concluded that TLECs originate from follicular cells and are not related to branchial-derived remnants.

All TLEC subjects had some of the associated pathological conditions in the remaining thyroid tissue (Table 1). Chronic lymphocytic thyroiditis, Hashimoto's thyroiditis, multinodular goiter, and nodular hyperplasia are reported in 38%, 31%, 19%, and 23% of cases, respectively. One case of heterotrophic intrathyroidal thymus and two cases of heterotrophic parathyroid are seen. Four cases of papillary carcinoma are found close to TLEC. When looking at Suzuki's research, 95% of patients were histologically associated with chronic thyroiditis.[27] Therefore, our subject with a solitary intrathyroidal lymphoepithelial cyst and otherwise normal thyroid tissue without signs of Hashimoto's thyroiditis is an interestingly rare example of this disease. In our case, immunohistochemistry of the lining cells of the cyst wall showed that the cells are epithelial (cytokeratin positive), and were not differentiated from the thyroid (thyroglobulin and TTF-1 negative) nor was the parathyroid (chromogranin negative) but may have originated from the branchial-derived remnants (CEA positive). The limitation was the absence of PAX8 immunomarker in our case, therefore it cannot be compared with the research by Suzuki et al.

When looking at all the reported cases of TLEC combined, one cannot propose a certain conclusion regarding the pathogenesis of TLEC. Suzuki et al. based their research on PAX8 immunomarker which was not tested in any other cases and therefore must be excluded. TTF-1 was positive in half of the tested specimens as well as CEA. In some cases, like our own, respiratory-type epithelium is found focally in the cyst wall. It remains uncertain why such diversity of pathological findings appears simultaneously in one diagnosis.

CONCLUSION

Intrathyroidal lymphoepithelial cysts are benign lesions usually found incidentally on the histological evaluation of a pathologically altered thyroid gland. Two proposed hypotheses regarding its pathogenesis are formed: branchial cleft origin and squamous metaplasia. Our case highlights the complexity of TLEC diagnosis. The immunohistochemical analysis suggesting a potential branchial cleft origin that challenges the conventional association with chronic inflammation. Furthermore, our comprehensive literature review revealed a lack of well-conducted scientific research regarding its pathogenesis, highlighting the need for standardized protocols for immunohistochemical staining in suspected cases.

Abbreviations

TLEC	Intrathyroidal lymphoepithelial cyst
PanCK	Pan-cytokeratin
CEA	Carcinoembryonic antigen
TTF-1	Thyroid transcription factor 1
PAX8	Paired box gene 8

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