CASE REPORT

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From simple neck pain to the diagnosis of Langerhans cell histiocytosis in the thyroid gland

Od bola u vratu do dijagnoze histiocitoze Langerhansovih ćelija u štitastoj žlezdi

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Abstract

Introduction. Langerhans cell histiocytosis (LCH), as a hematopoietic neoplasm, is a clonal proliferation of Langerhans dendritic cells. A comprehensive clinical examination is sometimes crucial for detecting rare adult diseases, such as LCH with concomitant autoimmune thyroid disease. **Case report.** A 43-year-old female patient first presented for an endocrinology consultation due to front neck pain and swelling accompanied by fatigue and malaise. The physical examination revealed an enlarged right thyroid gland lobe of extremely firm consistency that was painfully tender on palpation. Echosonographic findings confirmed that the right thyroid gland lobe was enlarged and was not clearly demarcated from the surrounding tissue while exhibiting pronounced parenchyma inhomogeneity characterized by reduced echogenicity of the anterior aspect and pronounced hypoechoicity of the posterior aspect, permeated with fibrous bands and calcifications. The structure of the left thyroid lobe was pseudonodular, with the characteristics of a chronic inflammatory process. Biohumoral findings indicated chronic autoimmune thyroiditis and primary hypothyroidism. Medical history, clinical findings, and personal and family predisposition to malignancy confirmed the need for accelerated additional diagnosis. Fine-needle aspiration biopsy was indicative of atypia of undetermined significance involving Hurthle cells, nuclear overlaps, anisocytosis, anisonucleosis, and the presence of nuclear incisions. Analyses performed after thyroidectomy pointed to the fibrous form of chronic thyroiditis, with suspected monoclonal proliferation of histiocytic and/or lymphoid cells. Immunohistochemical findings confirmed Hashimoto's thyroiditis and LCH. As the postoperative course was favorable, the patient was prescribed L-thyroxine replacement therapy, along with continuous and systematic monitoring for histiocytosis. **Conclusion.** Histiocytosis should be suspected more often, given the high incidence of autoimmune thyroid disease in adulthood. A timely LCH diagnosis largely determines the outcome.

Key words:
diagnosis, differential; histiocytosis, langerhans-cell; histological techniques; immunohistochemistry.

Apstrakt

Uvod. Histiocitoza Langerhansovih ćelija (HLĆ), hematopoetska neoplazma, predstavlja klonsku proliferaciju Langerhansovih dendritskih ćelija. Detaljan klinički pregled ponekad je presudan za otkrivanje retkih bolesti odraslog doba, kao što je HLĆ sa prisutnom autoimunskom bolešću štitaste žlezde. **Prikaz bolesnika.** Žena stara 43 godine prvi put se javila na pregled kod endokrinologa zbog bolova i otoka prednjeg dela vrata, praćenog umorom i malaksalošću. Inspekcijom i palpacijom utvrđen je uvećan desni režanj štitaste žlezde, izuzetno čvrste konzistencije, bolno osetljiv pri palpaciji. Ehosonografskim pregledom zapažen je uvećan desni režanj štitaste žlezde, nejasno ograničen od okolnog tkiva, sa izrazito nehomogenim parenhimom, smanjenom ehogenošću anteriornog aspekta i izraženom hipoehogenošću posteriornog aspekta parenhima štitaste žlezde, prožet fibroznim trakama i kalcifikacijama. Viđena je pseudonodularno izmenjena struktura levog režnja štitaste žlezde, sa karakteristikama hroničnog zapaljenskog procesa. Biohumoralni nalaz je ukazivao na hronični autoimunski tiroiditis i primarnu hipotireozu. Anamneza, klinički nalaz, lična i porodična sklonost ka malignitetu zahtevali su ubrzanu dopunsku dijagnostiku. Rezultat aspiracione biopsije tankom iglom odgovarao je atipiji neodređene značajnosti sa Hurthleovim ćelijama, nuklearnim preklapanjima, anizocitozom, anizonukleozom i prisustvom nuklearnih useka.

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Patohistološki nalaz nakon tireoidektomije odgovarao je fibroznoj formi hroničnog tiroiditisa, sa sumnjom na postojanje monoklonalne proliferacije histiocitnih i/ili limfoidnih ćelija. Imunohistohemijski nalaz potvrdio je Hashimoto tiroiditis i HLĆ. Postoperativni tok prošao je bez komplikacija i bolesnici je uvedena supstituciona terapija L-tiroksinom, uz nastavak kontinuiranog i sistemskog praćenja u pogledu histiocitoze. **Zaključak.** Na HLĆ treba češće posumnjati s obzirom na visoku učestalost autoimunske bolesti štitaste žlezde u odraslom životnom dobu. Pravovremena dijagnoza HLĆ u velikoj meri određuje ishod lečenja.

Ključne reči:
dijagnoza, diferencijalna; langerhansove ćelije, histiocitoza; histološke tehnike; imunohistohemija.

Introduction

Langerhans cell (LC) histiocytosis (LCH), as a hematopoietic neoplasm, is a rare granulomatous disease characterized by the proliferation of mononuclear dendritic cells (DC) in certain tissues and organs with an incidence of 4.0−5.4 per million individuals [1].

LCH can be unifocal or multifocal, whereby classification is based on the involvement of specific organs or organ systems. The diagnosis is confirmed by electron microscopy or immunohistochemical (IH) reactivity of histiocytes to CD1a and/or S-100 proteins [2]. The International Association for Histiocytosis has developed a risk prognostic system according to the prevalence, functional disorder severity, and age. According to these criteria, histiocytosis is divided into several clinical stages, with category I signifying low risk of multifocal histiocytosis, category II and III denoting moderately aggressive multifocal histiocytoses related to scores 1 and 2, respectively, and category IV comprising multifocal aggressive histiocytoses such as Letterer-Siwe disease, i.e., score 3 [3].

Case report

A 43-year-old overweight female patient was admitted to the clinic due to front neck pain and swelling accompanied by fatigue and malaise that have persisted for two months without febrile episodes or local signs of inflammation. The patient was unaware of any other ailments and had regular menstrual cycles. Her medical history revealed uterine cervical conization, pathohistologically (PH): cervical intraepithelial neoplasia (CIN)2 (high grade squamous intraepithelial lesion – H-Sil) and CIN1 (low grade squamous intraepithelial lesion – L-Sil), and obesity, along with the family history of thyroid disease, breast malignancy, lung malignancy, cardiovascular pathology, and obesity. During the physical examination, the patient did not exhibit any alterations in the state of consciousness or orientation and was afebrile, with a normal respiratory rate at rest, but was cyanotic without evident peripheral lymphadenopathy.

No visible pathological venous or arterial pulsations were present on neck examination, but further assessments revealed an enlarged and extremely firm right thyroid lobe that was excessively sensitive to palpation. The thorax was cylindrical and respiratory movements were normal. Auscultation revealed normal breath sounds without accompanying pathological phenomena; arterial tension was 120/75 mmHg, and electrocardiography (ECG) recorded sinus rhythm, with a frequency of 70 beats per minute, and nonspecific changes of ST segments and T wave, without rhythm and conduction disturbances. The abdomen was soft and insensitive to palpation; the liver was of normal size and consistency; the spleen was nonpalpable, while renal percussion was negative on both sides. No edemas or varicose veins were visible in the extremities, and the dorsal pedal pulses were symmetrically palpable. After the examination, an ultrasound of the thyroid gland was performed, and surgical treatment was advised, along with additional diagnostics, fine-needle aspiration biopsy (FNAB) of the right thyroid lobe under ultrasound control.

Except for pathological values of thyroid-stimulating hormone (TSH): 11.7 uIU/mL [reference range (RR) 0.27–4.20 uIU/mL], adrenocorticotropic hormone (ACTH): 30.7 pg/mL (RR < 15 pg/mL), anti-thyroid peroxidase (anti-TPO) antibodies > 1,000 IU/mL (RR < 34 IU/mL), and anti-thyroglobulin (anti-TG) antibodies: 122.0 IU/mL (RR < 115 IU/mL), other blood test results (complete blood count, biochemistry) were within their respective RRs. The control ACTH value was within the RR – 10.5 pg/mL.

Echosonographic findings of the thyroid gland (Figure 1 A–D) pointed to the enlarged right thyroid gland lobe, insufficiently demarcated from the surrounding tissues. It was characterized by pronounced parenchyma inhomogeneity, reduced echogenicity of the anterior, and pronounced hypoechogenicity of the posterior region, permeated with fibrous bands and calcifications The left thyroid gland lobe exhibited pseudonodular formations indicative of a chronic inflammatory process.

A fine needle biopsy (FNB) findings corresponded to atypia of undetermined significance (AUS) with the presence of lymphocytic thyroiditis according to the Bethesda classification (hypercellular smear, lymphocytes, Hurthle cells, nuclear overlap, anisocytosis, anisonucleosis, and the presence of nuclear incisions). In accordance with the cytological examination results, the patient was referred for surgical intervention, which was uneventful, with a favorable postoperative course.

FNAB was of exceptional importance. It was performed after the first clinical examination, followed by surgical treatment, PH verification, and additional immunohistochemistry, and thus the diagnosis of an early phase of histiocytosis (unifocal). Following the diagnosis and surgical treatment, L-thyroxine treatment was continued as a substitutional therapy for post-surgical hypothyroidism, with constant and systematic monitoring of the pathological and clinical course of histiocytosis.

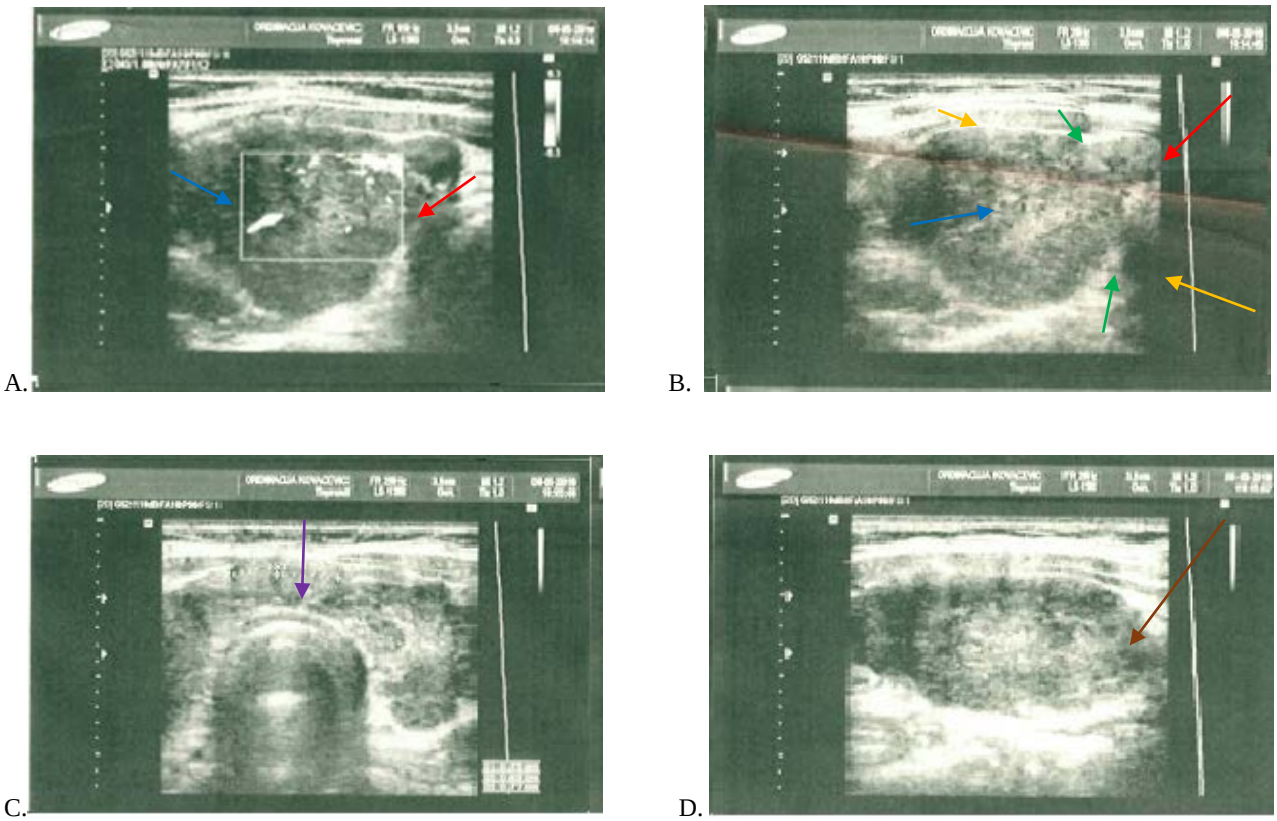

Fig. 1 – An echocardiogram of the thyroid gland: A) and B) the right lobe (indicated by red arrows); the right lobe has unclear boundaries (yellow arrows) from the surrounding tissue, heteroechogenic parenchyma with pronounced hypoechogenicity (marked with blue arrows) and calcifications (marked with green arrows) in the posterior aspect; C) The isthmic part (indicated by purple arrow); D) The left lobe (indicated by brown arrow) is pseudonodularly altered.

However, as PH findings corresponded to the fibrous form of chronic thyroiditis (Figures 2–4), the monoclonal proliferation of histiocyte and/or lymphoid cells could not be ruled out; hence, additional IH examination was indicated.

IH findings corresponded to Hashimoto's thyroiditis and LC tumor, i.e., histiocytosis. Regarding IH findings, LCs showed positive staining of S-100 protein and CD1a, whereby their negative reaction to cytokeratins, thyroglobulin, and TTF1 helped distinguish LCH from epithelial neoplasms of the thyroid gland (Figures 5–7).

In some cases, the infiltrative nature of these cells may indicate the proliferation of hematopoietic cells. Leukemias and lymphomas are diagnosed differently, and although LCs often exhibit poor diffuse LCA (CD45) staining, B and T lymphocyte markers are negative in the case of LCH. Even though S-100 positivity may raise suspicion of melanoma, LCs show negative staining of very specific melanoma markers such as HBM-45 and MART-1.

The final diagnosis was established as follows: tumor affecting the right thyroid gland lobe, autoimmune chronic thyroiditis, and primary hypothyreosis.

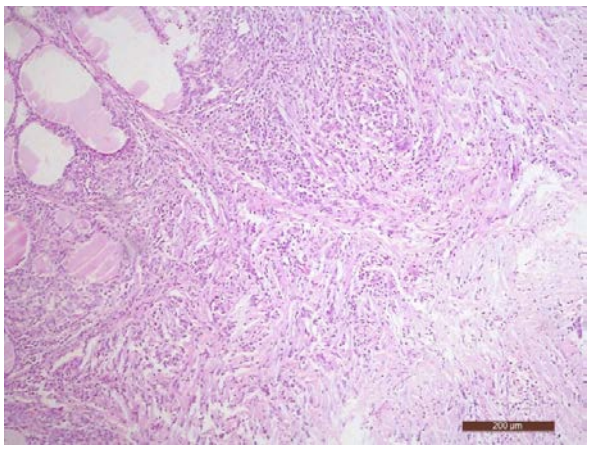

Fig. 2 – Reduced glandular tissue of thyroid gland with signs of oxyphilic metaplasia (hematoxylin and eosin staining, ×50).

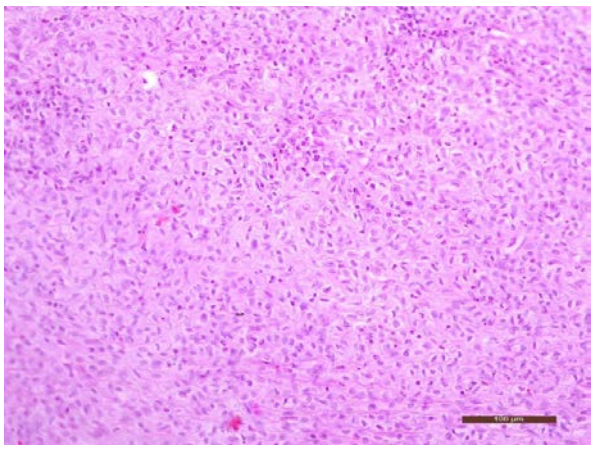

Fig. 3 – Langerhans cell (LC) histiocytosis composed of characteristic reniform irregular-border LC with interspersed eosinophils (hematoxylin and eosin staining, ×400).

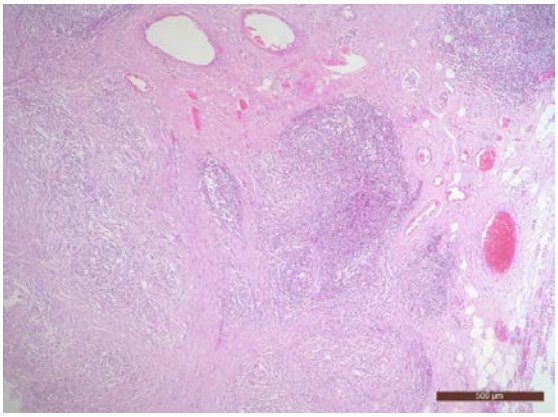

Fig. 4 – Langerhans cell histiocytosis stroma with signs of fibrosis, dense lymphocytic infiltrate, and formation of lymphoid follicles (hematoxylin and eosin staining, ×200).

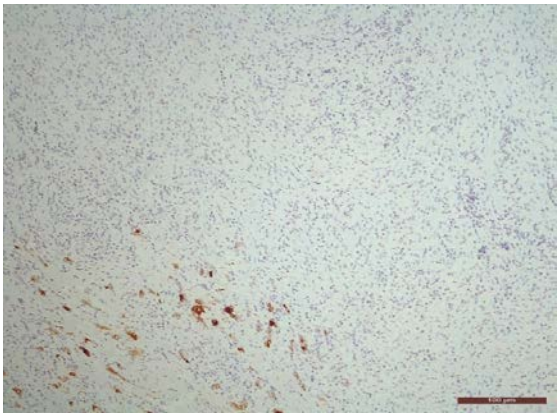

Fig. 5 – Lack of thyroglobulin expression in Langerhans cell histiocytes, with few entrapped thyrocytes that are positive for the applied immunohistochemical (IH) marker (thyroglobulin IH staining, ×200).

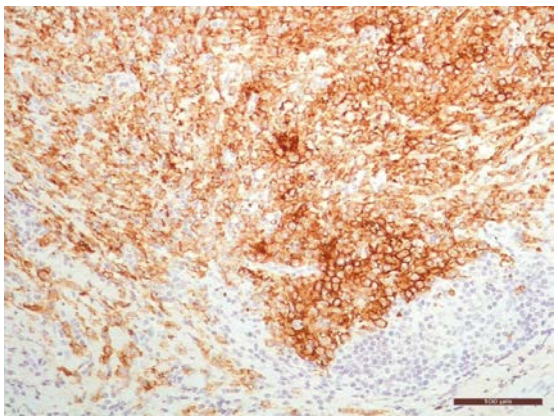

Fig. 6 – Diffuse and strong positivity of CD1a marker in Langerhans cells, with lack of expression for the applied marker in surrounding lymphocytes and thyrocytes (CD1a immunohistochemical staining, ×200).

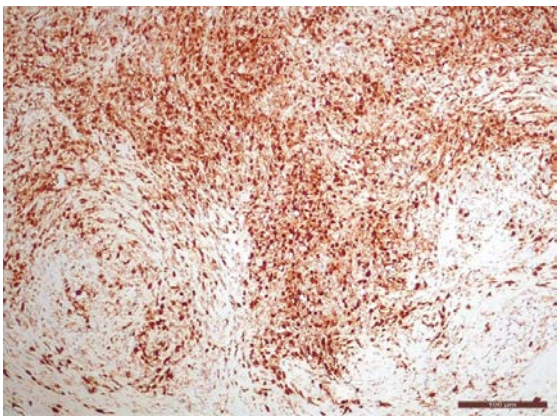

Fig. 7 – Positive expression of S-100 protein in Langerhans cells, with the lack of immunoreactivity of surrounding thyrocytes and lymphocytes (S-100 immunohistochemical staining, ×200).

The therapy ordered was L-thyroxine (Euthyrox) 100 μg tablet daily.

Guided by the IH findings, since histiocytosis may be a multifocal disease, in addition to commencing L-thyroxine replacement therapy, the patient underwent an additional functional examination of the pituitary gland along with an oncological examination.

Laboratory findings six months after the surgery and histiocytosis diagnosis showed normal values of leukocytes, hemoglobin, mean corpuscular volume, and platelets. Hormonal status showed normal values of follicle-stimulating hormone, luteinizing hormone, prolactin, ACTH, cortisol, TSH, and free thyroxine due to L-thyroxine therapy.

Chest computed tomography (CT) after surgery revealed the presence of three cystic changes in the lung parenchyma on the right side and one micronodule 4 mm in diameter in both lobes.

Abdominal and pelvic CT showed normal findings without any signs of pathological changes.

Follow-up examination 10 months after surgical treatment showed normal abdominal ultrasound findings, with biochemical markers within their respective reference values. A 6-month follow-up was scheduled, along with regular five-year-long monitoring by oncologists and endocrinologists.

Discussion

LCH lesions comprise large histiocytes with abundant cytoplasm and eosinophils, along with the proliferation of mononuclear DC with local and diffuse infiltration. Infiltrates are most commonly found in bone marrow, bones, lungs, endocrine glands, liver, and skin. LCs are characterized by rod-like cytoplasmic organelles (Birbeck granules), the so-called DC, expressing surface glycoproteins (CD11) and langerin (CD207), both of which are bound to the major histocompatibility complex of classes 1 and 2 [4]. LCH cells also possess Birbeck granules, but differ in shape from LCs in that they are rounded and have no dendritic extensions, and express CD1a, CD207, and S-100 proteins at the molecular level, but do not express markers that possess mature DC, such as CD83 [5]. More than 50% of cases involve *BRAF* mutations [6].

It has been considered that the *BRAF* V600E mutation in LCH could lead to papillary thyroid carcinoma by creating

a microenvironment that is appropriate for neoplastic transformation [7]. Most mutations activate signaling enzymes that result in the activation of extracellular signals by kinase. Given the significant clinical responses to the use of rapidly accelerated fibrosarcoma family inhibitors in patients with LCH and *BRAF* mutations, these mutations are likely authentic disease drivers in LCH. The *BRAF* mutation stimulates *via* RAS/RAF/MEK/ERK signaling pathway, which leads to constitutive transcription of genes involved in different cellular responses. Although histiocytosis mainly affects children and is mostly multisystemic, it also occurs in adults and can be isolated or multifocal. Only a small number of cases have been described in the literature, mostly pertaining to isolated thyroid gland histiocytosis [8, 9], which is associated with nearly 100% survival [10]. FNAB of the thyroid gland is crucial in cytological diagnosis, as it contributes to the distinction between benign and malignant processes in the distorted structure of the thyroid gland. Diagnostic puncture of the unusually altered thyroid gland, as well as parts affected by autoimmune disease, provides important information related to rare pathological changes in thyroid cells. Some cytomorphologic features of the LCH may be associated with thyroid diseases such as chronic lymphocytic thyroiditis and papillary thyroid cancer.

It typically affects bones, lungs, skin, hypothalamus, and the posterior thyroid gland lobe. Physical examination usually reveals an enlarged thyroid gland, as was the case with our patient. Although elevated antithyroglobulin antibodies are typically reported in the literature, antithyroid antibodies may also be elevated, as in our case. In some patients, LCH was initially misdiagnosed as poorly differentiated thyroid carcinoma. On the other hand, several authors noted an association between LCH and thyroid cancer in adults [11–13]. Compared to pituitary involvement, thyroid LCH is much rarer and usually occurs in adults. Thyroid function can be in the euthyroid range or be indicative of primary hypothyroidism, as in our case [14]. Most adults diagnosed with isolated thyroid LCH are only treated surgically, even though chemo- and radiotherapy can also be advised in some cases. The most optimal therapy mode is determined based on the disease severity and progression, i.e., involvement of high- or low-risk organs. Therapeutic options include conservative follow-up therapy, hormone substitution, cytokine inhibitors, organ transplantation, and stem cell therapy [15–17].

Cases of histiocytosis in the lungs that have been previously reported mainly indicated solitary localization, with a prevalence of 1 in 200,000 [18]. For our patient, continued monitoring was required, as lung CT revealed three cystic changes on the right side of the lung parenchyma. In adults, LCH with orbital histiocytosis is rare. Bermingham et al. [19] described a 45-year-old man with a right medial node that persisted for five weeks and a patient in whom a biopsy of the lesion showed histiocytic cells, basophils and LCs, posterior uveitis, vasculitis, and neurological symptoms stemming from the presence of LCH cells in the cerebrospinal fluid [20]. Chronic autoimmune thyroiditis is the most common cause of acquired primary hypothyroidism. It has an autoimmune etiology in which heredity plays a role. Moreover, autoimmunity has been proven based on PH findings of diffuse lymphocytic infiltration of the thyroid gland. It is an aberrant expression of class II major histocompatibility complex molecules, which present the antigen to CD4 T lymphocytes specific for thyroid antigens. The disease is eight times more common in women than men, and its incidence increases with age.

Conclusion

Histiocytosis is a rare disease, especially in adulthood, but autoimmune thyroid disease is quite common in adolescents as well as adults. Therefore, it is essential to take a detailed medical history and conduct a thorough clinical examination during the patient's first visit and consider histiocytosis in the differential diagnosis of autoimmune thyroid disease. Furthermore, unusual clinical presentation and/or ultrasound features of autoimmune thyroiditis should lead to prompt FNB and additional IH examination (when medically indicated).

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