

# Cytological, histopathological and immunological aspects of autoimmune thyroiditis: a review

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## Abstract

Autoimmune thyroiditis (AT) is a disease that may be associated with many other autoimmune endocrine and non-endocrine disorders. This disease is mediated by both humoral and cellular mechanisms and it is the result of combined effects of human leukocyte antigen (HLA) class II genes and non-HLA genes polymorphisms. The clinical course of AT is variable and may be characterized by spontaneous remission and by irreversible thyroid insufficiency as the consequence of atrophic and fibrous transformation of the thyroid gland in other cases. In this paper, the AT's etiology and immunological mechanism along with its cytological and histopathological features are reviewed in order to increase our understanding about the mechanism involved in pathogenesis of this disease and to open new directions of investigations that will be useful in a better clinical practice.

**Keywords:** autoimmune thyroiditis, cytology, histopathology.

## Introduction

Autoimmune thyroiditis (AT) is a term used to describe different pathogenetic forms of chronic lymphocytic thyroiditis. The disease is the main cause of acquired hypothyroidism and may be associated with many other autoimmune endocrine and non-endocrine disorders [1, 2]. It is considered to be a genetic disease caused by the combined effects of human leukocyte antigen (HLA) class II genes and non-HLA genes polymorphisms [3].

There is no internationally accepted classification of autoimmune thyroid diseases, as their development is not yet fully understood. Costa *et al.* (1989) [4] consider AT a histological diagnosis that can be subdivided into chronic lymphocytic thyroiditis, if only lymphocytic infiltration is present, and Hashimoto's thyroiditis, if atrophy and eosinophilic changes in thyroid cells and fibrosis are also seen.

Taken into consideration the thyroid function and histological findings, Mizukami *et al.* (1992) classifies chronic lymphocytic thyroiditis into four categories: (a) oxyphilic chronic thyroiditis, which includes the classical group of Hashimoto's thyroiditis; (b) mixed chronic thyroiditis, in which the inflammatory infiltrate is more reduced than in the first category, the fibrosis in

the interstice is more discrete, and the clinical picture ranges from euthyroidism to hypo- or hyperthyroidism; (c) hyperplastic chronic thyroiditis, which corresponds to Basedow–Graves disease and progresses with hyperfunction; (d) focal chronic thyroiditis, with a discrete focal lymphocytic inflammatory infiltrate, unaccompanied by germinative foci or oxyphilic metaplasia, and in which the thyroid status is euthyroidism [5].

Pal'tsev *et al.* (1993) [6] subdivided AT into primary ones (Hashimoto's thyroiditis, chronic lymphocytic thyroiditis, chronic atrophic thyroiditis) and the secondary ones, which are the manifestation of the organ-specific autoimmune diseases of the thyroid.

Tomer & Huber (2009) [7] affirmed that autoimmune thyroid diseases (AITDs) include Graves' disease (GD) and Hashimoto's thyroiditis (HT), both of them being characterized pathologically by infiltration of the thyroid by T- and B-cells, reactive to thyroid antigens, biochemically by the production of thyroid autoantibodies, and clinically by abnormal thyroid functions (hyperthyroidism in GD and hypothyroidism in HT). These researchers admitted that there are additional variants of AITDs that include post-partum thyroiditis, drug-induced thyroiditis, thyroiditis associated with polyglandular autoimmune syndromes.

Later, Weetman classifies chronic AT into six groups: (a) goitrous (Hashimoto's thyroiditis), characterized by goiter, lymphocytic infiltration, fibrosis, and thyroid-cell hyperplasia, (b) atrophic thyroiditis (primary myxedema), with atrophy and fibrosis, (c) juvenile thyroiditis, characterized by lymphocytic infiltration, (d) postpartum thyroiditis associated with small goiter and some lymphocytic infiltration, (e) silent (painless) thyroiditis, with small goiter and some lymphocytic infiltration, (f) focal thyroiditis, which is found in the 20% of people at autopsy [8].

### ✚ Etiological insights into autoimmune thyroiditis

The exact etiology of AT is not fully known [7], but it is considered to be multifactorial. The probability of developing an AT is determined by environmental, genetic, constitutional factors, and the associated disorders [1, 2].

Environmental factors play a critical role in the occurrence of immune system thyroiditis in the susceptible population because of the immune system activation. Some of these variables, such as dietary iodine from iodized salt, dairy products, eggs, iodized wholesome added substances, chocolate, and a few multivitamins, act in a particular way. Iodine increases the antigenicity of thyroglobulin and thus exacerbates thyroiditis [9].

Iodine has a vital role in thyroid hormone genesis and can trigger thyroid immunity in various ways. In the early phases of immune system formation, high quantities of iodine are quickly oxidized by thyroid peroxidase, which has a specific role in the iodination process and oxidation of iodotyrosine to iodothyronine. This procedure produces autoreactive products such as lipoic acid and oxygen reactive metabolites. Due to the oxidation of the lipid and protein segments of the cell layer, this oxidative species harm and initiate necrosis of the thyroid cells. Second, the iodination of thyroglobulin intensifies its immunogenicity by making new epitopes or uncovering "mysterious" epitopes that are not expressed in iodine deficiency conditions. These may account for the protective role of iodine deficiency contributing to lessened thyroid autoimmunity and in increased thyroid autoimmunity in areas with extreme iodine intake [9]. Increased iodinated thyroglobulin may encourage antigen take-up and handling by antigen-presenting cells. Also, iodine itself could lead to intercellular adhesion molecule-1 (ICAM-1) expression in the thyrocytes [9]. Thus, iodine overconsumption exacerbates local immune inflammation by immunological and biochemical patterns. The majority of ecological elements like vitamin D or selenium insufficiencies, medical or accidental exposure to ionizing radiation, medications (beta-blockers, Lithium, Amiodarone, Phenylbutazone, glucocorticoids, Furosemide, Carbamazepine and antiretroviral drugs) can affect thyroid autoimmunity [7, 10]. The higher number of AT cases in women is most likely due to the influence of sex steroids. Estrogen use is associated with a lower risk, and pregnancy with a higher risk for developing hyperthyroidism [11].

### ✚ Immunological mechanisms of autoimmune thyroiditis

AT is a model of both cell and humoral immune disorder. A noteworthy site of autoreactivity is inside the

thyroid organ itself. The antigenic structure of immune system reactivity can trigger viral infection that has protein sequence similar to the thyroid organ itself, or a self-protein that is introduced as an antigen. The target antigens of the thyroid antibodies are colloid constitutive protein – thyroglobulin (Tg), the enzyme necessary for thyroid hormone synthesis – thyroid peroxidase (TPO),  $\text{Na}^+/\text{I}^-$  symporter (NIS) and thyrotropin receptor (or TSH-R – thyroid-stimulating hormone receptor) [12].

In Hashimoto's thyroiditis, there is a broad invasion of the thyroid by lymphocytes, plasma cells and macrophages. The thyroid follicular cells are destroyed to a variable degree. The rest of the healthy cells will become hyperplastic and will undergo oxyphilic metaplasia and will become Askanazy or Hürthle cells or oncocytic cells, *i.e.*, large cells with abundant eosinophilic granular cytoplasm because of accumulation of altered mitochondria. All types of thyroid autoimmunity are related to a lymphocytic invasion of the thyroid, which will generate both T- and B-cell-interceded autoreactivity. Thyroid autoreactive lymphocytes may also be found in other places like lymph nodes and bone marrow [13].

High amounts of antithyroid antibodies are the principal perceptible sign of immune response in autoimmune thyroiditis.

TPO is the key thyroid enzyme catalyzing both the iodination and coupling reaction for the synthesis of thyroid hormone. It oxidizes iodide ions to iodine atoms that will be incorporated into thyroglobulin for the production of thyroxine (T4) or triiodothyronine (T3), the thyroid hormones. TPO is membrane bound and found in the cytoplasm and in high concentration on the apical microvillar surface of thyrocytes [14].

Anti-TPO autoantibodies, included in IgG class 1 and IgG4 subclasses, are found in over 90% of patients with autoimmune hypothyroidism and Graves' disease and are the predominant antibodies in autoimmune hypothyroidism. The serum values of TPO antibodies should be correlated with intracellular interferon-gamma (IFN- $\gamma$ ) and tumor necrosis factor-alpha (TNF- $\alpha$ ) levels in thyroid-infiltrating lymphocytes and thyrocytes. High levels of these two cytokines, which are involved in humoral and cellular immunity, correlated well with severe AT [15].

Thyroglobulin is a 660-kDa glycoprotein made out of two similar subunits of 330 kDa each. It is synthesized in the thyroid follicular cells, released in the follicular lumen, and deposited there as a colloid substance. Each thyroglobulin has around 100 tyrosine residues, and a quarter of them are iodinated. These residues couple with iodine to form T3 and T4 [14].

Thyroglobulin autoantibodies, polyclonal and mainly of IgG class, are found in less than 60% of patients with lymphocytic thyroiditis and 30% of Graves' disease patients [14, 16].

TSH-R is the prime autoantigen in Graves' disease and atrophic thyroiditis, being located on the basal surface of the thyroid follicular cells [16]. In Basedow's disease, thyroid-stimulating antibodies bind to the receptor and stimulate the thyroid cell to produce excessive amounts of thyroid hormones resulting in hyperthyroidism. In patients with atrophic thyroiditis, the major antibody is the TSH-R blocking antibody. After binding to the receptor, this

antibody blocks the binding of TSH to its receptor, thus preventing thyroid cell stimulation. Therefore, the thyroid hormone output diminished, the thyroid gland becomes atrophic, and a clinical state of hypothyroidism appears [17, 18].

NIS, a transmembrane glycoprotein which transports two sodium cations ( $\text{Na}^+$ ) for each iodide anion ( $\text{I}^-$ ) into the cell, mediates the uptake of iodide into follicular cells of the thyroid gland as the first step in the synthesis of thyroid hormone. NIS is another major thyroid auto-antigen. Around 33% of Basedow's disease cases and 15% of Hashimoto's cases contain antibodies that restrain *in vitro* NIS iodide take-up [12, 17].

### ✚ Ultrasonographic findings in autoimmune thyroiditis

The first basic diagnostic problem arises in patients with only minimally or moderately hypoechogenic pattern. If we do not notice this form in a euthyroid patient, our report will have false positive results in the case of a healthy thyroid. Alternatively, if hypoechogenicity is noticed in a euthyroid patient, we can consider the possibility of an underlying autoimmune thyroid disease and thus have the chance to recognize hypothyroidism later.

The other issue is caused by local hypoechogenicity. This is the most complicated differential diagnosis issue in thyroid ultrasound of a thyroid nodule. An accurate diagnosis requires the corroboration of clinical, laboratory and cytological data, and, in certain cases, of follow-up results and, in surgically treated patients, possibly with the macroscopic and microscopic pathological findings. There are some essential criteria that allow differentiation. Unlike the thyroid nodule, in autoimmune thyroiditis, most of the times, the limits of the lesion are not geometrical, but the hypoechogenic area is connected by echonormal parenchyma not yet affected by thyroiditis. Moreover, less than four hypoechogenic lesions are uncommon to autoimmune thyroiditis.

When the main echostructure of the thyroid is not echonormal but rather insignificantly or decently hypoechogenic, then it is a higher possibility to found an AT. It also important to analyze the volume of the thyroid as most of the time this gland is enlarged as a multinodular goiter. This means that a normal looking thyroid gland in the presence of numerous hypoechogenic lesions makes the diagnosis of AT as being very probable. However, when we have doubts, antibodies and hormone-levels on follow-up investigations will resolve the problem because there is a well-known close correlation between anti-thyroid peroxidase autoantibodies levels and hypoechogenicity [19, 20].

### ✚ Cytological and histological features of autoimmune thyroiditis

#### Fine-needle aspiration cytology

On smears, the typical image of AT includes lymphoid cells with follicular epithelial cells with varying degrees of degenerative changes and insignificant colloid in the background (Figures 1–6).

The presence of atypical cells is a common feature of autoimmune thyroiditis. Both thyroiditis itself and the dysfunction may cause anisonucleosis and even pleomorphism. The latter may have the appearance of an anaplastic carcinoma [21].

A serious differential diagnosis problem is caused by the presence of inclusion and grooves. The positive predictive value of these intranuclear figures is limited in the case of thyroiditis, therefore the diagnosis of a concomitant papillary carcinoma is a great challenge for the cytopathologist in certain cases [21].

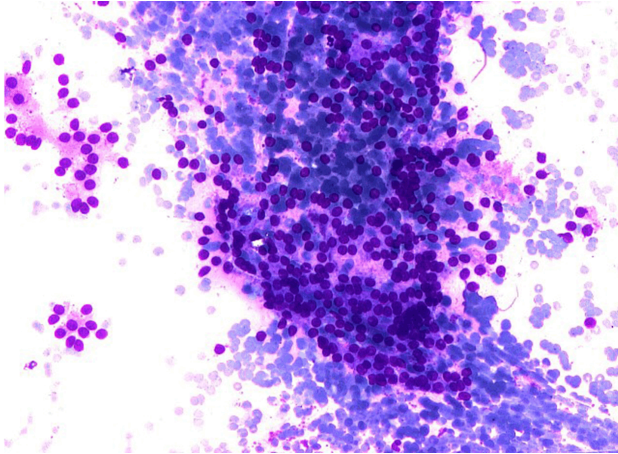
The presence of naked follicular cells in great number, without structure formation, may be challengeable as to the origin of these cells. They might be misjudged as little lymphocytes. The presence or absence of lymphoblast and the absence or abundant presence of colloid is of great help. The other problem is focal AT close to nodular goiters. In these cases, only scarce lymphocytes are available on the smear. Oxyphilic changes may be seen in a small number of follicular cells. The problem is that the term central autoimmune thyroiditis may be effectively used only in histopathological reports.

#### Histopathological principles and dilemmas

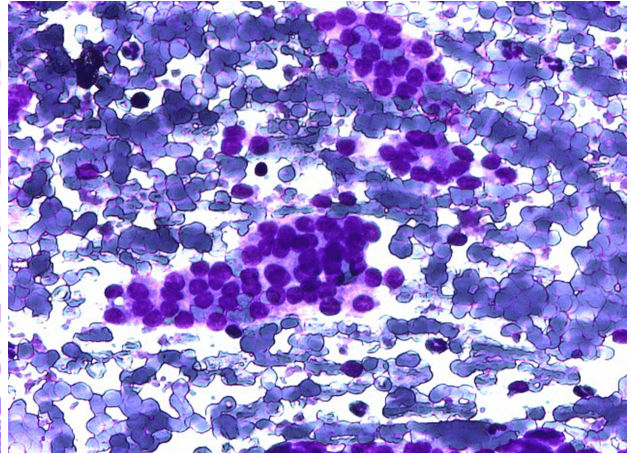
From the morphological point of view, Hashimoto's thyroiditis contains a rich lymphocytic infiltrate predominantly disposed in follicles with germinal center formation. Lymphocytes are predominantly T-cells. Thyrocytes with oxyphilic metaplasia, oncocytes, and large Hürthle cells with abundant eosinophilic cytoplasm may be noticed in their immediate vicinity. Hürthle cells could show moderate nuclear atypia, nuclear hyperchromasia or macronucleoli. As the disease progresses, fibrosis increases and numerous collagen fiber could be noticed in the interstice. As such, with disease progression, a multinodular appearance developed (Figures 7–9). The lymphoid nodular infiltrate is polymorphic and includes small amounts of T-lymphocytes, laid out on the margins of lymphoid follicles, along with numerous B-lymphocytes and rare macrophages (Figures 10–13). The mitotic rate is high in the germinative centers (Figure 14). When the inflammatory infiltrate is abundant, one should rule out a possible progression of the disease towards mucosa-associated lymphoid tissue (MALT) lymphoma, in which case the profile of the lymphoid tumor infiltrate is monoclonal. Focal chronic thyroiditis, which can coexists with other diseases [2], reveals discrete chronic inflammatory cell infiltrate, without lymphoid follicles or germinative center. Histological features of oxyphilic metaplasia are discrete. Fibrosis is reduced (Figures 15 and 16). The inflammatory cell infiltrate is polymorphic, made up of T-cells, B-cells, and randomly scattered macrophages (Figures 17 and 18).

Unfortunately, thyroid nodules have a similar frequency in both autoimmune and non-autoimmune thyroiditis patients. The major issue is to diagnose a thyroid nodule in a hypoechogenicity, which may cover a hypoechoic thyroid nodule. This can be done by thorough grayscale investigation and by differentiation between the vascularization of the nodular and the non-nodular part of the thyroid [22, 23].

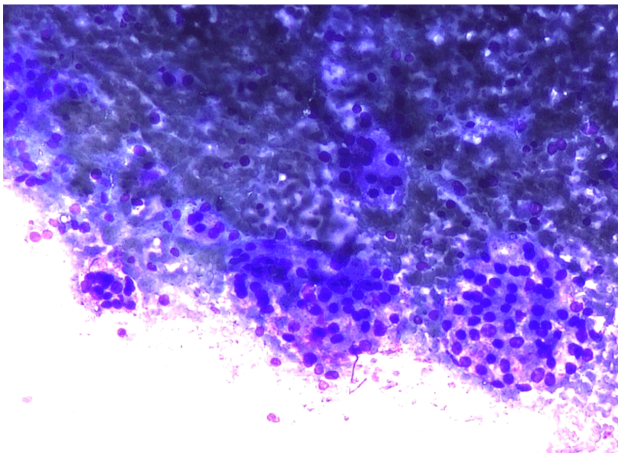




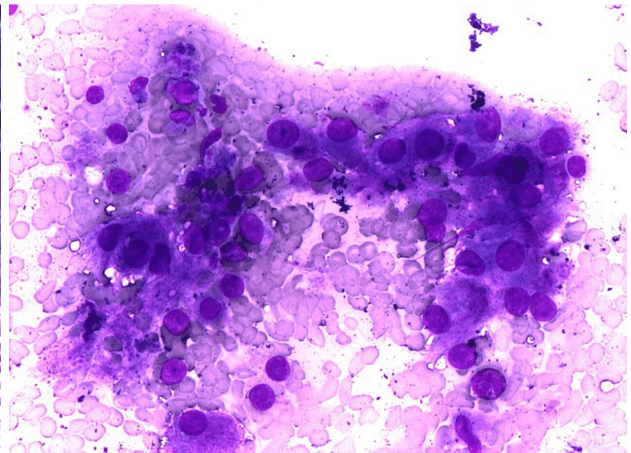
**Figure 1 – Chronic lymphocytic thyroiditis. Thyrocytes with monomorphous round nuclei and basophilic cytoplasm along with lymphocytes [May-Grünwald-Giemsa (MGG) staining,  $\times 100$ ].**



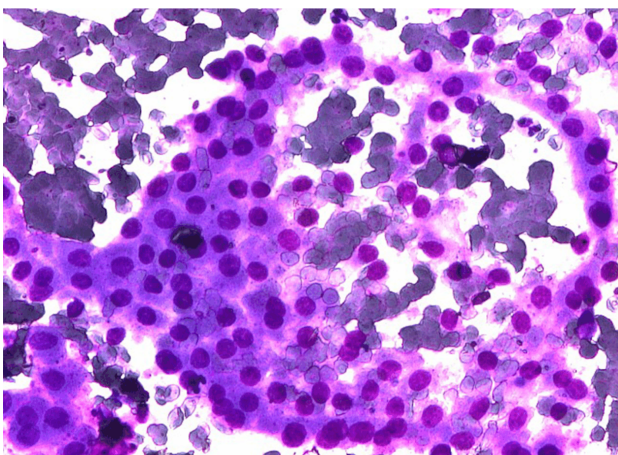
**Figure 2 – Chronic lymphocytic thyroiditis. Thyrocytes and diffuse lymphoid infiltrate (MGG staining,  $\times 200$ ).**



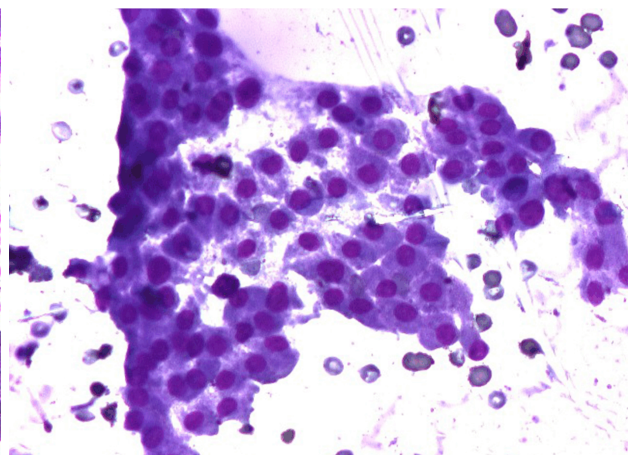
**Figure 3 – Basedow's disease. Abundant hematic background and sheets of follicular cells. Thyrocytes have discrete nuclear irregularities (MGG staining,  $\times 100$ ).**



**Figure 4 – Basedow's disease. Group of thyrocytes with nuclear irregularities (MGG staining,  $\times 200$ ).**

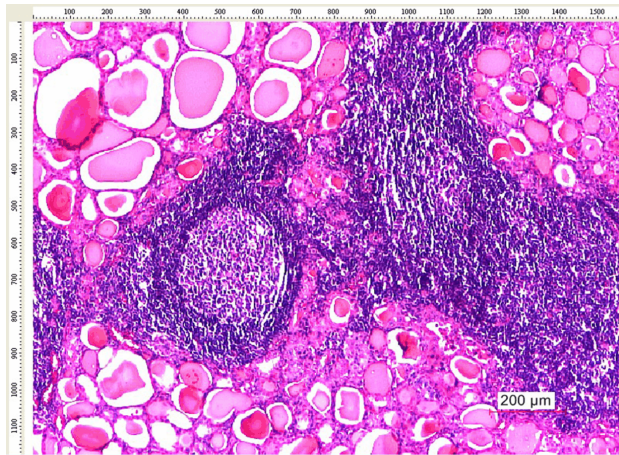


**Figure 5 – Hürthle-cell (oncocytic) tumor. Sheet of oncocytes with nuclear irregularities and eosinophilic cytoplasm (MGG staining,  $\times 200$ ).**

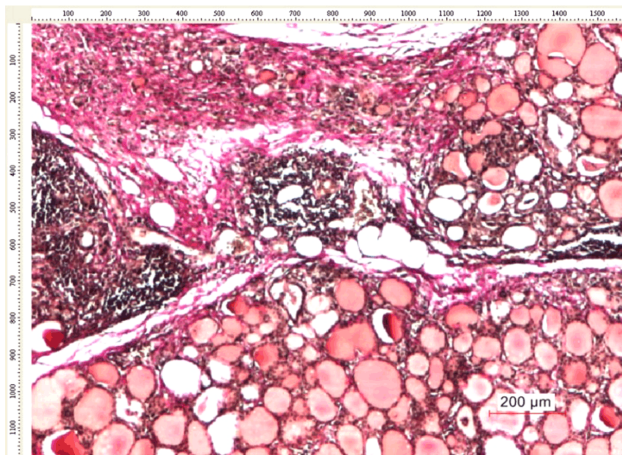


**Figure 6 – Hürthle-cell (oncocytic) tumor. Sheet of oncocytes with large size, distinct cell borders, eosinophilic cytoplasm, and large nucleus with irregularities (MGG staining,  $\times 200$ ).**

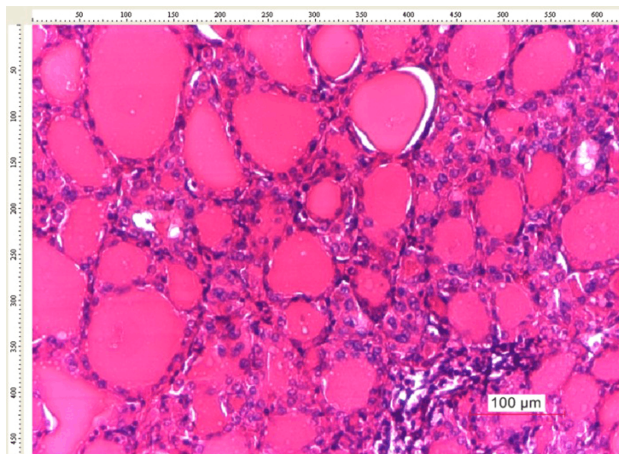




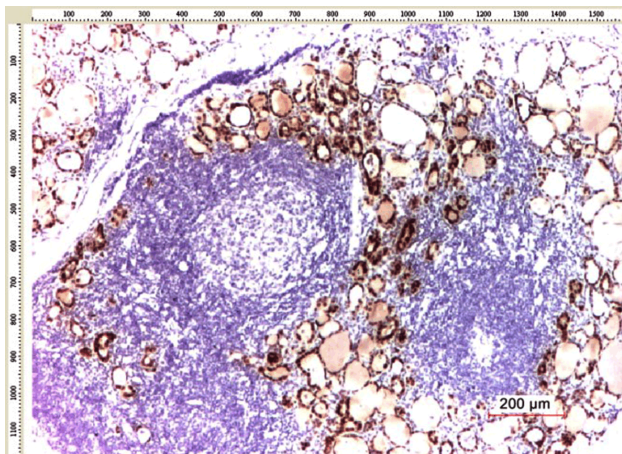
**Figure 7 – Hashimoto's thyroiditis. Prominent lymphoid follicles with germinal centers, oxyphilic metaplasia of the epithelium, and abundant colloid [Hematoxylin–Eosin (HE) staining,  $\times 40$ ].**



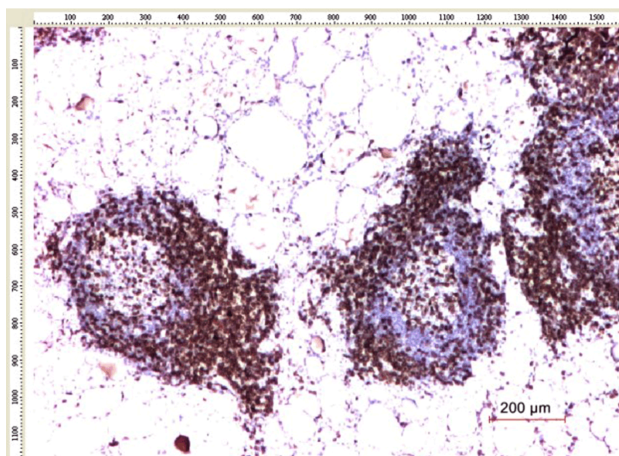
**Figure 8 – Hashimoto's thyroiditis. Increased interlobular fibrosis produced the atrophy of the follicles nearby [Van Gieson (VG) staining,  $\times 40$ ].**



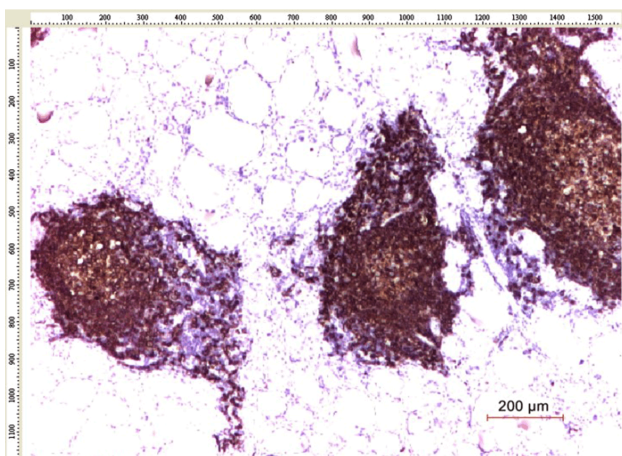
**Figure 9 – Hashimoto's thyroiditis. Oxyphilic metaplasia with discrete differences in nuclear size (HE staining,  $\times 100$ ).**



**Figure 10 – Hashimoto's thyroiditis. Lymphocytic infiltrate with germinal centre. Immunopositivity for TTF1 in oxyphilic areas (Immunostaining, anti-TTF1 antibody,  $\times 40$ ).**

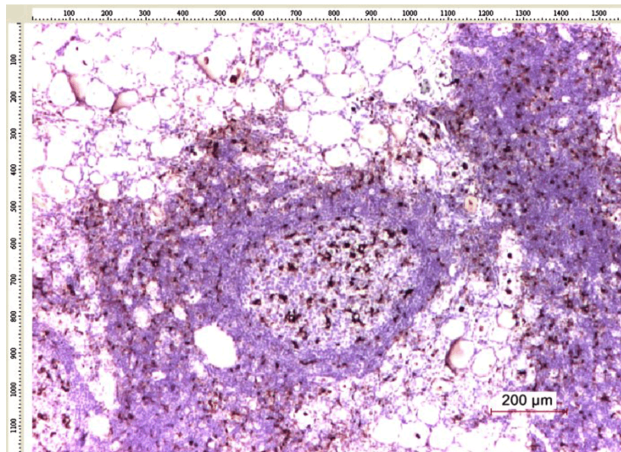


**Figure 11 – Hashimoto's thyroiditis. T-lymphocytes showed immunopositivity for CD3 in the periphery of lymphoid follicles (Immunostaining, anti-CD3 antibody,  $\times 40$ ).**

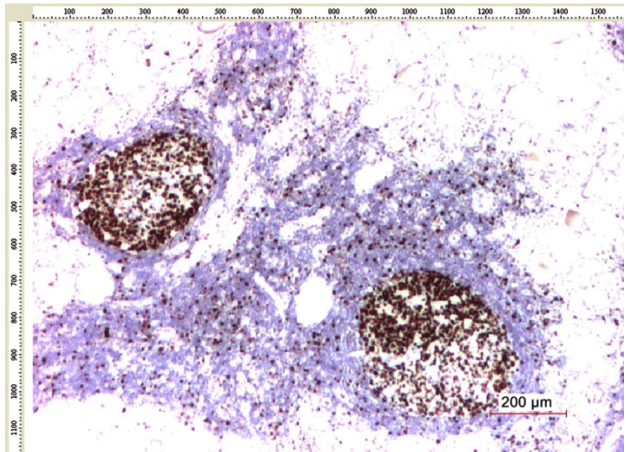


**Figure 12 – Hashimoto's thyroiditis. B-lymphocytes showed immunopositivity for CD20 inside the lymphoid follicles (Immunostaining, anti-CD20 antibody,  $\times 40$ ).**

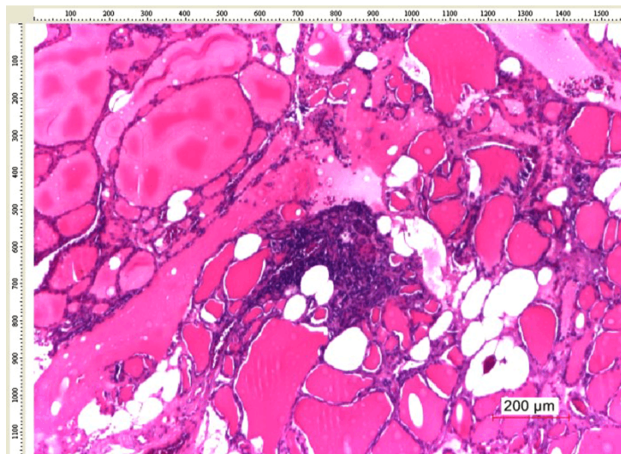




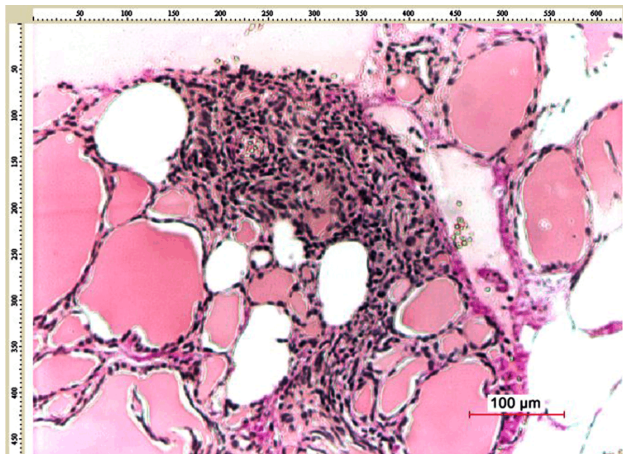
**Figure 13 – Hashimoto's thyroiditis. Immunopositivity for CD68 highlights the presence of macrophages in lymphoid follicles and in the diffuse lymphoid tissue. (Immunostaining, anti-CD68 antibody, ×40).**



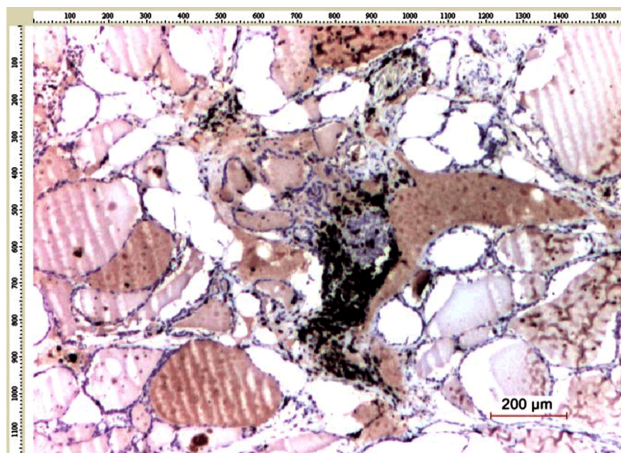
**Figure 14 – Hashimoto's thyroiditis. Intense nuclear positivity inside the germinal centre of lymphoid follicles (Immunostaining, anti-Ki67 antibody, ×40).**



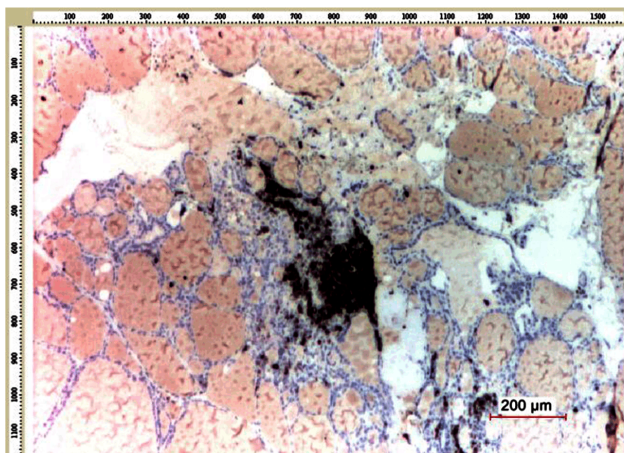
**Figure 15 – Focal chronic thyroiditis. Focal aggregates of lymphocytes in, inter- or intra-lobular fibrous tissue (HE staining, ×40).**



**Figure 16 – Focal chronic thyroiditis. Patchy lymphocytic inflammation with small lymphocytes (VG staining, ×100).**



**Figure 17 – Focal chronic thyroiditis. T-lymphocytes showed immunopositivity for CD3 in the chronic inflammatory cell infiltrate (Immunostaining, anti-CD3 antibody, ×40).**



**Figure 18 – Focal chronic thyroiditis. B-lymphocytes showed immunopositivity for CD20 in the chronic inflammatory cell infiltrate (Immunostaining, anti-CD20 antibody, ×40).**

## ☐ Differential diagnosis of autoimmune thyroiditis

### Hashimoto's thyroiditis versus Basedow's disease

From a clinical point of view, it is easy to differentiate between Hashimoto's thyroiditis and Basedow's disease, even though both of them are considered by some authors to be autoimmune thyroid diseases. The problematic cases are those with only slight hyperthyroidism [24].

Some clinicians cannot decide if a patient has or not a thyroiditis, as they cannot decide whether to prescribe the patient a particular thyroid drugs or not. It must be kept in mind that these patients typically have a diffuse enlargement of the thyroid [25].

It is vital to diagnose Hashimoto's thyroiditis due to its progression to hypothyroidism and to the fact that it requires long-term thyroxine supplementation. This is especially difficult, since there are two clinical types of a similar autoimmune thyroid disease.

In clinical practice, the progress of a hyperthyroid patient towards Basedow-Graves disorder takes years or even decades. The opposite is also possible, however just occasionally. Additionally, there is a higher risk of extranodal marginal B-cell lymphoma in patients with Hashimoto's thyroiditis [25] probably because the later is characterized by the presence of lymphoid follicles with germinal centers.

The incidence of carcinoma in patients with Hashimoto's thyroiditis ranges from 0.5% to 23.5% and this fact emphasizes the need for long-term follow-up. Fine-needle aspiration cytology smears of Hashimoto's thyroiditis reveals oxyphilic cells, invasion of follicles by lymphocytes/plasma cells and moderate amount of colloid in the background. In Basedow's disease, the smears have a hematic background, and there is negligible quantity of colloid, marginal vacuolization, the cells are round, with anisonucleosis and organized in groups, showing a follicular pattern, but, sometimes, there are some clinical cases when the smears are difficult to interpret [26].

However, Graves' disease – diffuse goiter with hyperthyroidism, ophthalmopathy, or both – is considered to be by some authors a related autoimmune thyroid disease but not autoimmune thyroiditis [27].

### Autoimmune thyroiditis versus de Quervain's thyroiditis

Subacute (de Quervain's) thyroiditis, which is a post-viral inflammation of the thyroid characterized by pain and tenderness, is not a form of AT [28]. There are some problems in distinguishing between autoimmune thyroiditis and de Quervain's thyroiditis. Most of the times, the cytological picture and the clinical information about the patient are clear enough. While an AT may give different clinical pictures, subacute thyroiditis has a deeply specific clinical picture in over 90% of the cases: fever, hard consistency and enlargement of the thyroid, and erythrocytes sedimentation rate exceed 60 mm/h. In some cases, it is exceptionally troublesome or even impossible to make a distinction between the two kinds of thyroiditis. If the clinical picture is clear (patient with either high titers of thyroid autoantibodies or a classical picture of subacute thyroiditis), the absence of typical

elements of the cytological picture is not important for the diagnosis [29].

### MALT lymphomas of the thyroid versus Hashimoto's thyroiditis

Primary thyroid MALT lymphoma is a rare subgroup of thyroid lymphoma, accounting for a quarter of all primary thyroid lymphomas [30]. MALT lymphomas of the thyroid have the same basis as Hashimoto's thyroiditis and this can lead to cytological differentiation difficulties. MALT lymphoma of the thyroid has a typical clinical appearance. The patient is usually over 60 years of age, the thyroid increases quickly (within two months) in size, acquires a hard consistency, and ultrasonography reveals a diffuse hypoechogenic design. These four components are rarely seen together in Hashimoto's thyroiditis as this disease may appear as a diffuse goiter that grows quickly in younger patients, but in the elderly, it is a gradually progressing illness. In those cases, when it is unrealistic to distinguish between the two conditions, immunocytochemical staining is mandatory [31].

### Hürthle-cell tumor versus Hashimoto's thyroiditis

In Hürthle-cell tumor, the enlarged nucleoli and the loosely arranged pattern of oncocytes with many dispersed cells are the characteristics of the lesion. The absence of nucleoli or of scattered cells supports a non-tumoral starting point. Despite these cytological signs, in the majority of the cases, we are not ready to make an obvious distinction between these two possibilities, and surgery is hence the most frequent treatment in order to make a decision [32]. The presence of a well-circumscribed lesion within an absolutely echonormal background rises the suspicion of a tumor, meanwhile a more hypoechogenic lesion is much less likely to be of a cancerous nature [33]. Two other vital parameters have to be analyzed: the changes in the size of the nodule and the changes in the sonographic appearance of the thyroid outside the nodule. Therefore, high titers of thyroid autoantibodies do not exclude the possibility of a concomitant Hürthle-cell tumor. However, the hard consistency of a nodule is a sign which rises the suspicion of a tumor [32, 34].

## ☐ Conclusions

Understanding the etiopathogenetic mechanisms, but also cytopathological features of autoimmune thyroiditis is particularly important for prompt therapeutic intervention necessary to prevent the effects of the disease.

### Conflict of interests

The authors do not have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of the manuscript.

## References

- [1] Jenkins RC, Weetman AP. Disease associations with autoimmune thyroid disease. *Thyroid*, 2002, 12(11):977–988.
- [2] Sava A, Dumitrescu G, Haba D, Hodorog D, Mihailov C, Şapte E. The Fahr syndrome and the chronic lymphocytic thyroiditis. *Rom J Morphol Embryol*, 2013, 54(1):195–200.



- [3] Kim EY, Shin CH, Yang SW. Polymorphisms of HLA class II predispose children and adolescents with type 1 diabetes mellitus to autoimmune thyroid disease. *Autoimmunity*, 2003, 36(3):177–181.
- [4] Costa A, Torchio B, Zoppetti G, Feyless E. What is meant today by Hashimoto's thyroiditis? *J Endocrinol Invest*, 1989, 12(5):355–356.
- [5] Mizukami Y, Michigishi T, Kawato M, Sato T, Nonomura A, Hashimoto T, Matsubara F. Chronic thyroiditis: thyroid function and histologic correlations in 601 cases. *Hum Pathol*, 1992, 23(9):980–988.
- [6] Pal'tsev MA, Zai'rat'iants OV, Vetshev PS, Tuntsova OI. [Autoimmune thyroiditis: pathogenesis, morphogenesis and classification]. *Arkh Patol*, 1993, 55(6):7–13.
- [7] Tomer Y, Huber A. The etiology of autoimmune thyroid disease: a story of genes and environment. *J Autoimmun*, 2009, 32(3–4):231–239.
- [8] Weetman AP. Chronic autoimmune thyroiditis. In: Braverman LE, Cooper D (eds). *Werner & Ingbar's the thyroid: a fundamental and clinical text*. 10<sup>th</sup> edition, Wolter Kluwer/Lippincott Williams & Wilkins, 2013, Philadelphia, 526.
- [9] Jensen E, Hyltoft Petersen P, Blaabjerg O, Hansen PS, Brix TH, Kyvik KO, Hegedüs L. Establishment of a serum thyroid stimulating hormone (TSH) reference interval in healthy adults. The importance of environmental factors, including thyroid antibodies. *Clin Chem Lab Med*, 2004, 42(7):824–832.
- [10] Sorodoc V, Sorodoc L, Ungureanu D, Sava A, Jaba IM. Cardiac troponin T and NT-proBNP as biomarkers of early myocardial damage in amitriptyline-induced cardiovascular toxicity in rats. *Int J Toxicol*, 2013, 32(5):351–357.
- [11] Whitacre CC. Sex differences in autoimmune disease. *Nat Immunol*, 2001, 2(9):777–780.
- [12] Czarnocka B. Thyroperoxidase, thyroglobulin, Na(+)/I(-) symporter, pendrin in thyroid autoimmunity. *Front Biosci (Landmark Ed)*, 2011, 16:783–802.
- [13] Prasad DV, Richards S, Mai XM, Dong C. B7S1, a novel B7 family member that negatively regulates T cell activation. *Immunity*, 2003, 18(6):863–873.
- [14] Iddah MA, Macharia BN. Autoimmune thyroid disorders. *ISRN Endocrinol*, 2013, 2013:509764.
- [15] Bossowski A, Harasymczuk J, Moniuszko A, Bossowska A, Hilczek M, Ratowski K. Cytometric evaluation of intracellular IFN- $\gamma$  and IL-4 levels in thyroid follicular cells from patients with autoimmune thyroid diseases. *Thyroid Res*, 2011, 4:13.
- [16] Adil A, Jafri RA, Waqar A, Abbasi SA, Matiul-Haq, Asghar AH, Jilani A, Naz I. Frequency and clinical importance of anti-Tg auto-antibodies (ATG). *J Coll Physicians Surg Pak*, 2003, 13(9):504–506.
- [17] Swain M, Swain T, Mohanty BK. Autoimmune thyroid disorders – an update. *Indian J Clin Biochem*, 2005, 20(1):9–17.
- [18] Szkudlinski MW, Fremont V, Ronin C, Weintraub BD. Thyroid-stimulating hormone and thyroid-stimulating hormone receptor structure-function relationships. *Physiol Rev*, 2002, 82(2):473–502.
- [19] Pedersen OM, Aardal NP, Larssen TB, Varhaug JE, Myking O, Vik-Mo H. The value of ultrasonography in predicting autoimmune thyroid disease. *Thyroid*, 2000, 10(3):251–259.
- [20] Tam AA, Kaya C, Üçler R, Dirikoç A, Ersoy R, Çakır B. Correlation of normal thyroid ultrasonography with thyroid tests. *Quant Imaging Med Surg*, 2015, 5(4):569–574.
- [21] Boi F, Lai ML, Marziani B, Minerba L, Faa G, Mariotti S. High prevalence of suspicious cytology in thyroid nodules associated with positive thyroid autoantibodies. *Eur J Endocrinol*, 2005, 153(5):637–642.
- [22] Loy M, Cianchetti ME, Cardia F, Melis A, Boi F, Mariotti S. Correlation of computerized gray-scale sonographic findings with thyroid function and thyroid autoimmune activity in patients with Hashimoto's thyroiditis. *J Clin Ultrasound*, 2004, 32(3):136–140.
- [23] Cornianu M, Stan V, Lazăr E, Dema A, Golu I, Tăban S, Vlad M, Faur A, Vărcuș F, Babău F. Evaluation of proliferation potential in thyroid normo-/hypofunctioning and hyperfunctioning nodules. *Rom J Morphol Embryol*, 2011, 52(2):545–553.
- [24] Ko HM, Jhu IK, Yang SH, Lee JH, Nam JH, Juhng SW, Choi C. Clinicopathologic analysis of fine needle aspiration cytology of the thyroid. A review of 1,613 cases and correlation with histopathologic diagnoses. *Acta Cytol*, 2003, 47(5):727–732.
- [25] MacDonald L, Yazdi HM. Fine needle aspiration biopsy of Hashimoto's thyroiditis. Sources of diagnostic error. *Acta Cytol*, 1999, 43(3):400–406.
- [26] Solymosi T, Toth GL, Bodo M. Diagnostic accuracy of fine needle aspiration cytology of the thyroid: impact of ultrasonography and ultrasonographically guided aspiration. *Acta Cytol*, 2001, 45(5):669–674.
- [27] Volpé R. Autoimmune thyroiditis. In: Braverman LE, Utiger RD (eds). *Werner and Ingbar's the thyroid: a fundamental and clinical text*. 6<sup>th</sup> edition, J.B. Lippincott, Philadelphia, 1991, 921–933.
- [28] Dayan CM, Daniels GH. Chronic autoimmune thyroiditis. *N Engl J Med*, 1996, 335(2):99–107.
- [29] Leung AKC, Hegde K. Hashimoto's thyroiditis simulating De Quervain's thyroiditis. *J Adolesc Health Care*, 1988, 9(5):434–435.
- [30] Pedersen RK, Pedersen NT. Primary non-Hodgkin's lymphoma of the thyroid gland: a population based study. *Histopathology*, 1996, 28(1):25–32.
- [31] Troch M, Woehrer S, Streubel B, Weissel M, Hoffmann M, Müllauer L, Chott A, Raderer M. Chronic autoimmune thyroiditis (Hashimoto's thyroiditis) in patients with MALT lymphoma. *Ann Oncol*, 2008, 19(7):1336–1339.
- [32] Stanciu M, Bera LG, Popescu M, Grosu F, Popa FL. Hashimoto's thyroiditis associated with thyroid adenoma with Hürthle cells – case report. *Rom J Morphol Embryol*, 2017, 58(1):241–248.
- [33] Barbu CG, Florin A, Neamțu MC, Avramescu ET, Terzea D, Miron A, Dănculescu Miulescu R, Poiană C, Fica S. Papillary thyroid carcinoma with anaplastic dedifferentiation in the lymph node metastasis – a rare form of presentation even for a tall cell variant. *Rom J Morphol Embryol*, 2015, 56(2):527–531.
- [34] Montone KT, Baloch ZW, LiVolsi VA. The thyroid Hürthle (oncocytic) cell and its associated pathologic conditions: a surgical pathology and cytopathology review. *Arch Pathol Lab Med*, 2008, 132(8):1241–1250.

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