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Review

Hashimoto thyroiditis: Clinical and diagnostic criteria

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ABSTRACT

Hashimoto thyroiditis (HT), now considered the most common autoimmune disease, was described over a century ago as a pronounced lymphoid goiter affecting predominantly women. In addition to this classic form, several other clinico-pathologic entities are now included under the term HT: fibrous variant, IgG4-related variant, juvenile form, Hashitoxicosis, and painless thyroiditis (sporadic or post-partum). All forms are characterized pathologically by the infiltration of hematopoietic mononuclear cells, mainly lymphocytes, in the interstitium among the thyroid follicles, although specific features can be recognized in each variant. Thyroid cells undergo atrophy or transform into a bolder type of follicular cell rich in mitochondria called Hürthle cell. Most HT forms ultimately evolve into hypothyroidism, although at presentation patients can be euthyroid or even hyperthyroid. The diagnosis of HT relies on the demonstration of circulating antibodies to thyroid antigens (mainly thyroperoxidase and thyroglobulin) and reduced echogenicity on thyroid sonogram in a patient with proper clinical features. The treatment remains symptomatic and based on the administration of synthetic thyroid hormones to correct the hypothyroidism as needed. Surgery is performed when the goiter is large enough to cause significant compression of the surrounding cervical structures, or when some areas of the thyroid gland mimic the features of a nodule whose cytology cannot be ascertained as benign. HT remains a complex and ever expanding disease of unknown pathogenesis that awaits prevention or novel forms of treatment.

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1. Definition

Hashimoto thyroiditis (HT) is a chronic inflammation of the thyroid gland initially described over a century ago but of still incompletely defined etiopathogenesis. It is now considered the most common autoimmune disease [1,2], the most common endocrine disorder [3], as well as the most common cause of hypothyroidism [4,5]. Based on the etiology, HT can be classified into primary and secondary forms (Table 1).

1.1. Primary

Primary HT is the most common form of thyroiditis and comprises the cases that do not currently have identifiable causes. Primary HT encompasses a clinico-pathological spectrum of six main entities: classic form [6], fibrous variant, IgG4-related variant [7], juvenile form [8], Hashitoxicosis, and painless (or silent) thyroiditis, the latter occurring either sporadically or in the post-partum [9] (Table 1). Clinically, the most common manifestation is an enlargement of the thyroid gland (goiter), with or without hypothyroidism. Pathologically, the common denominator to all variants is the marked lymphocytic infiltration of the thyroid. Primary HT can occur in isolation or associate with other autoimmune diseases (such as type 1 diabetes mellitus and Sjögren syndrome), or other thyroid diseases. In this later group, particularly noteworthy is the association with papillary thyroid cancer, which ranges from 0.5 to 30% of the cases (reviewed in [10] and discussed in [6]).

1.2. Secondary

Secondary HT is of more recent description. It includes the forms where an etiologic agent can be clearly identified. It is more commonly iatrogenic and induced by the administration of immunomodulatory drugs. For example, administration of interferon-alpha for the treatment of hepatitis C viral infection is well known to induce, or exacerbate the appearance of thyroiditis [11]. During the last decade, the explosion of the cancer immunotherapy field has brought to light a series of immune related adverse events including thyroiditis, which has been described for example after the administration of monoclonal antibodies that block CTLA-4 [12], or cancer vaccines [13].

HT is a prototypic example of organ-specific autoimmune diseases and often associates in the same patient (co-morbidity) or family (familial aggregation) with other autoimmune diseases [14], suggesting a shared genetic basis. Indeed, HT [15] and systemic lupus erythematous [16] were the first two diseases where a genetic basis was shown for autoimmunity in the early 1970s, in particular associated with MHC class II genes. Despite four decades of studies, however, only a few susceptibility genes have been identified for HT, each making a small contribution to the disease phenotype and through unknown mechanisms [17].

Table 1
Clinico-pathological spectrum of Hashimoto thyroiditis.

Primary forms
Isolated
Classic form
Fibrous (or fibrosing) variant
IgG4-related variant
Juvenile form
Hashitoxicosis variant
Painless (or silent, or subacute lymphocytic) thyroiditis
Sporadic
Post-partum
Associated with
Other thyroid diseases (papillary thyroid cancer)
Other autoimmune diseases
Secondary forms to the administration of
Interferon-alpha for hepatitis C infection
CTLA-4 blocking antibody for solid tumors
Cancer vaccines

2. History and epidemiology

HT was first described in Japan in 1912 by Dr. Hakaru Hashimoto, who examined the thyroid specimens of four middle-age women who had undergone thyroidectomy because of compressive symptoms [18]. The history and evolution of HT have been recently reviewed in an article written to celebrate the centennial of its description [6] and will not be repeated here. Suffices it to say that HT was considered a rarity until the late 1950s and is now the most frequent autoimmune disease, with an incidence of about 1 case per 1000 persons per year [19]. The prevalence is 8 cases per 1000 when estimated from a review of published articles [1], and 46 cases per 1000 when estimated from the biochemical evidence of hypothyroidism and thyroid autoantibodies in subjects participating to the 3rd National Health and Nutrition Examination Survey [20]. Women are at least 8 times more likely than men to have HT, which is also more common in Whites and Asians than in African-Americans. Smoking and iodine are the two environmental factors that have been studied more extensively in relation to HT. Smoking has a surprisingly beneficial effect on HT, in contrast to the detrimental effect it has on Graves disease [21]. Tobacco smoking decreases the levels of thyroid autoantibodies as well as the risk of hypothyroidism, findings that have been consistently reported in nine epidemiological studies [22–30]. The mechanisms underlying this protective effect of smoking on HT are unknown. We have previously shown that anatabine, a minor alkaloid of tobacco, was capable of ameliorating disease in an experimental model of autoimmune thyroiditis, likely by acting on the inflammasome pathway of innate immunity [31]. Increased levels of dietary iodine are associated with more cases of HT. In one study of three regions in China with low, adequate, or excessive iodine intake, the cumulative incidence of HT was 0.2%, 1%, and 1.3%, respectively [32,33]. Similar results were reported in Denmark by comparing data before (1997–98) and after (2008–10) the introduction of a mandatory program for iodization of salt. Addition of iodine increased the occurrence of antibodies to thyroperoxidase and the incidence of hypothyroidism [34]. The mechanism underlying the pro-immunogenic effect of iodine in humans remains to be explained [35], but in mice the incorporation of iodine increases the immunogenicity of thyroglobulin [36,37].

3. Pathological features

The pathological lesions of HT involve both the interstitium around the thyroid follicles and the thyroid cells themselves, and have distinct features in the various forms.

The *classic form* of HT, which features an enlarged, grayish, and firm thyroid gland, is characterized by the interstitial infiltration of hematopoietic mononuclear cells, mainly composed of lymphocytes with some plasma cells and macrophages. Lymphocytes organize into true lymphoid follicles (called tertiary or ectopic), with topological compartmentalization of T cells in the cortex and B cells in the center, often displaying clear germinal centers. Lymphocytes come in close contact with the thyrocytes and are believed to be the mediators of thyrocyte destruction. Occasionally, lymphocytes penetrate into the cytoplasm of the thyrocyte, a phenomenon known as emperipolesis. The interstitium also contains variable degrees of fibrosis, which imparts to the thyroid a firm consistency. Lesions of the thyrocyte vary in intensity from one part of the gland to another. In some areas, thyrocytes are atrophic and encircle small follicles that contain minimal colloid. In other areas, thyrocytes are enlarged and bold, acquiring a distinctive appearance as to be called Hürthle cells (or oxyphilic cells or oncocytes) [38]. Hürthle cells are thyrocytes that have increased size, hyperchromatic

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nucleus and, most characteristically, a cytoplasm that stains intensively pink with eosin because it is filled with mitochondria [39].

The *fibrous* (*or fibrosing*) *variant* of HT is characterized by an enlarged, hard, and lobulated thyroid. The term has created confusion through the years because interstitial fibrosis is also seen in Riedel's thyroiditis, IgG4-related thyroiditis, as well as the classic form of HT. In the fibrous variant, however, the fibrosis is dominant (in contrast to what seen in the classic form and the IgG4-related variant), still remaining contained within the thyroid capsule (thus distinguishing with Riedel's thyroiditis, which instead causes adhesion to the surrounding structures). Fibrosis forms dense keloid-like bands that subvert the normal thyroid architecture and impart to the gland a lobular appearance, so much so that some of these patients are considered to have thyroid nodules and thus undergone fine needle aspiration. The interstitium also contains chronic inflammatory mononuclear cells, often organized into lymphoid follicles. Thyrocyte lesions not only resemble those of the classic form, with follicular atrophy and Hürthle cell metaplasia, but also feature squamous cell metaplasia in some areas. The fibrous variant represents less than 10% of all HT forms, and was already described in one of the four patients initially reported by Dr. Hashimoto in 1912 [18]. It was later redefined by Katz and Vickery in 1974 [40]. In later disease stages and in older patients, the fibrous variant manifests as idiopathic myxedema, where the thyroid gland is reduced to a small fibrotic bud, almost unrecognizable if not for its fronto-tracheal location.

The *IgG4-related variant* of HT was initially reported by Li et al. in Japan in 2009 [7], and later refined [41,42]. Pathologically, it is characterized by a pronounced lympho-plasmacytic infiltrate that, in contrast to that observed in the other variants of HT, is enriched for IgG4-producing plasma cells (>20 cells per high powered field) [42]. Interstitial fibrosis is clearly seen, although not as dominantly as in the fibrous variant, and often associated with obliterative phlebitis [42].

The remaining three variants of HT (juvenile thyroiditis, Hashitoxicosis, and painless thyroiditis) rarely require thyroidectomy, so that information on their pathological appearance is scanty. They have similar histologic features and share the thyroidal lymphocytic infiltration of the classic (goitrous) form HT. However, germinal center formation is rare or absent, follicular atrophy absent or actually replaced by hyperplasia, Hürthle cell metaplasia less extensive, and fibrosis milder.

4. Diagnosis

The diagnosis of Hashimoto thyroiditis is currently established by a combination of clinical features, presence of serum antibodies against thyroid antigens (mainly to thyroperoxidase and thyroglobulin), and appearance on thyroid sonogram. Thyroid uptake of radioactive iodine and cytological examination of thyroid aspirate are used more rarely.

4.1. Clinical features

Clinical features include both local and systemic manifestations, with peculiarities specific to the individual forms of HT. Local manifestations originate from compression of the cervical structures that are anatomically close to the thyroid gland, and include dysphonia (from involvement of the recurrent laryngeal nerve), dyspnea (from restriction of the trachea), and dysphagia (from impingement upon the esophagus). Systemic manifestations originate from loss of function of the thyroid gland and subsequent primary hypothyroidism. Given the profound and broad action of thyroid hormones on most organs and tissues, the signs and symptoms of hypothyroidism are numerous and variable.

4.1.1. Gastrointestinal system

Constipation is the most common complaint reported by hypothyroid patients. Peristalsis is markedly decreased and can lead to occasional pseudo-obstruction or ileus. Gallbladder hypotonia and alterations in bile composition may result in increased bile duct stone formation.

4.1.2. Skin and appendages

The skin of hypothyroid patients is typically dry, cold, yellowish, and thickened. These changes are sustained by accumulation of hydrophilic mucoproteins (such as hyaluronic acid) in the derma with consequent myxedema, as well as by the atrophy of sweat glands. The hairs are coarse and fall off. The nails are thin and frail.

4.1.3. Cardiovascular system

Bradycardia and decreased amplitude of cardiac waves on the electrocardiogram are classic signs of hypothyroidism. Bradycardia, decreased ventricular contractility, and increased peripheral resistance contribute to an overall reduced cardiac output. Cardiomegaly may be present and accompanied by pericardial effusion. Coronary artery disease is common in patients with hypothyroidism, likely due to the effect of thyroid hormones on lipid metabolism. Hypothyroidism, in fact, decreases cholesterol and LDL cholesterol levels, well-known atherogenic factors.

4.1.4. Skeletal muscles

Muscles appear falsely hypertrophic due to the myxedematous infiltration of the connective tissue. Their contraction and relaxation times are delayed, and can be a source of pain and cramps.

4.1.5. Pulmonary system

Common respiratory abnormalities are bradypnea and hypoxia. They originate from obstruction of the upper airways by the enlarged soft tissues, respiratory muscle weakness, decreased chest wall and lung compliance, increased capillary permeability, and pleural effusion. Respiratory failure can occur in patients with myxedematous coma.

4.1.6. Hematopoietic system

Anemia is common in hypothyroidism. It can be normocytic (due to a reduction in the renal secretion of erythropoietin), hypochromic and microcytic (due to a defect in iron absorption), or megaloblastic (due to gastric atrophy with B12 vitamin malabsorption).

4.1.7. Reproductive system

Oligomenorrhea and/or menometrorrhagia are frequent. Menstrual cycles are often anovulatory due to impaired conversion of estrogen precursors. When hypothyroidism is present during pregnancy it has been associated with an increased rate of miscarriage.

4.1.8. Urinary system

Liquid retention from decreased glomerular filtration is described.

4.1.9. Neuro-psychiatric system

Inability to concentrate, memory loss, and depression are reported by HT patients. More controversial is the issue of the so-called Hashimoto encephalopathy, initially reported in 1966 [43]. It presents insidiously with truncal ataxia, mimicking spino-cerebellar degeneration [44], although paroxysmal dyskinesia has also been reported [45]. Patients then develop cognitive impairments in episodic memory, attention, executive function, and visuo-spatial ability but maintain naming ability [46]. There are no definite diagnostic criteria, so that the diagnosis relies on the exclusion of other causes of encephalopathy in a patient with HT. A Japanese group has reported the presence of antibodies against the N-terminus of alpha-enolase as a useful diagnostic marker [44], but the findings await confirmation. Some patients respond well and recover when treated with glucocorticoids; others experience continuous deterioration [47].

The *classic form* of HT typically presents during the 5th decade of life and is overwhelmingly more common in women (Table 2). The thyroid

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Table 2
Key features of the clinico-pathologic forms of Hashimoto thyroiditis.

	Classic	Fibrous	IgG4-related	Juvenile	Hashitoxicosis	Post-partum
Peak age (years) at onset	40–60	60–70	40–50	10–18	40–60	20–40
F:M ratio	12:1	10:1	3:1	6:1	5:1	N/A
Thyroid function at presentation	Normal in most patients	Hypothyroidism	Hypothyroidism	Normal/subclinical hypothyroidism	Hyperthyroidism	Hyperthyroidism or hypothyroidism
Sonographic findings	Hypoechogenicity	Hypoechogenicity with nodularity	Pronounced hypoechogenicity	Hypoechogenicity	Hypoechogenicity	Hypoechogenicity
24 h RAI uptake	Variable	Decreased	Unknown	Variable	Increased	Decreased
Fibrosis	Yes	Severe	Yes	No	No	No

gland is enlarged and firm. Most patients (approximately 75%) are euthyroid at diagnosis, whereas the remaining minority show a range of dysfunctions from subclinical hypothyroidism (defined by elevated TSH levels but with thyroid hormones still within the normal range) to overt hypothyroidism.

The *fibrous variant* of HT is also more common in women but of older ages. It also presents goiter, which is however often symptomatic. The thyroid is lobulated, imparting the appearance of bona fide thyroid nodules. Most patients are hypothyroid and require prompt thyroid hormone replacement. In older ages this fibrous form evolves into a severe form of thyroid atrophy that manifests clinically as idiopathic myxedema. The thyroid gland is not palpable, and patients have the symptoms of hypothyroidism, which are however more difficult to identify given the overlap with the manifestations of aging.

The *IgG4-related variant* of HT, like the classic form, occurs most commonly during the 5th decade of life but at a younger age [42]. Like for other IgG4-related diseases, men are frequently affected, decreasing the extremely high female to male ratio of the classic form to 3:1. The IgG4-related variant tends to have a more rapid and aggressive course, so that many patients are still found to have subclinical hypothyroidism despite being replaced with synthetic thyroid hormones. Thyroid autoantibodies reach the highest values [41].

The *juvenile variant* is the form of HT presenting before 18 years of age, with a mean age at presentation of 11 years [48]. It is more common in females, although with a smaller female to male ratio (Table 2). Most children have goiter but are usually asymptomatic [49]. At the time of diagnosis, 43% of the children are euthyroid, 24% have subclinical hypothyroidism, 21% overt hypothyroidism, 9% overt hyperthyroidism, and 3 subclinical hyperthyroidism [48,50]. The natural history is variable, with remission, recurrence, and evolution into permanent hypothyroidism all being described.

The *Hashitoxicosis variant*, initially described by Fatourechi in 1971 [51], has the clinical features of Graves hyperthyroidism and the pathological appearance of HT. The initial hyperthyroid phase is virtually indistinguishable from Graves's disease, including the elevated thyroid uptake of radioactive iodine and the presence of thyroid-stimulating immunoglobulins. The hyperthyroidism however, is transient, and after a period of 3 to 24 months [52] it evolves into permanent hypothyroidism.

Painless (or silent) thyroiditis is a lymphocytic inflammation of the thyroid gland that can occur sporadically or, more commonly, within 12 months after delivery. The two forms are indistinguishable except for the relation of the latter form to pregnancy, so that is called post-partum thyroiditis. Painless thyroiditis tends to be more prevalent in areas of higher dietary iodine intake [53], and is scholarly described as having a triphasic pattern consisting of an initial phase of thyrotoxicosis, followed by hypothyroidism, and then recovery. Post-partum occurs in about 8% of all pregnancies [9], although estimates vary depending on the population studied and the frequency of monitoring [54]. Thyrotoxicosis usually appears two to five months after delivery and lasts for about a month. It is mild and rarely requires therapy, but beta-blockers can be used. Since the mechanism of the increased serum levels of thyroid hormones is not their excessive production by the thyroid gland (hyperthyroidism) but rather the release of preformed hormones from the thyroid follicles caused by the destructive inflammation, antithyroid drugs are not indicated. This phase is followed by a hypothyroid phase, again lasting about two to 6 months. Its symptoms are subtle and patients can be mistaken as having post-partum depression [55]. Most women (>80%) then recover a normal thyroid function within one year after delivery. Permanent hypothyroidism is more likely in women with multiple pregnancies and history of post-partum thyroiditis [56].

4.2. Thyroid antibodies

Circulating antibodies to thyroperoxidase are now considered the best serological marker to establish a diagnosis of HT. They are found in about 95% of HT patients but are rare in healthy controls. In post-partum thyroiditis they also have a unique predictive role since pregnant women who have thyroperoxidase antibodies at the beginning of pregnancy are at greater risk of developing hypothyroidism in the first year after delivery, as well as long-lasting thyroid impairment. The titer of thyroperoxidase antibody correlates well with the number of autoreactive lymphocytes infiltrating the thyroid [57] and the degree of sonographic hypoechogenicity.

Antibodies to thyroglobulin, the most abundant protein of the thyroid gland, are less sensitive (positive in only 60–80% of HT patients) and less specific (positive in a greater proportion of healthy controls) than thyroperoxidase antibodies. Nevertheless, they have their own utility [58]. Although they are requested together with thyroperoxidase antibodies by engrained clinical practices and fluctuate in parallel after therapeutic interventions, the two thyroid antibodies correlate poorly. For example, using a cohort of 145 patients with newly diagnosed autoimmune hypothyroidism Carlé et al. noted that the thyroglobulin and thyroperoxidase autoantibodies had a significant ($p < 0.001$) and positive correlation but a low (0.11) r-squared value [59]. We analyzed for this review the 2007–2008 NHANES survey, which tested the two antibodies in over 6200 serum samples, and obtained a similarly low r-squared value of 0.21. In addition, analysis of approximately 5000 serum samples tested by the Johns Hopkins Immunology Laboratory independently of the clinical suspicion showed a significant ($p < 0.0001$) and positive (beta of 0.83 WHO units) correlation between thyroperoxidase and thyroglobulin antibodies, but with an r-squared value of just 0.46 (Fig. 1). In this unselected laboratory dataset, 3424 of 4977 samples (69%) were negative for both antibodies, 642 (13%) positive for both, 704 (14%) positive only for thyroperoxidase antibodies, and 206 (4%) positive only for thyroglobulin antibodies (Fig. 1).

Overall these findings suggest to us that thyroglobulin and thyroperoxidase antibodies represent two different aspects of the autoimmune response against the thyroid gland. Thyroglobulin antibodies could reflect a more initial (innate) type of immune response, whereas thyroperoxidase antibodies could characterize a later adaptive immune response, a sort of immune escalation [60]. In line with this hypothesis, thyroglobulin antibodies should be the ones present at disease onset. In fact, in mouse models of spontaneous autoimmune thyroiditis thyroglobulin antibodies precede the appearance of thyroperoxidase

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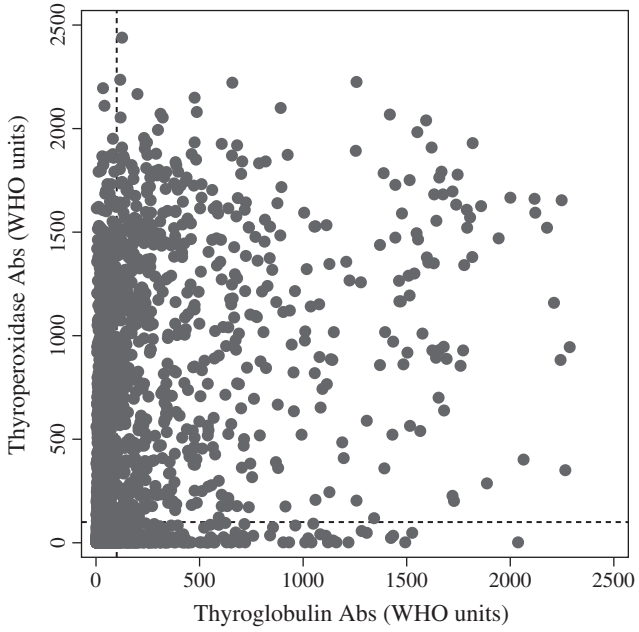

Fig. 1. Correlation between thyroperoxidase and thyroglobulin antibodies performed in 4977 serum samples received by The Johns Hopkins Immunology Laboratory between Sep 10, 2008 and May 7, 2013.

antibodies [61]. In human autoimmune diseases, disease onset is rarely observable. For HT, for example, when most patients receive a clinical diagnosis they already had the disease for a minimum of 7 years [62]. In humans, thus, it has to be expected that thyroperoxidase antibodies should be more prevalent and at higher titers than thyroglobulin antibodies, and this is what has been reported [59].

4.3. Thyroid ultrasonography

Neck ultrasound has become the most commonly used imaging tool in patients with thyroid diseases [63]. In HT, it characteristically shows reduced echogenicity. The normal thyroid gland, being composed of thyroid follicles of various dimensions, scatters the ultrasounds significantly so that the lobes appear bright. In HT, on the contrary, thyroid follicles are destroyed and replaced by small lymphocytes so that the echogenicity of the thyroid parenchyma markedly decreases, becoming similar to that of the surrounding strap muscles. There are unique features in the various forms of HT. For example, in the IgG4-related variant the hypoechogenicity is more pronounced [41], and in the fibrous variant it is accompanied by irregularity and nodularity given the conspicuous deposition of collagen fibers. Thyroid ultrasound can also inform and quantify the volume of the thyroid gland. The field of thyroid ultrasound is expanding rapidly. There are efforts to quantify more precisely the visual impressions [64], applications at the point of use by endocrinologists and surgeons alike [65], as well as combination with Doppler or elastography to obtain additional information [66]. Finally, ultrasound is used in several centers to guide the insertion of the needle during fine needle aspiration for a more proper targeting of the thyroid nodule.

4.4. Thyroid function tests, radio-iodine uptake, and fine-needle aspiration

The evaluation of thyroid function in patients with HT is carried out by measuring the serum levels of thyrotropin (TSH) and free thyroxine (FT4). TSH is the most important index to monitor thyroid function since its levels adjust precisely to even minimal variations in circulating thyroid hormones. The 24-h thyroidal uptake of radioactive iodine is now used rarely for diagnosing HT since results are variable. It does, however, have a utility in painless thyroiditis. During the hyperthyroid phase of this HT variant the radioiodine uptake is actually decreased (<5%, Table 2) rather than increased, as one would predict in hyperthyroidism. As discussed before, the reason is that the increase in circulating thyroid hormones is not due to an increased function of the thyroid gland (hyperthyroidism) but to a destruction of the thyroid follicles and release of pre-formed thyroid hormones (thyrotoxicosis).

Fine needle aspiration is performed when a patient has a thyroid nodule, which is a very common encounter. Most thyroid nodules are true tumorous nodules, and of them the majority are benign tumors. But in the fibrous variant of HT there can be “pseudo-nodules”, given that the dense keloid-like fibrosis distorts the thyroid architecture and imparts to the gland a lobular appearance. When thyroid antibodies and a nodule are present it is difficult to establish whether the patient has two concomitant thyroid diseases or just the fibrous variant of HT. Fine-needle aspiration is therefore performed, and its cytological results can be of difficult interpretation. In HT, cytology scholarly shows a polymorphic population of lymphoid cells (small mature lymphocytes, larger activated lymphocytes, and occasional plasma cells) accompanied by Hürthle cells. Lymphocytes are often in contact with groups of thyroid cells, a feature that is considered useful to distinguish HT from thyroid neoplasms [67]. Some aspirates, however, lack lymphoid cells and consist almost exclusively of Hürthle cells, making it difficult to establish whether these are the Hürthle cells found in HT or instead those found in other oncocytic lesions of the thyroid, such as oncocytic adenomatoid nodule, Hürthle cell adenoma, or Hürthle cell carcinoma [68]. Indeed a recent study has shown that the presence of Hürthle cells alters the distribution and outcome of categories in the Bethesda system for reporting thyroid cytopathology [69]. For these aspirates predominantly composed of Hürthle cells, the cytopathologist uses the term “atypia of undetermined significance” [70] to indicate features that are neither benign nor malignant. Although the recommendation of the Bethesda system for this category is conservative management [71] and although most of these Hürthle cell lesions are benign [72], many patients are referred to a surgeon and often undergo thyroidectomy.

5. Treatment

HT is mainly a medical disease. Thyroidectomy is nowadays performed when there are signs and symptoms of severe cervical compression, upon patient's request for cosmetic reasons, or, more commonly, when the patient has a thyroid nodule with a cytology “suspicious” for malignancy and the clinician does not know whether the patient has just HT (where no surgery would be required) or HT and thyroid cancer (where instead surgery is indicated) [6]. These cases of HT with suspected malignancy that turn out to be benign on final histology are unfortunate because an invasive surgery and the subsequent life-long requirement of synthetic thyroid hormones could be spared. Avoiding thyroidectomy is particularly relevant in HT since the surgical complications, both transient and permanent, are more numerous in this disease than in thyroidectomy performed for other thyroid pathologies [73].

The therapy of the primary and permanent hypothyroidism seen in many forms of HT consists in the daily, lifelong, oral administration of synthetic levo-thyroxine (L-T4) [74], which is given at doses of 1.6–1.8 μg per kg of body weight. It is therefore a symptomatic treatment, which addresses the symptoms rather than the pathogenesis of HT. The treatment is economical: for example, a one-year supply of daily 112 microgram tablets purchased in the US without insurance costs about $320 for brand name and $120 for generic drug. There is, therefore, no incentive for pharmaceutical companies in developing new drugs to replace a medication that is effective and economic. The result is that synthetic thyroxine (first crystallized by Kendall in 1915, made commercially available in 1930s, and then produced on a large scale in the 1960s) remains the only effective drug available to patients with HT. This treatment is effective in most patients but remains controversial.

A short-course of glucocorticoids should be tried in patients with the IgG4-related variant of HT, since this treatment can actually cure the

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disease avoiding the development of permanent hypothyroidism and thus the need of life-long monitoring and thyroxine replacement [75].

Dietary supplementation with selenium is being evaluated as a tool to protect the thyroid gland from autoimmune damage [76], but results from randomized clinical trials are not univocal [77].

Mechanistic treatments are being tested in other autoimmune endocrinopathies that are more clinically significant than HT. For example, in Addison's disease Pearce et al. have shown that injection of a monoclonal antibody that destroys the patient's B cells can provide a long-lasting and medication-free solution [78], shifting the paradigm from simply replacing the hormones in a chronic and incurable disease to actually curing the disease. Equally important is the notion that this type of studies opens novel patho-physiological avenues, such as the realization that adrenal hormonogenic function is plastic and rescuable despite the chronicity of the disease and that the suppression of the pituitary trophic hormone (corticotroph in Addison's disease and TSH in HT) is actually deleterious to rescuing the function of the target gland.

Finally, it is worth mentioning that the ultimate tool to correct thyroid hormone deficiency in a patient who does not have a functional thyroid gland would be thyroid transplantation. Although no longer just a dream [79], it still remains a futuristic approach.

In conclusion, HT remains a complex and ever expanding disease of unknown pathogenesis that awaits prevention or novel forms of treatment.

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