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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.



**Contents**



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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 ethiopathogenesis. 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

*T* 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

*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 field of cancer immunotherapy 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 impart 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 nucleus and, most characteristically, a cytoplasm that stains intensely 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



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