CHAPTER 16. HASHIMOTO'S THYROIDITIS

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ABSTRACT

Hashimoto's thyroiditis is characterized clinically as a commonly occurring, painless, diffuse enlargement of the thyroid gland occurring predominantly in middle-aged women. The patients are often euthyroid, but hypothyroidism may develop. The thyroid parenchyma is diffusely replaced by a lymphocytic infiltrate and fibrotic reaction; frequently, lymphoid germinal follicles are visible. Persons with Hashimoto's thyroiditis have serum antibodies reacting with TG, TPO, and against an unidentified protein present in colloid. In addition, many patients have cell mediated immunity directed against thyroid antigens, demonstrable by several techniques. The incidence is on the order of three to six cases per 10,000 population per year, and prevalence among women is at least 2%. The gland involved by thyroiditis tends to lose its ability to store iodine, produces and secretes iodoproteins that circulate in plasma, and is inefficient in making hormone. Thus, the thyroid gland is under increased TSH stimulation, fails to respond to exogenous TSH, and has a rapid turnover of thyroidal iodine.
Diagnosis is made by the finding of a diffuse, smooth, firm goiter in a young woman, with strongly positive titers of TG Ab and/or TPO Ab and a euthyroid or hypothyroid metabolic status. A patient with a small goiter and euthyroidism does not require therapy unless the TSH level is elevated. The presence of a large gland, progressive growth of the goiter, or hypothyroidism indicates the need for replacement thyroid hormone. Surgery is rarely indicated. Development of lymphoma, though very unusual, must be considered if there is growth or pain in the involved gland.

HISTORICAL REVIEW

In 1912 (Fig. 8-1) Hashimoto described four patients with a chronic disorder of the thyroid, which he termed struma lymphomatosa. The thyroid glands of these patients were characterized by diffuse lymphocytic infiltration, fibrosis, parenchymal atrophy, and an eosinophilic change in some of the acinar cells.(1) Clinical and pathologic studies of this disease have appeared frequently since Hashimoto's original description. The disease has been called Hashimoto's thyroiditis, chronic thyroiditis, lymphocytic thyroiditis, lymphadenoid goiter, and recently autoimmune thyroiditis. Classically, the

disease occurs as a painless, diffuse enlargement of the thyroid gland in a young or middle-aged woman. It is often associated with hypothyroidism. The disease was thought to be uncommon for many years, and the diagnosis was usually made by the surgeon at the time of operation or by the pathologist after thyroidectomy. The increasing use of the needle biopsy and serologic tests for antibodies have led to much more frequent recognition, and there is reason to believe that it may be increasing in frequency.(2) It is now one of the most common thyroid disorders.

Figure 1. Dr. Hakaru Hashimoto
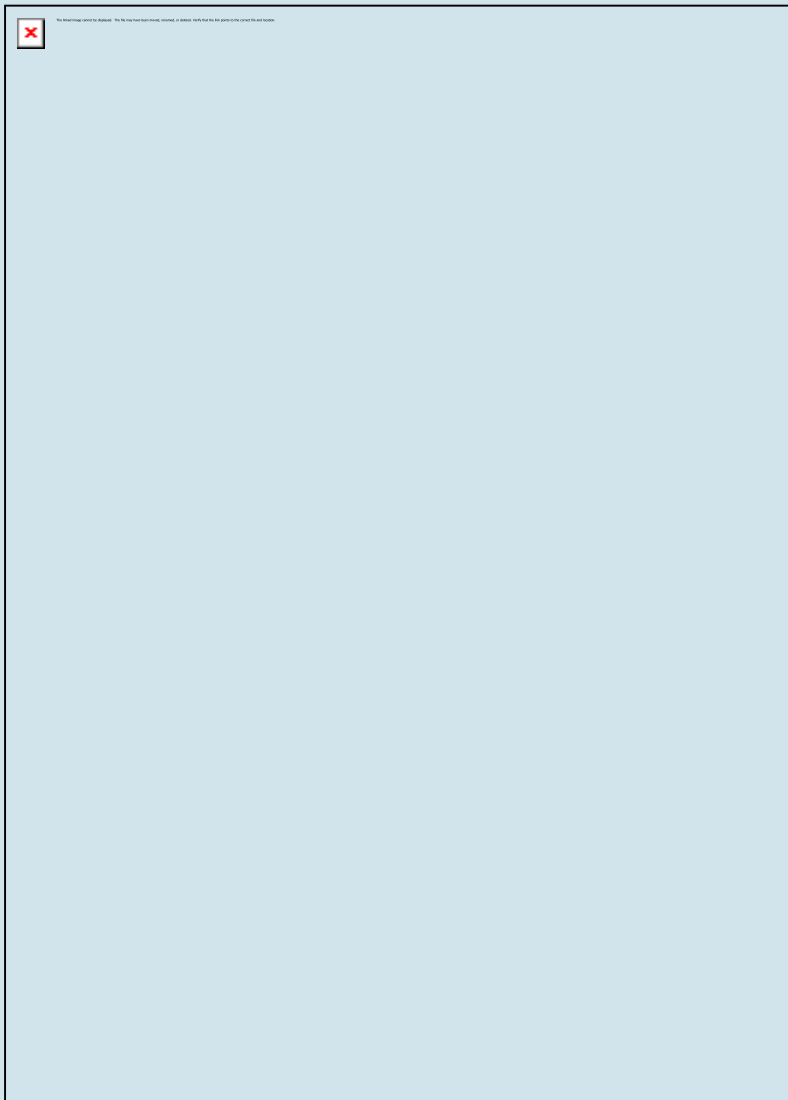
The first indication of an immunologic abnormality in this disease was an elevation of the plasma gamma globulin fraction detected by Fromm et al.(3) This finding, together with abnormalities in serum flocculation test results(4) indicated that the disease might be related to a long-continued autoimmune reaction. Rose and Witebsky(5) showed that immunization of rabbits with extracts of rabbit thyroids produced histologic changes in the thyroid glands resembling those seen in Hashimoto's thyroiditis. They also found antithyroglobulin antibodies in the blood of the animals. Subsequently, Roitt et al.(6) observed that a precipitate formed when an extract of human thyroid gland

was added to serum from a patient with Hashimoto's thyroiditis. Thus, it appeared that the serum contained antibodies to a constituent of the human thyroid and that these antibodies might be responsible for the disease process. These original observations led directly to entirely new concepts of the causation of disease by autoimmunization.

PATHOLOGY

The goiter is generally symmetrical, often with a conspicuous pyramidal lobe. Grossly, the tissue involved by Hashimoto's thyroiditis is pinkish-tan to frankly yellowish and tends to have a rubbery firmness. The capsular surface is gently lobulated and non-adherent to peri-thyroid structures. Microscopically, there is a diffuse process consisting of a combination of epithelial cell destruction, lymphoid cellular infiltration, and fibrosis. The thyroid cells tend to be slightly larger and assume an acidophilic staining character; they are then called Hurthle or Askanazy cells and are packed with mitochondria. The follicular spaces shrink, and colloid is absent or sparse. Fibrosis may be completely absent or present in degrees ranging from slight to moderate; it may be severe, as observed in subacute or Riedel's thyroiditis. Foreign body giant cells and granulomas are not features of Hashimoto's thyroiditis, in contrast to subacute thyroiditis. In children, oxyphilia and fibrosis are less prominent, and hyperplasia of epithelial cells may be marked. Deposits of dense material representing IgG are found along the basement membrane on electron microscopy (Fig. 8-2).

Figure 2. Electron microscopy image of thyroid tissue from a patient with Hashimoto's thyroiditis, showing electron dense deposits of IgG and TG along the basement membrane of follicular cells.

Within the follicles may be seen clusters of macrophage-like cells. The lymphoid infiltration in the interstitial tissue is accompanied by actual follicles and germinal centers (Fig. 8-3, below). Plasma cells are prominent. Totterman has studied the characteristics of the lymphocytes in the thyroid and reports that they are made up of equal proportions of T and B cells.(7) Most infiltrating T cells have alpha/beta T cell receptors. Gamma/delta T cells are rare(8), although their proportion in intrathyroidal lymphocytes is higher than that in peripheral lymphocytes(9). CD4+CD8+ cells and

CD3lo-TCRalpha/beta-lo/CD4-CD8- cells also are present in the infiltrate in the thyroid(9). Infiltrating T cells are considered to be a highly restricted population, based on the study of T cell receptor V alpha(10) and beta(11) gene expression. Heuer et al. studied cytokine mRNA expression in intrathyroidal T cells and found increased expression of IFN-gamma, IL-2 and CD25, which are Th1-related cytokines(12) in Hashimoto's thyroiditis. Thyroglobulin-binding lymphocytes were increased in percentage relative to their occurrence in blood.

Figure 3. Pathology of Hashimoto's thyroiditis. In this typical view of severe Hashimoto's thyroiditis, the normal thyroid follicles are small and greatly reduced in number, and with the hematoxylin and eosin stain are seen to be eosinophilic. There is marked fibrosis. The dominant feature is a profuse mononuclear lymphocytic infiltrate and lymphoid germinal center formation.

The quantity of parenchymal tissue left in the thyroid is variable. In some instances it is actually increased, perhaps as a compensatory hyperplastic response to inefficient iodide metabolism. Typically, the pathologic process involves the entire lobe or gland. Focal thyroiditis, which is microscopically similar, may be found in thyroid glands with diffuse hyperplasia of Graves' disease, in association with thyroid tumors, or in multinodular thyroid glands. The thymus, which is frequently enlarged in thyroiditis as it is in Graves' disease, does not present the picture of enhanced immunologic activity(13),(14). Histologic feature in painless (or silent) thyroiditis is almost similar to that of Hashimoto's thyroiditis. All specimens show chronic thyroiditis, focal or diffuse type: and lymphoid follicles were present in about half of the specimen(15). The follicular distruptions are characteristic and common histologic feature at the time of destructive thyrotoxicois but disappear during the late recovery phase of disease. Thus painless thyroiditis may be induced by the activation of autoimmune reaction within the thyroid gland in patients with Hashimoto's thyroiditis.

PATHOGENESIS

The putative causes of autoimmune thyroid disease (AITD) are reviewed in Chapter 7, and the basic concepts reviewed there apply of course to Hashimoto's thyroiditis. In Hashimoto's thyroiditis, the immunologic attack appears to be typically aggressive and destructive, rather than stimulatory, as in Graves' disease, and the difference is most likely due to the characteristics of the immune response. Hashimoto's thyroiditis is reported to occur in two varieties, an atrophic variety, perhaps associated with HLA-DR3 gene inheritance, and a goitrous form associated with HLA-DR5. The large UK Caucasian HT case control cohort study demonstrated clear differences in association within the HLA class II region between Hashimoto's thyroiditis and Graves' disease, differences in HLA class II genotype may, in part, contribute to the different immunopathological processes and clinical presentation of these related diseases (15a). In studies of autoimmune hypothyroidism in monozygotic twins, the concordance rate is below 1 and thus environmental factors are also etiologically important.(16) Concerning susceptibility genes for Hashimoto's thyroiditis, non-MHC class II genes have been recently investigated. A number of data accumulated, demonstrating an association between cytotoxic T cell antigen-4 (CTLA-4), which is a major negative regulator of T-cell mediated immune functions, and autoimmune diseases including Hashimoto's thyroiditis. New studies have appeared on the zinc-finger gene in AITD susceptibility region gene (ZFAT), the thyroglobulin gene, and the protein tyrosine phosphatase-22 (PTPN22) gene. Genome-wide association studies (GWAS) detected other genes including FCRL3, FOXE1 and IL2RA. (16a) Many of the genes associated with AITD are also associated with other autoimmune diseases, which highlights a key role for disrupted T cell central tolerance, antigen monitoring and peripheral immune tolerance in autoimmune onset. Association of polymorphisms in miroRNA genes (miR499A and miR125A) with autoimmune thyroid diseases were reported (16b).

Regarding environmental factors, high iodine intake, selenium deficiency, pollutants such as tobacco smoke, infectious diseases such as chronic hepatitis C, and certain drugs are implicated in the development of autoimmune thyroiditis (16.1: Duntas LH. Environmental factors and autoimmune thyroiditis. Nat Clin Pract Endocrinol Metab. 2008 Jul 8. [Epub ahead of print]). Long-term iodine exposure leads to increased iodination of thyroglobulin, which increases its antigenicity and initiates the autoimmune process in genetically susceptible individuals. Selenium deficiency decreases the activity of selenoproteins, including glutathione peroxidases, which can lead to raised concentrations of hydrogen peroxide and thus promote inflammation and disease. Such environmental pollutants as smoke, polychlorinated biphenyls, solvents and metals have been implicated in the autoimmune process and inflammation. Environmental factors have not yet, however, been sufficiently investigated to clarify their roles in pathogenesis, and there is a need to assess their effects on development of the autoimmune process and the mechanisms of their interactions with susceptibility genes.

High titers of antibody against thyroglobulin (TG) and thyroid peroxidase (TPO) are present in most patients with Hashimoto's thyroiditis(17), and TPO antibodies are complement fixing and may be cytotoxic. However, the evidence for cytotoxicity is scant, especially since normal transplacental antibody passage of anti-TPO Ab to the human fetus does not usually induce thyroid damage.

Thus it is speculated that cytotoxic T cells, or killer (K) or natural killer (NK) cells, or regulatory T (Treg) or suppressor T cells, may play an important role. A few reports do show T cell line or clone cytotoxicity toward isologous thyroid epithelial cells, and experimental thyroiditis can be transferred by lymphocytes. T cells from patients with Hashimoto's disease proliferate when exposed to TG and TPO. These responses are known to be directed to specific sequences in the TPO molecule, including epitopes at aa 110-129, 210-230, 420-439, and 842-861(18). T cells from mice immunized to TPO react strongly to TPO sequence 540-559, and when immunized with this peptide, develop hypothyroidism and thyroiditis. This peptide may be a central factor in immunity to TPO(18.1). Muixí et al. identified natural HLA-DR-associated peptides in autoimmune organs that will allow finding peptide-specific T cells in situ (18.2). This study reports a first analysis of HLA-DR natural ligands from ex vivo Graves' disease-affected thyroid tissue. Using mass spectrometry, they identified 162 autologous peptides from HLA-DR-expressing cells, including thyroid follicular cells, with some corresponding to predominant molecules of the thyroid colloid. Most interestingly, eight of the peptides were derived from a major autoantigen, thyroglobulin. In vitro binding identified HLA-DR3 as the allele to which one of these peptides likely associates in vivo. Computer modeling and bioinformatics analysis suggested other HLA-DR alleles for binding of other thyroglobulin peptides. Increased K and NK cell function has been reported in Hashimoto's thyroiditis (19). Dysfunction of regulatory (or suppressor) CD4+ T cell populations may lead to the development of various organ-specific autoimmune diseases including Hashimoto's thyroiditis (19.1). Despite the lack of understanding of the primary cause(s), it is certain that thyroid autoimmunity drives the lymphocyte collection in the thyroid and is responsible for thyroid epithelial cell damage. Progressive thyroid cell damage can change the apparent clinical picture from goitrous hypothyroidism to that of primary hypothyroidism, or "atrophic" thyroiditis. Primary hypothyroidism is considered to be the end stage of Hashimoto's thyroiditis. In the TSHR-immunized murine model of Graves' disease, Treg depletion (particularly CD25) induced thyroid lymphocytic infiltrates with transient or permanent hypothyroidism (19.2). Lymphocytic infiltration was associated with intermolecular spreading of the TSHR antibody response to other self thyroid antigens, murine thyroid peroxidase and thyroglobulin. These data suggest a role for Treg in the natural progression of hyperthyroid Graves' disease to Hashimoto's thyroiditis and hypothyroidism in humans.

An alternative cause of "atrophic" hypothyroidism is the development of thyroid stimulation blocking antibodies (TSBAb), which, as the name implies, prevent TSH binding to TSH-R, but do not stimulate thyroid cells and produce hypothyroidism. It has been proposed that TSBAb bind to epitopes near the carboxyl end of the TSH-R extracellular domain, in contrast to thyroid stimulating antibodies (TSAb), which bind to epitopes near aa 40 at the amino terminus(20). This syndrome occurs in neonates, children and adults. The prevalence of TSBAb in adult hypothyroid patients has been reported to be 10%(21). However, in contrast to the usual progressive and irreversible thyroid damage occurring in the usual setting, these blocking antibodies tend to follow the course of TSAb--that is, they decrease or disappear over time, and the patient may become euthyroid again(22). A change from a predominant TSAb response to a predominant TSBAb response can cause patients to have sequential episodes of hyper- and hypothyroid function(23). HLA antigens of hypothyroid patients with TSBAb were found to be different from patients with idiopathic myxedema or Hashimoto's thyroiditis, and rather similar to patients with Graves' disease(24).

In patients with autoimmune hypothyroidism, thyroid dysfunction might be induced by cytokine-mediated apoptosis of thyroid epithelial cells and infiltrating T lymphocytes may not directly be involved in thyrocyte cell death during Hashimoto' s thyroiditis. Fragmented DNA, a characteristic feature of apoptosis, was frequently found in the thyroid follicular cells in Hashimoto's thyroiditis(25). The ligand for Fas(Fas L)was shown to be constitutively expressed on thyrocytes and IL-1alpha, abundantly produced in the thyroid gland of Hashimoto's thyroiditis, induced Fas expression on thyrocytes. Thus Fas-FasL interaction on thyrocytes may induce apoptosis and thyroid cell destruction(26). In the thyroid follicle cells of Hashimoto's thyroiditis, Fas and FasL are strongly stained and immunostaining of Bcl-2 is weak, suggesting that cytokines cause up-regulation of apoptosis(27). Increased serum TSH may inhibit Fas-mediated apoptosis of thyrocytes(28). In contrast TSBAb block the inhibitory action of TSH toward Fas-mediated apoptosis and thus induce thyroid atrophy. On the other hand, transgenic expression of Fas L on thyroid follicular cells actually prevents autoimmune thyroiditis, possibly through inhibition of lymphocyte infiltation(29). Other death-receptor ligands might participate in and TNF-related apoptosis-includingαthyrocyte killing, including TNF- ligand(TRAIL)(30) . In relation to the Fas-Fas L system, Dong et al. reported that mutations of Fas, which induce loss of function, were found in thyroid lymphocytes in 38.1% of patients with Hashimoto's thyroiditis(31). These mutations are found in 65.4% of patients with malignant lymphoma(32), which usually develops from Hashimoto's thyroiditis. These changes are possibly important for progression of Hashimoto's thyroiditis.

Apparent de-novo development of antibodies, augmentation of pre-existing thyroid autoimmunity, goiter, and hypothyroidism, are induced in some cancer patients, when given courses of IL2, IL2a plus lymphokine activated K cells and/or IFN-gamma. It is thought that the phenomenon may reflect activation of lymphocytes by the lymphokine and lymphokine and cell-mediated attack on thyroid tissue(33). Activated lymphocytes release TNFalpha and IFNgamma, which can injure or suppress TEC function. IFNgamma may also augment thyrocyte HLA-DR expression, which could make the thyrocyte able to present self-antigens. Interferon alpha therapy for chronic active type C hepatitis also augments pre-existing thyroid autoimmunity and can induce autoimmune hypothyroidism. A humanised anti-CD52 monoclonal antibody, Campath-1H may permit the generation of antibody-mediated thyroid autoimmunity (33a,b). Campath-1H depletes lymphocytes and monocytes, and may cause the immune response to change from the Th1 phenotype.

T helper type 17 (Th17) lymphocytes, which produce a proinflammatory cytokine IL-17, have recently been shown to play a major role in numerous autoimmune diseases that had previously been thought to be Th1-dominant diseases, such as Hashimoto's thyroiditis. It is reported that there is an increased differentiation of Th17 lymphocytes and an enhanced synthesis of Th17 cytokines in Hashimoto's disease (33c). In a mouse model of Hashimoto's thyroiditis, iodine-induced autoimmune thyroiditis in nonobese diabetic-H2(h4) mice, both Th1 and Th17 cells are found to be critical T(eff) subsets for the pathogenesis of spontaneous autoimmune thyroiditis (33d). Imbalance of Th17/Treg is reported in different subtypes of autoimmune thyroid diseases. Increased Th17 lymphocytes may play a more important role in the pathogenesis of HT and GO while decreased Treg may be involved in Graves' disease (33d.1). In contrast, a significant decrease in the ratios of CD4 + IL17+/CD4 + CD25 + CD127 - ($p < 0.0001$) and CD4 + IL17+/CD4 + CD25 + CD127 - FoxP3 + ($p < 0.0001$) T cells was obseeved in Hashimoto's thyroiditis in comparison to healthy children (33d.2).

The IgG4-related disease (IgG4-RD) is a new disease entity first proposed in relation to autoimmune pancreatitis (AIP) by Hamano et al. in 2001 (33e). A high prevalence of hypothyroidism has been reported in patients with AIP (33f). In 2009, it was reported that on the basis of the immunohistochemistry of IgG4, HT can be divided into two groups, which were proposed as IgG4 thyroiditis (IgG4-positive plasma cell-rich group) and non-IgG4 thyroiditis (IgG4-positive plasma cellpoor group) (33g). The IgG4 thyroiditis group shows indistinguishable histological features and may have a close relationship with IgG4-RD in other organs. In 2010, it was demonstrated that IgG4 thyroiditis is clinically associated with a lower female-to-male ratio, more rapid progress, subclinical hypothyroidism, diffuse low echogenicity, and a higher level of circulating thyroid autoantibodies than non-IgG4 thyroiditis (33h). Riedel thyroiditis (RT) is another candidate for IgG4-RD. It is a rare form of chronic thyroiditis, characterized by inflammatory proliferative fibrosis which involves the thyroid parenchyma and surrounding tissue structures. In 2010, Dahlgren et al. reported that IgG4-RD was the underlying condition in a part of the cases of RT (33i). When IgG4-RD occurs in a systemic pattern, the thyroid involvement may present as RT rather than HT (33j).

Iodine consumption influences the incidence of Hashimoto's thyroiditis and hypothyroidism (see below: "Iodide Metabolism and Effects" in this chapter). Smoking has also been identified as a risk factor for hypothyroidism, but the reason for the association is unknown (34).

An increase in the prevalence of thyroid autoantibodies (ATAs) was reported 6-8 yr after the Chernobyl accident in radiation-exposed children and adolescents (34a). TPOAb prevalence in adolescents exposed to radioactive fallout was still increased in Belarus 13-15 yr after the Chernobyl accident (34b). This increase was less evident than previously reported and was not accompanied by thyroid dysfunction. These data suggest that radioactive fallout elicited a transient autoimmune reaction, without triggering full-blown thyroid autoimmune disease. Longer observation periods are needed to exclude later effects.

Celiac disease was positively associated with hypothyroidism (Hazard Ratio = 4.4; 95% Confidence Interval = 3.4-5.6; $p < 0.001$), thyroiditis (3.6; 1.9-6.7; $p < 0.001$) and hyperthyroidism (2.9; 2.0-4.2; $p < 0.001$) (34c). The highest risk estimates were found in children (hypothyroidism 6.0; 3.4-10.6, thyroiditis 4.7; 2.1-10.5 and hyperthyroidism 4.8; 2.5-9.4). In post-hoc analyses, where the reference population was restricted to inpatients, the adjusted HR for hypothyroidism was 3.4 (2.7-4.4; $p < 0.001$), thyroiditis 3.3 (1.5-7.7; $p < 0.001$) and hyperthyroidism 3.1 (2.0-4.8; $p < 0.001$).This indicates shared etiology and that these individuals are more susceptible to autoimmune disease.

Hashimoto thyroiditis is often associated with type 1 diabetes and other autoimmune disorders such as coeliac disease, type 2 and type 3 polyglandular autoimmune disorders (APS). Type 2 APS is defined by the occurrence of Addison's disease with thyroid autoimmune disease and/or Type 1 diabetes mellitus. Type 3 APS is thyroid autoimmune diseases associated with other autoimmune diseases (excluding Addison's disease and/or hypoparathyroidism). Clinically overt disorders are considered only the tip of the autoimmune iceberg, since latent forms are much more frequent (34d). Hashimoto thyroiditis is also often associated in lymphocytic hypophysitis (34e).

There is a report that microRNAs (miRNAs) miR-146a1, miR-155_2, and miR-200a1 are altered in AITD. In the thyroid tissue of the GD group, miR-146a1 was significantly decreased in comparison to the control group (mean relative expression 5.17 vs. 8.37, respectively, p = 0.019). In the HT group, miR-155_2 was significantly decreased in comparison to the control group (8.30 vs. 11.20, respectively, p = 0.001), and miR-200a1 was significantly increased (12.02 vs. 8.01, p = 0.016) (34f). The expression levels of miRNAs in plasma and peripheral blood mononuclear cells showed wide individual variation, and the these levels may be associated with the pathogenesis of autoimmune thyroid diseases (34g). Accumulating data suggest that miRNAs crucially control innate and adaptive immune responses, and implicate some miRNAs as having an important role in the pathophysiology of immunity and autoimmunity. (34h) For example, miR-155_2 was previously shown to possess important functions in the mammalian immune system. (34i) MicroRNA-142-5p may contribute to Hashimoto's thyroiditis by targeting CLDN1.(34j)

INCIDENCE AND DISTRIBUTION

The incidence of Hashimoto's thyroiditis seen in practice is unknown but is roughly equal to that of Graves' disease (on the order of 0.3 - 1.5 cases per 1,000 population per year.)(35-37) The disease is 15 - 20 times as frequent in women as in men. It occurs especially during the decades from 30 to 50, but may be seen in any age group, including children. It is certain that it exists with a much higher frequency than is diagnosed clinically, and its frequency seems to be increasing. Family studies always bring to light a number of relatives with moderate enlargement of the thyroid gland suggestive of Hashimoto's thyroiditis. Many of these persons have TG and TPO antibodies, and most are entirely asymptomatic. Inoue et al. found 3% of Japanese children aged 6 - 18 to have thyroiditis(38). In most instances, biopsy revealed focal rather than diffuse thyroiditis.

In addition to overt thyroiditis, roughly 10% of most populations have positive TG and TPO antibody test results(35-37) in the apparent absence of thyroid disease by physical examination. In a classic study of an entire community, Tunbridge et al.(37) found that 1.9 - 2.7% of women had present or past thyrotoxicosis, 1.9% had overt hypothyroidism, 7.5% had elevated TSH levels, 10.3% had test results positive for TPO (microsomal antigen) Ab measured by hemagglutination assay (MCHA), and about 15.0% had goiter. Men had 10 to 4-fold lower incidence of thyroid abnormalities. In a study of children whose parents had history of thyroid disease, Carey et al.(39) found a 24% prevalence of thyroid "abnormalities", including a prevalence of 6.9% abnormal thyroids, and 9.3% with positive TG Ab measured by hemagglutination assay (TGHA) and 7.8% positive MCHA assays. Gordin et al.(35) found that 8% of adult Finns had positive TGHA results, and 26% had positive MCHA results. TSH levels were elevated in 30% of these persons. On the basis of positive antibody titers and elevated TSH levels, 2 - 5% were believed to have asymptomatic thyroiditis. These test results correlate with focal collection of lymphocytes on histologic examination of the thyroid glands(40), are frequently associated with elevated levels of TSH(41), and probably represent one end of a spectrum of thyroid damage. Women with both positive antibody test results and raised TSH levels become hypothyroid at the rate of 5%/year(42). A reasonable approximation of the prevalence of positive antibody tests in women is greater than 10%, and of clinical disease is at least 2%. Men have one-tenth this prevalence. A number of small datasets have suggested a potential role for skewed X chromosome activation (XCI), away from the expected 50:50 parent of origin

ratio, as an explanation for the strong female preponderance seen in the common autoimmune thyroid diseases (AITD), Graves' disease (GD) and Hashimoto's thyroiditis (HT). (42a) A possible role for fetal cell microchimerism in triggering an autoimmune process has been repeatedly proposed, based on the evidence that autoimmune diseases have a higher prevalence in females, with peak incidence in women of childbearing age. Fetal microchimeric cells have been found to be significantly more represented within the thyroid gland of women with Hashimoto's thyroiditis and Graves' disease compared to those without thyroid autoimmunity, suggesting a pathogenic role. (42b, c, d)

COURSE OF THE DISEASE (Table 8-1)

Hashimoto's thyroiditis begins as a gradual enlargement of the thyroid gland and gradual development of hypothyroidism. It is often discovered by the patient, who finds a fullness of the neck or a new lump while self-examining because of a vague discomfort in the neck. Perhaps most often, it is found by the physician during the course of an examination for some other complaint.

Table 1. Presentations of Hashimoto's Thyroiditis

1. Euthyroidism and goiter
2. Subclinical hypothyroidism and goiter
3. Primary thyroid failure
4. Hypothyroidism
5. Adolescent goiter
6. Painless thyroiditis or silent thyroiditis
7. Postpartum painless thyrotoxicosis
8. Alternating hypo- and hyperthyroidism

In some instances the thyroid gland may enlarge rapidly; rarely, it is associated with dyspnea or dysphagia from pressure on structures in the neck, or with mild pain and tenderness. Rarely, pain is persistent and unresponsive to medical treatment and requires medical therapy or surgery. The goiter of Hashimoto's thyroiditis may remain unchanged for decades(37), but usually it gradually increases in size. Occasionally the course is marked by symptoms of mild thyrotoxicosis, especially during the early phase of the disease. Symptoms and signs of mild hypothyroidism may be present in 20% of patients when first seen(41), or commonly develop over a period of several years. Progression from subclinical hypothyroidism (normal FT_4 but elevated TSH) to overt hypo-thyroidism occurs in a certain fraction (perhaps 3-5%) each year. Eventually thyroid atrophy and myxedema may occur(43). This assertion is based on the clinical observation that patients with Hashimoto's thyroiditis often develop myxedema, and the knowledge that patients with myxedema due to atrophy of the thyroid have a high incidence of TG Ab in their serum. The disease frequently produces goitrous myxedema in young women, and we have occasionally observed a goitrous and hypothyroid patient who went on to develop thyroid atrophy.Occasionally, patients with Hashimoto 痴 thyroiditis have persistent pain which is unresponsive to nonsteroidal anti-inflammatory drugs, replacement with thyroid hormone, and recurs after therapy

with steroids. Kon and DeGroot recently reported seven patients who finally came to subtotal or near-total thyroidectomy, some of whom received subsequent radioactive iodide thyroid ablation, with final relief of symptoms (Kon, YC; DeGroot, LJ. Painful Hashimoto 痴 thyroiditis as an indication for thyroidectomy: clinical characteristics and outcome in seven patients. J Clin Endocrinol Metab 88 2667-2672 2003).

Generally the progression from euthyroidism to hypothyroidism has been considered an irreversible process due to thyroid cell damage and loss of thyroidal iodine stores (Fig. 8-4). However, it is now clear that up to one-fourth of patients who are hypothyroid may spontaneously return to normal function over the course of several years. This sequence may reflect the initial effect of high titers of thyroid stimulation blocking antibodies which fall with time and allow thyroid function to return(23).

Figure 4. Fluorescent thyroid scan in thyroiditis. The normal thyroid scan (left) allows identification of a thyroid with normal stable (127I) stores throughout both lobes. A marked reduction in 127I content is apparent throughout the entire gland involved with Hashimoto's thyroiditis (right).

Within the past few years, several unusual syndromes believed to be associated with or part of the clinical spectrum of Hashimoto's thyroiditis have been described. Occasional patients develop amyloid deposits in the thyroid (44). Shaw et al.(45) described five patients with a relapsing steroid-responsive encephalopathy including episodes like stroke and seizures, high CSF protein, abnormal EEG, and normal CAT scans (see Hashimoto's encephalopathy below). Khardon et al.(46) described a steroid responsive lymphocytic interstitial pneumonitis in four patients. It remains uncertain how these illnesses relate to lymphocytic thyroiditis, which has until now been largely identified as an organ specific disease.

At 5 years of follow-up of the natural course of euthyroid Hashimoto's thyroiditis in Italian children, more than 50% of the patients remained or became euthyroid (46-1). The presence of goiter and elevated TGab at presentation, together with progressive increase in both TPOab and TSH, may be predictive factors for the future development of hypothyroidism.

Hashimoto's thyroiditis and hypothyroidism are associated with Addison's disease, diabetes mellitus, hypogonadism, hypopara-thyroidism, and pernicious anemia. Such combinations are described as the polyglandular failure syndrome. Two forms of polyglandular autoimmunity have been recognized(47). In the Type I syndrome patients have hypoparathyroidism, muco-cutaneous candidiasis, Addison's disease, and occasionally hypothyroidism. Type II, more frequent, often includes familial associations of diabetes mellitus, hypothyroidism, hypoadrenalism, and occasionally gonadal or pituitary failure. In these syndromes, antibodies reacting with the affected end organs are characteristically present. Vitiligo, hives, and alopecia are associated with thyroiditis. There is also a clear association with primary and secondary Sjogren's syndrome(48). Some patients appear to start with Hashimoto's thyroiditis, and progress with time to the picture of Riedel's thyroiditis including the frequently-associated retroperitoneal fibrosis(49).

Musculoskeletal symptoms, including chest pain, fibrositis, and rheumatoid arthritis, occur in one-quarter of patients(50), and of course, any of the musculoskeletal symptoms of hypothyroidism may likewise occur.

It has been suggested that thyroiditis predisposes to vascular disease and coronary occlusion. Abnormally elevated titers of thyroid autoantibodies and the morphologic changes of thyroiditis are said to occur with an increased frequency among patients with coronary artery disease. Mild hypothyroidism(51) associated with asymptomatic atrophic thyroiditis could predispose patients to heart disease. Others have failed to find increased TG Ab in-patients with coronary artery disease(52) or increased coronary disease in association with thyroiditis.

Although chronic inflammation, leading to neoplastic transformation, is a well-established clinical phenomenon, the link between Hashimoto's thyroiditis and thyroid cancer remains controversial (52a, b). Larson et al. reported that patients with Hashimoto's thyroiditis were three times more likely to have thyroid cancer, suggesting a strong link between chronic inflammation and cancer development (52-1). PI3K/Akt expression was increased in both Hashimoto's thyroiditis and well-differentiated thyroid cancer, suggesting a possible molecular mechanism for thyroid carcinogenesis. Thyroid cancer may be associated with less aggressive disease and better outcome in patients with coexisting Hashimoto's thyroiditis. (52b, c, d)

In children, retarded growth, retarded bone age, decreased hydroxyproline excretion, and elevated cholesterol levels may be seen (Fig. 8-5).

Figure 5. Identical male twins with Hashimoto's thyroiditis were photographed at age 12. At age 8, they had the same height and appearance. During the intervening 4 years, small goiters developed and the growth of the twin on the right almost stopped. Biopsy indicated Hashimoto's thyroiditis in each twin's thyroid.

Hashimoto's Thyroiditis in Identical Twin Boys*

D.L. was seen at age 12 for failure to grow over the past 4 years. The patient had an identical twin, whose development up to age 8 had been entirely normal. Pubertal changes had developed at age 11. No goiter had been noted.

On physical examination, he was a short, cooperative, pubertal boy of normal intelligence, 129 cm in height and 35 kg in weight. The thyroid gland was smooth and firm, and of normal size. The skin was dry, cool, and mottled. Reflex relaxation was delayed. Estimated T_4 levels were < 4 ug/dl, and the 24-hour RAIU was 4%. Thyroid scan showed a normal thyroid gland. Bone age was 8 years. The potassium thiocyanate discharge test result was negative. Thyroid biopsy showed a moderately diffuse lymphocytic infiltrate with lymphoid germinal centers and a diffuse, dense fibrous reaction.

R.L. was seen simultaneously with D.L. and was an active, healthy-appearing boy with early pubertal changes. His height was 149 cm, and his weight was 39.7 kg. The pulse

was 104. The skin was normal. The thyroid gland was enlarged to about three times the normal size and was not nodular. PBI levels were 6.4 and 7.2 ug/dl, and the 24-hour RAIU was 21%. Bone age was 11 years. A potassium thiocyanate discharge test caused no decrease in neck radioactivity. Biopsy showed diffuse lymphocytic infiltration, lymphoid follicles and germinal centers, atrophy of thyroid follicles, oxyphilic cytoplasm, and dense fibrosis.

Similar fingerprints, similar lip and ear shapes, and identity of 15 blood factors indicated that they were identical twins. There was no family history of thyroid disease.

Iodide kinetic studies showed rapid turnover of thyroid iodide and production of excess quantities of plasma butanol-insoluble iodine. Hemagglutination test results for TG Ab were negative, but an immunofluorescence assay showed a strongly positive reaction against a cytoplasmic antigen. Bioassay of the serum for thyroid-stimulating activity gave a TSH-type response.* These patients were studied in cooperation with Dr. William H. Milburn, to whom we are greatly indebted.

When goiter is induced by iodine administration, lymphocytic thyroiditis is frequently found and thyroid autoantibodies are often present(53).

Remission of Hashimoto's thyroiditis, with loss of goiter, hypothyroidism, and serum thyroid autoantibodies, has been reported during pregnancy, with relapse after delivery(54). Antibody levels usually fall during pregnancy(55). These phenomena may reflect the immunosuppressive effects of pregnancy. After delivery thyroid autoantibody levels rise, and after 2-6 months there may be sudden development (? return) of goiter and hypothyroidism (56). Concerning management of thyroid dysfunction during pregnancy and postpartum, an Endocrine Society Clinical Practice Guideline was developed (56a, Chapter 14). Management of thyroid diseases during pregnancy requires special considerations because pregnancy induces major changes in thyroid function, and maternal thyroid disease can have adverse effects on the pregnancy and the fetus. Care requires coordination among several healthcare professionals. Avoiding maternal (and fetal) hypothyroidism is of major importance because of potential damage to fetal neural development, an increased incidence of miscarriage, and preterm delivery. Maternal hyperthyroidism and its treatment may be accompanied by coincident problems in fetal thyroid function. Autoimmune thyroid disease is associated with both increased rates of miscarriage, for which the appropriate medical response is uncertain at this time, and postpartum thyroiditis. Fine-needle aspiration cytology should be performed for dominant thyroid nodules discovered in pregnancy. Radioactive isotopes must be avoided during pregnancy and lactation. Universal screening of pregnant women for thyroid disease is not yet supported by adequate studies, but case finding targeted to specific groups of patients who are at increased risk is strongly supported. One report recommended screening all pregnant women for autoimmune thyroid disease in the first trimester in terms of cost-effectiveness (56b).

Of course maternal antibodies cross the placenta, and as in Graves' disease, may affect the fetus and neonate. TPO and TG Ab typically appear to have no adverse effect. Some evidence suggests cytotoxic antibodies, which are thought to be different from TPO Ab or TG Ab, could cause fetal hypothyroidism(57). However, TSBAb can rarely produce neonatal hypothyroidism, which is self-limiting over 4-6 weeks as the maternal IgG is metabolized. Women with positive TPO antibody before assisted reproduction have a significantly increased risk for miscarriage, with an odds ratio of

3.77 (Poppe, K; Glinoer, D; Tournaye, H; Devroey, P; van Steirteghem, A; Kaufman, L; Velkeniers, B. Assisted reproduction and thyroid autoimmunity: an unfortunate combination? J Clin Endocrinol Metab 88 4149-4152 2003).

Y.L.C., 24-Year-Old Woman, Postpartum, Not-So-Transient Hypothyroidism

The patient had menarche at age 16 and had regular periods. She married at age 24 and was not able to conceive. After receiving danazol therapy for 7 months for treatment of extensive endometriosis, she became pregnant and delivered after 36 weeks' gestation. During the course of this pregnancy, her thyroid gland was noted to be normal; no thyroid function tests were done. After delivery, she nursed the infant for 1 week. She then stopped nursing, but galactorrhea and amenorrhea continued for the next 5 months. After the fourth month, she was noted to have an enlarged thyroid gland; the FT_4I was found to be 3.4 (normal, 6.0 - 10.5) and TSH level 27 uU/ml. There were symptoms of mild hypothyroidism, with some lowering of the voice and increase in fatigue. A sister had an overactive thyroid and mild exophthalmos.

Her thyroid was estimated to weigh about 40 g, with a smooth surface and an enlarged lobe. Skin was dry, and there was some delay in the reflex relaxation. TGAb were present at a titer of 1/160 and TPOAb at 1/20480. Serum T_3 level was 123 ng/dl, and the RAIU was 16% at 4 hours and 32% at 24 hours. The thyroid scan was within normal limits. Prolactin (PRL) level was elevated at 43 ng/ml. Sella turcica X-ray films and a CT scan of the head were normal.

It was hypothesized that the patient had postpartum hypothyroidism due to transient exacerbation of thyroiditis and that this condition might resolve spontaneously. Whether the hyperprolactinemia, amenorrhea, and galactorrhea were secondary to the hypothyroidism or were independent problems was at first unclear. The patient was treated expectantly, since she appeared to be in no distress and there was no evidence of pituitary tumor. One month after the initial observations, the TSH level had fallen to 13.5 uU/ml and the T_3 level remained at 126 ng/dl. Eight weeks later, the FT_4I had risen to 5.8, the T_3 level was 113 ng/dl, TSH 9.1 uU/ml, and the PRL remained at 66 ng/ml. Later, all test results became normal.

Painless (silent) and Postpartum Thyroiditis

In the last decade several syndromes involving clinically significant, but self-limited, exacerbations of AITD have been delineated(54)-(59). Silent (painless) thyroiditis is a syndrome that has a clinical course of thyroid dysfunction similar to subacute thyroiditis but with no anterior neck pain and no tenderness of the thyroid. Initially, patients have a thyrotoxic phase, later passing through euthyroidism to hypothyroidism and, finally, return to euthyroidism. Postpartum thyroiditis occurs within 6 months after delivery and runs an identical clinical course(57). Postpartum thyroiditis is now considered to be identical to silent thyroiditis, and this term is used for patients who developed silent thyroiditis in the postpartum period(57). After delivery, other forms of autoimmune thyroid dysfunction also occur, including Graves' disease, transient hypothyroidism without preceding destructive thyrotoxicosis, and persistent hypothyroidism (Fig. 8-6). In recent years, the term painless thyroiditis also has been used frequently, and the same disorder has been described using different names, such as thyrotoxicosis with painless thyroiditis(60), occult subacute thyroiditis(61), hyperthyroiditis(64), lymphocytic thyroiditis with spontaneously resolving hyperthyroidism(62), painless thyroiditis and

transient hyperthyroidism without goiter(63), and transient hyperthyroidism with lymphocytic thyroiditis(65). The thyrotoxicosis is induced by leakage of intrathyroidal hormones into the circulation caused by damage to thyroid epithelial cells from inflammation. Thus the thyroid radioactive iodine uptake (RAIU) is low(59). Therefore, the early phase of thyrotoxicosis in silent thyroiditis, postpartum thyroiditis, and subacute thyroiditis can be grouped together as destruction-induced thyrotoxicosis or simply as destructive thyrotoxicosis(66). When the measurement of radioactive iodine uptake is difficult, the measurement of anti-TSH receptor antibody and/or thyroid blood flow by ultrasonography may be useful to differentiate between destruction-induced thyrotoxicosis and Graves' thyrotoxicosis. The quantitative measurement by power Doppler ultrasonography was more effective than that of anti-TSH receptor antibody for differential diagnosis of these two types of thyrotoxicosis and may omit the radioactive iodine uptake test (66-1).

Figure 6.

Much evidence, including histopathological and immunological studies, indicates that this disorder is an autoimmune thyroid disease(68). It is believed to be due to autoimmune induced damage to the thyroid causing excess hormone release, and for this reason is not responsive to antithyroid drugs, KI or $KCLO_4$, but does, if treatment is necessary, respond to prednisone(67). During the clinical course of subclinical or very mild autoimmune thyroiditis, aggravating factors cause exacerbation of the destructive process. All women with subclinical autoimmune thyroiditis(40) and antithyroid microsomal antibodies of more than 1:5120 before pregnancy develop postpartum thyroiditis(57). A significant percentage of patients with silent thyroiditis have personal or family histories of autoimmune thyroid disease. Most patients have a complete remission, but some develop persistent hypothyroidism(70). Some patients have had alternating episodes of typical "high-uptake" thyrotoxicosis and episodes of "transient" low-uptake thyrotoxicosis(69). Recurrence of disease is common in silent thyroiditis but very rare in subacute thyroiditis. Considering all these data, it is assumed that silent thyroiditis is caused by an exacerbation of autoimmune thyroiditis induced by aggravating factors. Thyroiditis frequently recurs, and seasonal allergic rhinitis is reported to be an initiation factor(71). Physically vigorous massage on the neck also was reported to be a contributing factor for silent thyroiditis(72). The prevalence of silent thyroiditis, including postpartum disease, is around 5 per cent of all types of thyrotoxicosis. Spontaneous silent thyroiditis is three times more frequent than postpartum thyroiditis.

An immune rebound mechanism has been established for the induction of postpartum thyroiditis(57). Postpartum thyroid destruction is associated with an increase in NK cell counts and activity(57). Cessation of steroid therapy has initiated silent thyroiditis in a patient with autoimmune thyroiditis and rheumatoid arthritis(73), presumably because this also allows immune rebound. In patients with Cushing's syndrome who have associated subclinical autoimmune thyroiditis, silent thyroiditis has occurred after unilateral adrenalectomy(74). Typically, painless thyroiditis or destructive thyrotoxicosis occurs at 2 to 4 months postpartum. The prevalence of postpartum thyroiditis ranges from 3 to 8 per cent of all pregnancies(57).POSSIBLE PREVENTION OF PPT-In a randomized prospective controlled study, 77 TPO+ pregnant women received 200 ug selenomethionine daily starting at the 12th week of pregnancy, and 74 TPO+ women received a placebo. The treated group had significantly lower TPO antibody levels at the end of pregnancy and during the post-partum while on treatment. The incidence of PPT was reduced from 48.6 to 28.6% in the treated group, and the incidence of permanent hypothyroidism was equivalently reduced. Thyroid hormone levels did not differ.(Negro R, Greco G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. The influence of selenium supplementation on postpartum thyroid status in pregnant women with thyroid peroxidase autoantibodies. J Clin Endocrinol Metab. 2007 Apr;92(4):1263-8) .

Hashimoto's encephalopathy

Hashimoto's encephalopathy or encephalitis is a very rare complication of Hashimoto's thyroiditis. Neurological complications are sometimes associated with thyroid dysfunction but patients with this encephalopathy are usually euthyroid. It is treatable, steroid-responsive, progressive or relapsing encephalopathy associated with elevation of thyroid specific autoantibodies (75). This condition was first described in 1966 (76) and may present as a subacute or acute encephalopathy with seizures and stroke-like episodes, often in association with myoclonus and tremor (77). It is associated with abnormal EEG and high CSF proteins without pleocytosis. Some patients suffer from a significant residual disability(78). Antibody to α-enolase has been identified in some patients (79) but this antibody is also frequently found in other autoimmune diseases. Sawka et al. reported that this condition is not caused by thyroid dysfunction or antithyroid antibodies but represents an association of an uncommon autoimmune encephalopathy with a common autoimmune thyroid disease (80). Identification of antibodies to brain specific antigens may disclose the real pathogenesis of this condition. Recently, autoantibodies against the amino (NH_2)-terminal of α-enolase (referred to as NAE) were reported to be highly specific in sera from a limited number of HE patients (68-83% with HE; 11%, 2 of 17 with HT without any neuropsychiatric features; none of controls [50 individuals] including those with other neurological or immunological conditions involving encephalopathy [25 individuals]) (80.1, 80.2). Steroid reversible cerebral hypometabolism was recently documented by PET scanning in this condition. (80.3) There is a report that Hashimoto's encephalopathy associated with elevated intrathecal and serum IgG4 levels. (80.3a) Additional case studies, including histological investigations as well as measurements of IgG4, are needed to elucidate the pathological role of IgG4 in Hashimoto's encephalopathy.

Hashimoto's ophthalopathy

Thyroid-associated orbitopathy (TAO) usually occurs in Graves's disease with hyperthyroidism, and sometimes in euthyroid and hypothyroid patients. Since most

euthyroid and hypothyroid patients with orbitopathy are thyrotropin receptor antibody (TRAb)-positive, they are diagnosed as having euthyroid Graves' disease or hypothyroid Graves' disease. When euthyroid and hypothyroid patients with orbitopathy are TRAb-negative but associated with Hashimoto's thyroiditis, "Hashimoto's ophthalopathy" may be considered (80.4, 80.5). Because patients with Hashimoto's thyroiditis test negative for TRAb, other autoantibodies against an eye muscle antigen, such as calsequestrin, flavoprotein, or G2s are postulated (80.6).

IODIDE METABOLISM AND EFFECTS

Many patients with Hashimoto's thyroiditis do not respond to injected TSH with the expected increase in RAIU or release of hormone from the gland(81). These findings probably mean that the gland is partially destroyed by the autoimmune attack and is unable to augment iodine metabolism further. Further, the thyroid gland of the patient with Hashimoto's disease does not organify normally(82) (Fig. 8-4). Administration of 400 mg potassium perchlorate 1 hour after giving a tracer iodide releases 20 - 60% of the glandular radioactivity. Also, a fraction of the iodinated compounds in the serum of patients with Hashimoto's thyroiditis is not soluble in butanol, as are the thyroid hormones, but is an abnormal peptide-linked iodinated component. This low-weight iodoprotein is probably serum albumin that has been iodinated in the thyroid gland. A similar iodoprotein is also found in several other kinds of thyroid disease, including carcinoma, Graves' disease, and one form of goitrous cretinism. It may be formed as part of the hyperplastic response. TG is also detectable in their serum.

Iodide is actively transported from blood to thyrocytes and recently the sodium / iodide symporter (NIS) has been cloned. Antibodies against NIS were found in autoimmune thyroid disease(83). This antibody has an inhibitory activity on iodide transport and may modulate the thyroid function in Hashimoto's thyroiditis. More recent studies reported rather low prevalence (less than 10%) of anti-NIS antibodies in Hashimoto's disease and clinical relevance is still unknown(84),(85).

In animal experiment iodine depletion prevents the development of autoimmune thyroiditis(86). It is suggested that mild iodine deficiency partly protect against autoimmune thyroid disease(87), although it is controversial(88). In a region where iodine-containing food (such as seaweed) is common, as in Japan, excessive dietary iodine intake (1000 micro g/day or more) may cause transient hypothyoidism in patients with subclinical autoimmune thyroiditis. This condition is easily reversible with a reduction in iodine intake(89). Iodine is important not only for thyroid hormone synthesis but also for induction and modulation of thyroid autoimmunity. In general, iodine deficiency attenuates, which iodine excess accelerates autoimmune thyroiditis in autoimmune prone individuals(90). In animal experiment, it is revealed that enhanced iodination of thyroglobulin facilitates the selective processing and presentation of a cryptic phatogenic peptide in vivo or in vitro. Moreover, it is suggested that iodine excess stimulates thymus development and effects function of various immune cells(91).

DIAGNOSIS

Diagnosis involves two considerations -- the differential diagnosis of the thyroid lesion and the assessment determination of the metabolic status of the patient.

A diffuse, firm goiter with pyramidal lobe enlargement, and without signs of thyrotoxicosis, should suggest the diagnosis of Hashimoto's thyroiditis. Most often the gland is bosselated or "nubbey." It is usually symmetrical, although much variation in symmetry (as well as consistency) can occur. The trachea is rarely deviated or compressed. The association of goiter with hypothyroidism is almost diagnostic of this condition, but is also seen in certain syndromes due to defective hormone synthesis or hormone response, as described in Chapter 9. Pain and tenderness are unusual but may be present. A rapid onset is also unusual, but the goiter may rarely grow from normal to several times the normal size in a few weeks. Most commonly the gland is two to four times the normal size. Satellite lymph nodes may be present, especially the Delphian node above the isthmus. Multinodular goiter occurs in significant incidence in adult women; thus the co-occurrence of multinodular goiter and Hashimoto's thyroiditis is not rare, and may provide the finding of a grossly nodular gland in a patient who is mildly hypothyroid and has positive antibody tests.

The T_4 concentration and the FT_4 range from low to high but are most typically in the normal or low range(92). The RAIU (rarely required) is variable and ranges from below normal to elevated values, depending on such factors as TSH levels, the efficiency of use of iodide by the thyroid, and the nature of the components being released into the circulation. Gammaglobulin levels may be elevated, although usually they are normal(93). This alteration evidently reflects the presence of high concentrations of circulating antibodies to TG, for an antibody concentration as high as 5.2 mg/ml has been reported.

T_4 and FTI are normal or low(92). Serum TSH reflects the patient's metabolic status. However, some patients are clinically euthyroid, with normal FTI and T_3 levels, but have mildly elevated TSH. Whether this "subclinical hypothyroidism" represents partial or complete compensation is a matter of debate. TPOAb, and less frequently TGAb are present in serum. High levels are diagnostic of autoimmune thyroid disease. TGAb are positive in about 80% of patients, and if both TGAb and TPOAb are measured, 97% are positive. Young patients tend to have lower and occasionally negative levels. In this age group, even low titers signify the presence of thyroid autoimmunity.

FNA can be a useful diagnostic procedure but is infrequently required, except in patients that seem to have- or have- a discreet nodule in the gland. FNA typically reveals lymphocytes, macrophages, scant colloid, and a few epithelial cells which may show Hurthle cell change. In this context Hurthle cells do not represent a discrete adenoma. However if only abundant Hurthle cells dominate the specimen, and there are few or no lymphocytes or macrophages, the biopsy must be interpreted as a possible Hurthle cell tumor. Biopsy results are less frequently diagnostic in children(95).

Thyroid isotope scan is not usually necessary, but can be helpful. The image is characteristically that of a diffuse or mottled uptake in an enlarged gland, in striking contrast to the focal "cold" and "hot" areas of multinodular goiter. Focal loss of isotope accumulation may occur in severely diseased portions of the thyroid.

Table 2. Guideline for the diagnosis of Hashimoto's thyroiditis (Chronic thyroiditis)

* **Some clinicians don't use the term Hashimoto's thyroiditis if patients have no**

goiter, although association of positive antibodies and lymphocytic infiltration in the thyroid gland was proved by histological examination.

1. Clinical findings Diffuse swelling of the thyroid gland without any other cause (such as Graves' disease)
2. Laboratory findings
   a. Positive for anti-thyroid microsomal antibody or anti-thyroid peroxidase(TPO) antibody
   b. Positive for anti-thyroglobulin antibody
   c. Lymphocytic infiltration in the thyroid gland confirmed with cytological examination

1. A patient shall be said to have Hashimoto's thyroiditis if he/she has satisfied clinical criterion and any one laboratory criterion.Notes
   a. A patients shall be suspected to have Hashimoto's thyroiditis, if he/she has primary hypothyroidism without any other cause to induce hypothyroidism.
   b. A patient shall be suspected to have Hashimoto's thyroiditis, if he/she has anti-thyroid microsomal antibody and/or anti-thyroglobulin antibody without thyroid dysfunction nor goiter formation.*
   c. If a patient with thyroid neoplasm has anti-thyroid antibody by chance, he or she should be considered to have Hashimoto's thyroiditis.
   d. A patient is possible to have Hashimoto's thyroiditis if hypoechoic and/or inhomogeneous pattern is observed in thyroid ultrasonography.

Ultrasound may display an enlarged gland with normal texture, a characteristic picture with very low echogenicity, or a suggestion of multiple ill-defined nodules. Diagnostic guidelines made by The Japan Thyroid Association are shown in Table 8-2. The flow chart of diagnosis is shown in Figure 8-7.The incidental finding of diffusely increased (18)F-FDG uptake in the thyroid gland is mostly associated with chronic lymphocytic (Hashimoto's) thyroiditis and does not seem to be affected by thyroid hormone therapy (95.1).

DIFFERENTIAL DIAGNOSIS

Hashimoto's thyroiditis is to be distinguished from nontoxic nodular goiter or Graves' disease. The presence of gross nodularity is strong evidence against Hashimoto's thyroiditis, but differentiation on this basis is not infallible. In multinodular goiter, thyroid function test results are usually normal, and the patient is only rarely clinically hypothyroid. Thyroid autoantibodies tend to be absent or titers are low, and the scan result is typical. FNA can resolve the question but is usually unnecessary. In fact, the two conditions quite commonly occur together in adult women. Whether this is by chance, or due to the effect of thyroid growth stimulating antibodies (or other causes) is unknown.

Moderately and diffusely enlarged thyroid glands in teenagers are usually the result of thyroiditis, but some may be true adolescent goiters; that is, the enlargement may result from moderate hyperplasia of the thyroid gland in response to a temporarily increased demand for hormone. This condition is more often diagnosed than proved. Thyroid function test results should be normal. Antibody assays may resolve the issue.

The diagnosis can be settled with certainty only by a biopsy disclosing normal or hyperplastic thyroid tissue and absence of findings of thyroiditis. The possibility of colloid goiter may be entertained in the differential diagnosis. Colloid goiter is a definite pathologic entity, as described in Chapter 17. Presumably it is the resting phase after a period of thyroid hyperplasia.

Tumor must also be considered in the differential diagnosis, especially if there is rapid growth of the gland or persistent pain. The diffuse nature of autoimmune thyroiditis, the characteristic hypothyroidism and involvement of the pyramidal lobe are usually sufficient for differentiation. FNA is indicated if there is uncertainty. However, it must be remembered that lymphoma or a small-cell carcinoma of the thyroid can be and has been mistaken for Hashimoto's thyroiditis. Clusters of nodes at the upper poles strongly suggesting papillary cancer may disappear when thyroid hormone replacement therapy is given. However, we have seen a sufficient number of patients with both thyroiditis and tumor to know that one diagnosis in no way excludes the other. Thyroid lymphoma must always be considered if there is continued (especially asymmetric) enlargement of a Hashimoto's gland, or if pain, tenderness, hoarseness, or nodes develop. Thyroiditis is a risk factor for thyroid lymphoma, although the incidence is very low. Thyroid lymphoma develops in most cases in glands which harbor thyroiditis. Distinguishing thyroid lymphoma from Hashimoto's thyroiditis is sometimes quite difficult Reverse transcription-polymerase chain reaction (RT-PCR) detecting the monoclonality of immunoglobulin heavy chain mRNA is useful for differentiation between the two(99). This condition and its management are discussed in Chapter 18.

Occasionally the picture of Hashimoto's thyroiditis blends rather imperceptibly into that of thyrotoxicosis, and some patients have symptoms of mild thyrotoxicosis, but then develop typical Hashimoto's thyroiditis. In fact, it is best to think of Graves' disease and Hashimoto's thyroiditis as two very closely related syndromes produced by thyroid autoimmunity. Categorization depends on associated eye findings and the metabolic level, but the pathogenesis, histologic picture, and function may overlap.

Likewise, we have seen patients who appear to have a mixture of Hashimoto's thyroiditis and subacute thyroiditis, with goiter, positive thyroid autoantibodies, normal or low FT_4, and biopsies which have suggested Hashimoto's on one occasion and included giant cells on another. A form of painful chronic thyroiditis with amyloid infiltration has also been described, and is probably etiologically distinct from Hashimoto's thyroiditis(100).

THERAPY

Many patients need no treatment, for frequently the disease is asymptomatic and the goiter is small. This approach is justified by the study of Vickery and Hamlin(101), who found, on both clinical and pathologic grounds, that the disease may remain static and the clinical condition unchanged over many years.

If the goiter is a problem because of local pressure symptoms, or is unsightly, thyroid hormone therapy is indicated. Thyroid hormone often causes a gratifying reduction in the size of the goiter after several months of treatment(100). We have been especially impressed with this result in young people. It seems likely that in older patients there may be more fibrosis and therefore less tendency for the thyroid to shrink. In young patients the response often occurs within 2 - 4 weeks, but in older ones the thyroid

decreases in size more gradually. Aksoy et al (100a) report that "prophylactic" thyroid hormone treatment is associated after 15 months with a decrease in thyroid size and in thyroid antibody levels. Thyroid hormone in a full replacement dose is, of course, indicated if hypothyroidism is present. Therapy is probably indicated if the TSH level is elevated and the FT_4 is low normal, since the onset of hypothyroidism is predictable in such patients. There is no evidence that thyroid replacement actually halts the ongoing process of thyroiditis, but in some patients receiving treatment, antibody levels gradually fall over many years(102).

Figure 7. Diagnosis of Hashimoto's thyroiditis (chronic thyroiditis)

The dosage of thyroxine should normally be that required to bring the serum TSH level to the low normal range, such as .3 - 1 uU/ml. This is typically achieved with 1 ug L-T_4/lb body weight/day, ranges from 75 - 125 ug/day in women, and 125 - 200 ug/day in men. It is sensible to initiate therapy with a partial dose, since in some instances the thyroid gland may be nonsuppressible even though functioning at a level below normal. Once thyroxine treatment is initiated, it is required indefinitely in most patients. However, it has been found that up to 20% of initially hypothyroid individuals will later recover and have normal thyroid function if challenged by replacement hormone withdrawal. This may represent subsidence of cytotoxic antibodies, modulation of TSBAb, or some other mechanism(22). These individuals can be identified by administration of TRH, which will induce an increase in serum T_4 and T_3 if the thyroid has recovered(103). Replacement T_4 therapy should be taken several hours before or after medications such as cholesterol binding resins, carafate, and FSO4, which can reduce absorption(104). (See Chapter 9) Autoimmune disease is usually takes an ongoing process and Hashimoto's thyroiditis develops into hypothyroidism. Recent trial of proplylactic treatment with T_4 (1.0 ~ 2.0µg/Kg/day) for one year in euthyroid patients

with Hashimoto's thyroiditis showed decrease of anti-TPO antibodies and thyroid B-lymphocytes(105), suggesting prophylactic T_4 therapy might be useful to stop progression of disease. The long-term clinical benefit should be established in the future.Whether or not subclinical hypothyroidism should be treated is still under debate (see Chapter 9.10 SUBCLINICAL HYPOTHYROIDISM). Cardiac dysfunction may be associated with subclinical hypothyroidism, even when serum TSH is still in the normal range. These abnormalities are reversible with l-T_4 replacement therapy (22-1).

In some instances the acute onset of the disease, in association with pain, has prompted therapy with glucocorticoids. This treatment alleviates the symptoms and improves the associated biochemical abnormalities, and in some studies has been shown to increase plasma T_3 and T_4 levels by suppression of the autoimmune process(106). Blizzard and co-workers(107) have given steroids over several months to children in an attempt to suppress antibody production and possibly to achieve a permanent remission. The adrenocortical hormones dramatically depress clinical activity of the disease and antibody titers, but all return to pre-therapy levels when treatment is withdrawn. We cannot recommend steroid therapy for this condition because of the undesirable side effects of the drug. Chloroquine has been reported in one study to reduce antibody titers(108). Because of toxicity, its use is not advised. X-ray therapy also results in a decrease in goiter size, and frequently in myxedema, but should not be used because of the possible induction of thyroid carcinoma.

SELENIUM- In a randomized prospective controlled study, 77 TPO+ pregnant women received 200 ug selenomethionine daily starting at the 12th week of pregnancy, and 74 TPO+ women received a placebo. The treated group had significantly lower TPO antibody levels at the end of pregnancy and during the post-partum while on treatment. The incidence of PPT was reduced from 48.6 to 28.6% in the treated group, and the incidence of permanent hypothyroidism was equivalently reduced. Thyroid hormone levels did not differ. This one report is certainly most interesting, but needs confirmation before this treatment can be suggested for general application (108.1). Confirming earlier studies, in Hashimoto's patients, 200 mug Se in the form of l-selenomethionine orally for 6 months caused a significant decrease of 21% in serum anti-TPO levels. Cessation caused an increase in the anti-TPO concentrations.(108.2). A slightly opposing study, however, was reported no immunological benefit of selenium in patients with moderate disease activity (in terms of TPOAb and cytokine production patterns) may not (equally) benefit as patients with high disease activity (108.3). Selenium responsiveness may be different among patients with Hashimoto's thyroiditis. A systematic review and meta-Analysis revealed that selenium supplementation reduced serum TPOAb levels after 3, 6, and 12 months in an LT4-treated Hashimoto's population, and after three months in an untreated population (108.4). However, no effect of selenium supplementation on thyroid stimulating hormone, health-related quality of life or thyroid ultrasound was found in levothyroxine substitution-untreated individuals, and sporadic evaluation of clinically relevant outcomes in levothyroxine substitution-treated patients (108.5). Future well-powered RCTs, evaluating e.g. disease progression or health-related quality of life, are warranted before determining the relevance of selenium supplementation in autoimmune thyroiditis. Further, combined treatment with Myo-inositol and selenium was reported that the beneficial effects obtained by selenomethionine treatment on patients affected by subclinical hypothyroidism were further improved by cotreatment with Myo-Inositol (108.6). Myo-Inositol s an isomer of a C6 sugar alcohol an plays an important role in several cellular processes. In particular, it has been demonstrated that Myo-Inositol is the precursor for

the synthesis of phosphoinositides, which are part of the phosphatidylinositol (PtdIns) signal transduction pathway. In one study. the administration of myo- inositol plus selenium has been reported to be effective in decreasing TSH, TPOAb, and TgAb levels, as well as enhancing thyroid hormones and personal wellbeing, therefore restoring euthyroidism in patients diagnosed with Hashimoto's thyroiditis (108.7).

ANATABINE- Anatabine, an alkaloid found in Solanaceae plants including tobacco, has been reported to ameliorate a mouse model of Hashimoto's thyroiditis. (108.8). In a double-blind, randomized, placebo-controlled multi-site study for three months, anatabine treated patients had a significant reduction in absolute serum TgAb levels from baseline by study end relative to those on placebo (p=0.027) (108.9). Further studies are warranted to dissect longer-term effects and possible actions of anatabine on the course of Hashimoto's thyroiditis.

Surgery has been used as a method of therapy. This treatment, of course, removes the goiter but usually results in hypothyroidism. We believe that it is not indicated unless significant pain, cosmetic, or pressure symptoms remain after a fair trial of thyroid therapy, and probably steroid therapy, but is appropriate in some cases. Among patients with postpartum thyroid dysfunction, the most common type is destructive thyrotoxicosis and simple symptomatic treatment, using beta-adrenergic--antagonists, is usually sufficient(109). In the case of postpartum hypothyroidism, replacement with a submaximal dose of T_3 is useful to relieve symptoms more quickly and to predict spontaneous recovery which is detected by an increase of T_4.

Some patients do not fit easily into the usual diagnostic categories; accordingly, choosing an appropriate course of therapy is more difficult. Frequently, it is impossible to differentiate Hashimoto's thyroiditis from multinodular goiter short of performing an open biopsy. In these cases, if there is no suggestion of carcinoma, it is logical to treat the patient with hormone replacement and to observe closely. A reduction in the goiter justifies continuation of the therapy, even in the absence of a diagnosis.

In some patients, especially teenagers, the examination discloses peri-thyroidal lymph nodes or an apparent discrete nodule, in addition to the diffusely enlarged thyroid of Hashimoto's thyroiditis. Such nodules should be evaluated by FNA, ultrasound and possibly scintiscan. Thyroid hormone treatment may cause regression of the nodes or nodule. If after full evaluation uncertainty persists, if nodes remain present, or if a nodule grows, surgical exploration is indicated.

Treatment of children and adolescents with 1.3ug/kg/day thyroxine for 24 months was shown in a recent study to cause significant reduction in thyroid size in patients with Autoimmune thyroiditis, but not affect antibody levels, or significantly alter TSH or freeT4. (110)

Occasionally, symptoms of serositis or arthritis suggest the coincident occurrence of another autoimmune disorder. We have given thyroid hormone to decrease thyroid activity and possibly reduce a tendency to antibody formation, and have treated the generalized disorder independently as indicated.

SUMMARY

Hashimoto's thyroiditis is characterized clinically as a commonly occurring, painless, diffuse enlargement of the thyroid gland occurring predominantly in middle-aged women. The patients are often euthyroid, but hypothyroidism may develop. The thyroid parenchyma is diffusely replaced by a lymphocytic infiltrate and fibrotic reaction; frequently, lymphoid germinal follicles are visible. Attention has been focused on this process because of the demonstration of autoimmune phenomena in most patients. Persons with Hashimoto's thyroiditis have serum antibodies reacting with TG, TPO, and against an unidentified protein present in colloid. In addition, many patients have cell mediated immunity directed against thyroid antigens, demonstrable by several techniques. Cell mediated immunity is also a feature of experimental thyroiditis induced in animals by injection of thyroid antigen with adjuvants.

All theories also emphasize a basic abnormality in the immune surveillance system, which in some way allows autoimmunity to develop against thyroid antigens, and as well against other tissues, including stomach, adrenal, and ovaries, in many patients with thyroiditis.

We suggest that Hashimoto's thyroiditis, primary myxedema, and Graves' disease are different expressions of a basically similar autoimmune process, and that the clinical appearance reflects the spectrum of the immune response in the particular patient. This response may include cytotoxic antibodies, stimulatory antibodies, blocking antibodies, or cell mediated immunity. Thyrotoxicosis is viewed as an expression of the effect of circulating thyroid stimulatory antibodies. Hashimoto's thyroiditis is predominantly the clinical expression of cell mediated immunity leading to destruction of thyroid cells, which in its severest form produces thyroid failure and idiopathic myxedema.

The clinical disease is more frequent than Graves' Disease when mild cases are included. The incidence is on the order of three to six cases per 10,000 population per year, and prevalence among women is at least 2%.

The gland involved by thyroiditis tends to lose its ability to store iodine, produces and secretes iodoproteins that circulate in plasma, and is inefficient in making hormone. Thus, the thyroid gland is under increased TSH stimulation, fails to respond to exogenous TSH, and has a rapid turnover of thyroidal iodine.

Diagnosis is made by the finding of a diffuse, smooth, firm goiter in a young woman, with strongly positive titers of TG Ab and/or TPO Ab and a euthyroid or hypothyroid metabolic status. A patient with a small goiter and euthyroidism does not require therapy unless the TSH level is elevated. The presence of a large gland, progressive growth of the goiter, or hypothyroidism indicates the need for replacement thyroid hormone. Surgery is rarely indicated. Development of lymphoma, though very unusual, must be considered if there is growth or pain in the involved gland.

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