Dayan CM, Daniels GH. Chronic autoimmune thyroiditis

2 authors, including:

Medical Progress

Chronic Autoimmune Thyroiditis

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I N 1912, Hashimoto described four women in whom the thyroid gland was enlarged and appeared to have been transformed into lymphoid tissue ("struma lymphomatosa").[1] Although the patients were not initially hypothyroid, they became so after thyroid surgery. Over 40 years later, the presence of antithyroid antibodies was reported in patients with this disorder.[2] Hashimoto's disease, or Hashimoto's thyroiditis, is now recognized as a form of chronic autoimmune thyroiditis.

There is no internationally accepted classification of autoimmune thyroid diseases.[3] Some investigators consider autoimmune thyroiditis a histologic diagnosis that can be subdivided into lymphocytic thyroiditis, if only lymphocytic infiltration is present, and Hashimoto's thyroiditis, if atrophy and eosinophilic changes in thyroid cells and fibrosis are also seen.[4] Chronic autoimmune thyroiditis has two clinical forms: a goitrous form often referred to as Hashimoto's disease, and an atrophic form called atrophic thyroiditis. Both are characterized by the presence of thyroid autoantibodies in serum and by varying degrees of thyroid dysfunction; they differ only in the absence or presence of goiter.

Graves' disease — diffuse goiter with hyperthyroidism, ophthalmopathy, or both — is a related autoimmune thyroid disease but not autoimmune thyroiditis.[5] Silent (or painless) thyroiditis is a transient disorder characterized by lymphocytic thyroiditis, painless goiter, and hyperthyroidism, hypothyroidism, or both. When this condition occurs after parturition, it is referred to as postpartum thyroiditis. Both silent thyroiditis and postpartum thyroiditis are now believed to be manifestations of chronic au-

toimmune thyroiditis.[6] Subacute (de Quervain's) thyroiditis, which is a postviral inflammation of the thyroid characterized by pain and tenderness, is not a form of autoimmune thyroiditis.

HISTOLOGIC FEATURES

Goitrous autoimmune thyroiditis is characterized by diffuse lymphocytic infiltration with occasional germinal centers, thyroid follicles of reduced size containing sparse colloid, and fibrosis (Fig. 1). Although the follicles are small, the individual thyroid cells often appear enlarged and contain cytoplasm that is granular and pink (oxyphil change); such cells are known as Hürthle or Askanazy cells.[7] When lymphocytic infiltration alone is the only histologic finding, chronic autoimmune thyroiditis can be diagnosed with confidence only if the patient has high serum titers of antithyroid autoantibodies.

In atrophic autoimmune thyroiditis, the thyroid gland is small, with lymphocytic infiltration and fibrous tissue replacing the thyroid parenchyma. Although it is tempting to think of atrophic autoimmune thyroiditis as the end stage of goitrous disease, little histologic progression has been noted in patients undergoing second biopsies up to 20 years after the first.[8,9]

PATHOGENESIS

T-Cell Activation

The autoimmune process is believed to begin with the activation of CD4 (helper) T lymphocytes specific for thyroid antigens.[10] Such antigen-specific T cells have been isolated from thyroid tissue from patients with Graves' disease but not yet from thyroid tissue from those with chronic autoimmune thyroiditis.[11] How these cells become activated is not known; current thinking is divided between two hypotheses. One hypothesis is that infection with a virus or bacterium that contains a protein similar to a thyroid protein may result in the activation of thyroid-specific T cells, a concept referred to as molecular mimicry. Such a cross-reaction would be expected to activate only T cells specific for the cross-reactive sequence, thus involving only a limited number of T-cell clones. Oligoclonality of lymphocytes has been reported in thyroid tissue from patients with autoimmune thyroiditis,[12] but the finding remains controversial.[13] Serologic evidence of recent bacterial and viral infection,[14,15] as well as an increased frequency of antiretroviral antibodies not specific for the human immunodeficiency virus,[16] has been reported in patients with chronic autoimmune
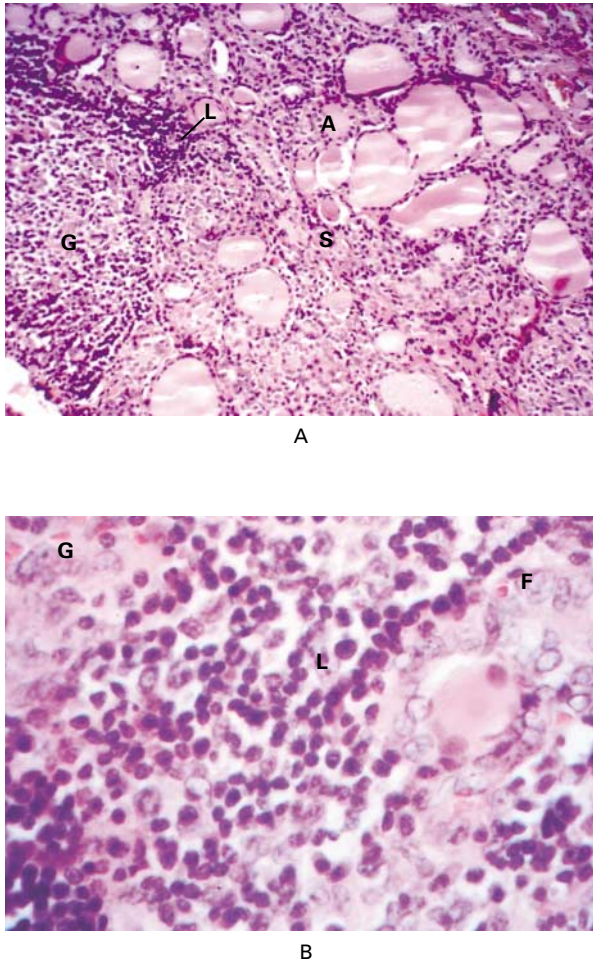
Figure 1. Microscopical Section of Thyroid Tissue Showing Typical Features of Chronic Autoimmune Thyroiditis (Panel A, Hematoxylin and Eosin, ×175; Panel B, Hematoxylin and Eosin, ×550).

A denotes atrophic follicle, S fibrotic stroma, G germinal center, L lymphocytoplasmoid infiltrate, and F follicle with oxyphilic change. (Courtesy of Dr. Wanda Szyfelbein.)

thyroiditis, but the evidence that an infectious agent precipitated the condition remains unconvincing.[17]

The alternative hypothesis is that the thyroid epithelial cells present their own intracellular proteins to helper T cells. This view is supported by the finding that thyroid cells in patients with autoimmune thyroiditis, but not normal thyroid cells, express major-histocompatibility-complex (MHC) class II proteins (HLA-DR, HLA-DP, and HLA-DQ),[18] molecules that are required for antigen presentation to CD4 T cells. Interferon gamma, a cytokine product of activated T cells, can induce the expression of MHC class II molecules by thyroid cells.[19] Hence, interferon gamma released from activated T cells may induce the expression of MHC class II molecules by thyroid cells, thereby leading to T-cell restimulation by thy-

roid cells and perpetuation of the autoimmune process.[11,20,21] The mechanism underlying the initial activation of T cells in this model is not clear but may be less antigen-specific than in molecular mimicry, since the thyroid itself promotes further expansion of the relevant population of T cells. This scheme is likely to be an oversimplification, because many non-MHC costimulatory molecules are required for the activation of T cells, and thyroid cells have yet to be shown to express such molecules.[22]

Generation of an Autoantibody Response

Once activated, self-reactive CD4 T cells can stimulate autoreactive B cells to be recruited into the thyroid and to secrete thyroid antibodies. The three main target antigens for thyroid antibodies are thyroglobulin, the storage protein for thyroid hormones; the thyroid microsomal antigen, which has been identified as thyroid peroxidase,[23] the rate-limiting enzyme in thyroid hormone biosynthesis; and the thyrotropin receptor. Antibodies to other thyroid antigens and thyroid-growth–promoting immunoglobulins distinct from thyrotropin-receptor–stimulating antibodies have been described but not fully characterized.[24]

Mechanism of Hypothyroidism

Activated CD4 T cells recruit cytotoxic (CD8) T cells as well as B cells into the thyroid.[25] The direct killing of thyroid cells by CD8 cells is believed to be the main mechanism responsible for hypothyroidism. However, thyroid autoantibodies may also have a pathogenic role. Anti–thyroid peroxidase antibodies inhibit the activity of thyroid peroxidase in vitro but are unlikely to have a primary effect in vivo.[26] Some patients have cytotoxic antibodies capable of fixing complement and causing thyroid-cell lysis,[27-29] and terminal complement complexes have been detected on thyroid cells.[30] Antibody-dependent, cell-mediated cytotoxicity involving natural killer cells has also been described. The relative contributions of these various mechanisms of thyroid destruction in vivo remain uncertain.

Anti–thyrotropin-receptor antibodies may also contribute to hypothyroidism by blocking the action of thyrotropin. These antibodies have been reported in about 10 percent of patients with goitrous autoimmune thyroiditis and in about 20 percent of those with atrophic autoimmune thyroiditis.[31-33] How often anti–thyrotropin-receptor antibodies are the sole cause of hypothyroidism is uncertain. Among adults in whom these antibodies spontaneously disappear during treatment with thyroxine, only 40 percent remain euthyroid after therapy has been discontinued,[33] suggesting that thyrotropin-receptor–blocking antibodies contribute to hypothyroidism in about 5 to 10 percent of patients with chronic autoimmune thyroiditis.

PREDISPOSING FACTORS

Genetic Factors

Thyroid autoimmunity is familial. Up to 50 percent of the first-degree relatives of patients with chronic autoimmune thyroiditis have thyroid antibodies, apparently inherited as a dominant trait.[34,35] Graves' disease or chronic autoimmune thyroiditis may develop in affected relatives.[36,37]

In early studies in whites, the HLA-B8, DR3 haplotype was associated with atrophic autoimmune thyroiditis, and HLA-DR5 with goitrous autoimmune thyroiditis, suggesting that the two disorders have separate causes.[10] In Japanese persons, HLA-DR2 or HLA-DQ1 appears to be protective.[38,39] These associations are weak, however, and not consistently reproducible. Furthermore, specific HLA loci often fail to segregate with the presence of thyroid autoantibodies or the expression of disease within families.[35,40] The high prevalence of thyroid autoimmunity in patients with Down's syndrome (16 to 28 percent)[41] and in those with familial Alzheimer's disease[42] has drawn attention to chromosome 21. However, up to 50 percent of patients with Turner's syndrome, particularly those with an X isochromosome, also have chronic autoimmune thyroiditis.[43]

Exogenous Factors

The prevalence of chronic autoimmune thyroiditis is correlated with iodine intake, with the highest prevalence in countries with the highest intake of iodine, such as the United States and Japan.[44] Iodine supplementation in areas where iodine is deficient increases the prevalence of lymphocytic infiltration of the thyroid threefold,[45] and the prevalence of positive serum tests for thyroid antibodies in such areas rises to over 40 percent within 0.5 to 5 years.[46] In areas with sufficient iodine, further supplementation can induce reversible hypothyroidism. However, iodine reduces thyroid secretion in both subjects with thyroid autoantibodies and those without thyroid autoantibodies, suggesting that it acts by inhibiting the biosynthesis and release of thyroid hormone rather than by augmenting thyroid autoimmunity.[47,48] Euthyroid patients with (subclinical) chronic autoimmune thyroiditis would be expected to be more susceptible to the antithyroid effects of iodine because of the inability of the thyroid to escape from the inhibitory effects of excess iodine on the biosynthesis of thyroid hormone (Wolff–Chaikoff effect).[49] Amiodarone is a common cause of iodine-induced hypothyroidism because of its long half-life and high iodine content (35 percent by weight). Amiodarone-induced hypothyroidism usually occurs within 18 months after the initiation of therapy and is seven times more likely to develop in patients with thyroid antibodies than in those without thyroid antibodies.[50]

Hypothyroidism, which is often transient, develops in up to one third of patients treated with lithium and is more common in patients with thyroid antibodies than in those without antibodies.[51,52] As with iodine, this condition may represent a direct effect of lithium on the release of thyroid hormone, but thyroid autoantibodies are found in a larger proportion of lithium-treated patients than normal subjects (24 percent vs. 12 percent).[52]

Thyroid autoantibodies, hypothyroidism, or less commonly, Graves' disease or transient hyperthyroidism may develop in patients with cancer, myeloproliferative or myelodysplastic syndromes, or chronic viral hepatitis who are treated with interferon alfa.[53-55] The antibodies are detected in up to 20 percent of patients treated with interferon alfa, and clinical hypothyroidism develops in about 5 percent.[53,55,56] Both effects are usually reversible when therapy is stopped. Treatment with interleukin-2 or granulocyte–macrophage colony-stimulating factor has similar effects.[57,58] Patients with thyroid antibodies before treatment are more likely to have thyroid dysfunction during treatment.[59] Treatment with interferon gamma, in contrast, does not induce chronic autoimmune thyroiditis, despite its proposed role in the pathogenesis of this disease.[60]

PREVALENCE

Chronic autoimmune thyroiditis is common, but the prevalence reported in studies varies with the criteria for diagnosis, the decade when the study was performed, and the patients studied. Diagnostic criteria have included a positive test for thyroid autoantibodies in serum, an elevated serum thyrotropin concentration, and the presence of lymphocytic infiltration of the thyroid at autopsy. Forty to 45 percent of women and 20 percent of men in the United Kingdom and the United States have some degree of focal thyroiditis at autopsy (1 to 10 foci per square centimeter). When more severe thyroiditis (more than 40 foci per square centimeter) is considered, the prevalence declines to 5 to 15 percent in women and 1 to 5 percent in men.[61,62]

Patients with other thyroid diseases, such as multinodular goiter and thyroid cancer, may have low serum titers of thyroid antibodies, especially anti–thyroid peroxidase antibodies, but high titers — for example, in excess of 1:6400 in the case of anti–thyroid microsomal antibodies, or 200 IU per milliliter in the case of anti–thyroid peroxidase antibodies — are strongly suggestive of chronic autoimmune thyroiditis[63,64] or Graves' disease. Titers of antithyroid microsomal antibodies higher than 1:100 were found in 10 to 13 percent of women and 3 percent of men in community surveys in Whickham, United Kingdom, and New South Wales, Australia,[65,66] but only 1 percent of the subjects had titers higher than 1:6400. The prevalence of positive tests for thyroid

antibodies increases with age, with frequencies as high as 33 percent in women 70 years old or older.[67]

In areas with sufficient iodine, an elevated serum thyrotropin concentration is often viewed as evidence of chronic autoimmune thyroiditis, and in studies in these areas, at least half the subjects with serum thyrotropin values higher than 5 mU per liter and 80 percent with values higher than 10 mU per liter have thyroid antibodies.[65,68] In community surveys in Detroit,[69] Baltimore,[70] and Whickham[65] and a survey of general practices in Birmingham, United Kingdom,[68] 8 to 17 percent of subjects older than 55 to 60 years had subclinical hypothyroidism (a high serum thyrotropin concentration [>5 mU per liter] and a normal serum thyroxine concentration), and 3 to 7 percent had serum thyrotropin values higher than 10 mU per liter.[69,71] Despite these high figures, the prevalence of overt hypothyroidism (high serum thyrotropin and low serum thyroxine concentrations) was only 1.4 percent in women in Whickham and only about 3 percent in elderly women in Framingham, Massachusetts.[71] The rates of subclinical or overt hypothyroidism are up to seven times higher in women than in men and up to two times higher in whites than in blacks.[69,72]

CLINICAL PRESENTATION

Patients with chronic autoimmune thyroiditis present with hypothyroidism, goiter, or both. Women are five to seven times more likely to be affected than men, and a higher proportion of women have goiter.[72-74] In the Whickham survey, only 9 percent of the subjects in whom hypothyroidism developed were under the age of 45 years. After the age of 45, the hazard (incidence) rate for the development of
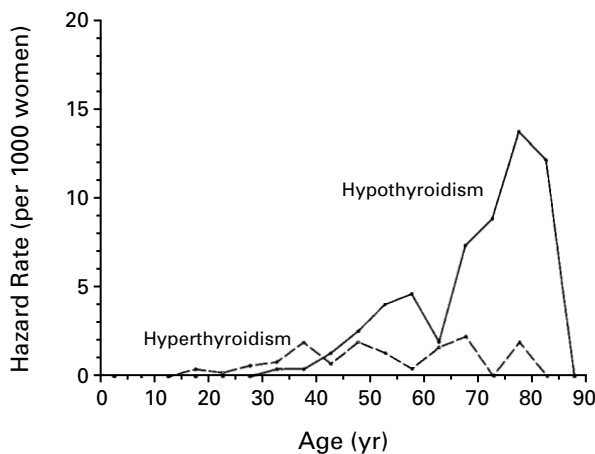

Figure 2. Age-Specific Hazard Rates for the Development of Hypothyroidism and Hyperthyroidism in Women in Whickham, United Kingdom.
Adapted from Vanderpump et al.[72] with the permission of the publisher.

hypothyroidism increased with age (Fig. 2), with 51 percent of cases diagnosed in subjects between 45 and 64 years of age. The overall mean age at the time of the diagnosis was 59 years among the women and 58 years among the men.[72] Chronic autoimmune thyroiditis is rare in children younger than five years of age, but it does occur in children and accounts for 40 percent or more of cases of goiter in adolescents.[75]

In classic Hashimoto's disease (goitrous autoimmune thyroiditis), the thyroid gland, including the pyramidal lobe if present, is diffusely enlarged, its consistency firm, and its surface often irregular. In up to 13 percent of cases, particularly in the elderly, extensive fibrosis results in an enlarging, hard goiter that may be confused with malignant disease.[76] The increase in the size of the thyroid ranges from minimal to massive (up to 350 g), but in most cases the thyroid weighs about 40 g (two to three times the normal weight).[77,78] Compression of the trachea, esophagus, or recurrent laryngeal nerves is very rare. Such changes or rapid growth of the goiter can occur, particularly in the fibrous variant, but these findings should also raise suspicion of thyroid lymphoma or carcinoma. Although a feeling of tightness in the neck is common, thyroid pain and tenderness are rare.[79] The goiter may be asymmetric and in a euthyroid patient may be mistaken for a solitary nodule or multinodular goiter. By definition, patients with atrophic autoimmune thyroiditis have no goiter. Thyroid-associated ophthalmopathy can occur in patients with chronic autoimmune thyroiditis but is far more common in those with Graves' disease.

DIAGNOSTIC STUDIES

Laboratory Findings

When chronic autoimmune thyroiditis is suspected clinically, a test for thyroid antibodies and measurement of the serum thyrotropin concentration are generally sufficient to confirm the diagnosis. The hallmark of chronic autoimmune thyroiditis is the presence of thyroid-specific autoantibodies in serum. Antithyroglobulin antibodies have been reported in about 60 percent of patients with diffuse goiter, hypothyroidism, or both, and antithyroid microsomal antibodies in 95 percent.[64] The titers tend to be higher in patients with the atrophic form of autoimmune thyroiditis than in those with the goitrous form.

Most laboratories test for antithyroid microsomal antibodies by hemagglutination or test for anti–thyroid peroxidase antibodies by enzyme-linked immunoassay or radioimmunoassay. A positive test for anti–thyroid peroxidase antibodies is a slightly more sensitive indicator of chronic autoimmune thyroiditis than a positive test for antithyroid microsomal antibodies.[63] However, since low titers of antithyroid antibodies may be present in patients with other

thyroid diseases, tests for anti–thyroid peroxidase antibodies offer little advantage over tests for anti-thyroid microsomal antibodies in routine clinical practice. The higher prevalence and higher titers of both types of antibodies, as compared with antithyroglobulin antibodies, make measurements of the latter superfluous.[80]

In community surveys, 50 to 75 percent of subjects with positive tests for thyroid antibodies are euthyroid, but 25 to 50 percent have subclinical hypothyroidism and 5 to 10 percent have overt hypothyroidism. Some patients with chronic autoimmune thyroiditis may also have an elevated erythrocyte sedimentation rate, polyclonal hypergammaglobulinemia, monoclonal gammopathy, or antinuclear antibodies.

Radionuclide Imaging and Ultrasonography

Thyroid imaging is unnecessary in patients suspected of having goitrous autoimmune thyroiditis. Sometimes, however, the diagnosis is not suspected, and imaging is performed as part of an investigation of goiter. The radionuclide scan can be very misleading in such cases, because the pattern of uptake may mimic that of Graves' disease, multinodular goiter, or even a hyperfunctioning or hypofunctioning nodule.[81] The uptake of radionuclide is characteristically normal or elevated in patients with goitrous autoimmune thyroiditis, even in the presence of hypothyroidism, whereas in those with subacute or silent thyroiditis, the uptake is low. Ultrasonography shows an enlarged thyroid gland with a diffusely hypoechogenic pattern in 18 to 77 percent of patients,[77,78] but the findings are not specific.

Biopsy

The clinician should not be sidetracked by the presence of thyroid autoantibodies in a patient who has a suspicious nodule or a rapidly enlarging goiter; a fine-needle aspiration biopsy or large-needle biopsy is necessary. Fine-needle aspiration should be reserved for clinically suspicious areas, because oxyphil cells showing atypia may be misinterpreted as a follicular neoplasm, leading to unnecessary surgery (Fig. 3).[82,83] The diagnosis of high-grade lymphoma poses little difficulty. Lower grades of lymphoma may be suspected on the basis of the presence of monomorphic lymphocytes and appropriate immunohistochemical studies, in which case a biopsy with a larger-core needle or even an open biopsy is indicated for confirmation.[84]

NATURAL HISTORY

Progression of Subclinical Disease

In patients with chronic autoimmune thyroiditis, subclinical hypothyroidism can develop into overt hypothyroidism, but the progression is often extremely slow. In a 20-year follow-up study of the Whickham cohort, clinical or biochemical hypothyroidism de-
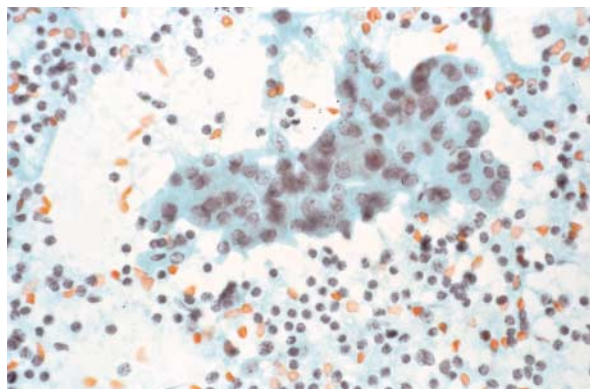

Figure 3. Specimen of Thyroid Obtained by Fine-Needle Aspiration Biopsy in a Patient with Chronic Autoimmune Thyroiditis, Showing a Clump of Oxyphilic Thyroid Follicular Cells Surrounded by Lymphocytes (Papanicolaou's Stain, ×600). (Courtesy of Dr. Wanda Szyfelbein.)

veloped in 55 percent of the women who initially had both positive tests for thyroid antibodies and elevated serum thyrotropin values (>6 mU per liter) but normal serum thyroxine values — a rate of progression of 4.3 percent per year.[72] Among the women who initially had either a raised serum thyrotropin value or thyroid antibodies (but not both), only one had overt hypothyroidism after 4 years,[85] but the 20-year rates of progression were 2.6 percent per year among the subjects with elevated serum thyrotropin values and 2.1 percent per year among those with antithyroid antibodies, resulting in rates of overt hypothyroidism of 33 and 27 percent, respectively, at the end of the follow-up period. The risk of a progression to overt hypothyroidism was five times higher among the men than among the women and increased markedly with age in women who were 45 years old or older. Higher initial serum thyrotropin concentrations predicted higher rates of progression (Fig. 4), as did higher initial titers of thyroid antibodies. These findings are consistent with the results of several smaller, shorter-term follow-up studies.[68,86-88] Among patients with serum thyrotropin values higher than 20 mU per liter or titers of antithyroid microsomal antibodies higher than 1:100,000, overt hypothyroidism develops in 25 percent per year.[87,89] Serum thyrotropin values that are only mildly elevated may return to normal, and subsequent tests for thyroid autoantibodies become negative in about 10 percent of patients.[72]

Graves' Disease and Chronic Autoimmune Thyroiditis

Graves' hyperthyroidism occasionally develops in patients with hypothyroidism caused by chronic autoimmune thyroiditis,[90] confirming the fact that the latter condition does not always result in irreversible destruction of the thyroid. In contrast, among pa-
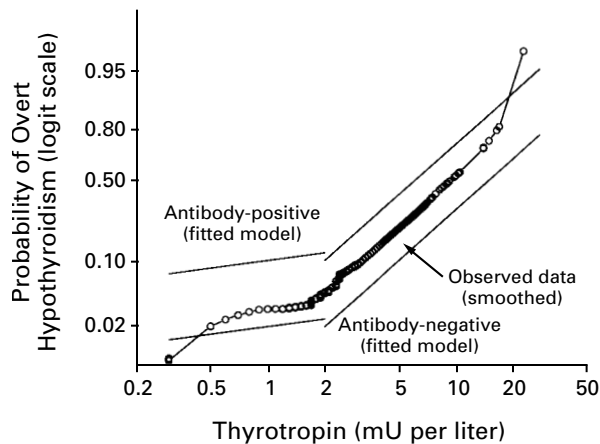
Figure 4. Probability of the Development of Overt Hypothyroidism in Women within 20 Years after the Initial Measurement of the Serum Thyrotropin Concentration.

The estimated probabilities are also shown according to whether the thyroid-antibody test was negative or positive. Data are from the Whickham study. Adapted from Vanderpump et al.[72] with the permission of the publisher.

tients with Graves' hyperthyroidism who remain euthyroid after treatment with antithyroid agents or a partial thyroidectomy, hypothyroidism, presumably due to chronic autoimmune thyroiditis, develops in about 10 to 20 percent after 10 to 25 years.[91-93]

Thyroid Lymphoma

Thyroid lymphoma is a very rare but serious complication of chronic autoimmune thyroiditis. Among 5592 Japanese women with chronic autoimmune thyroiditis who were followed for an average of eight years, thyroid lymphoma developed in 0.1 percent, a prevalence 80 times higher than expected.[94] Eighty to 100 percent of patients with thyroid lymphoma have evidence of chronic autoimmune thyroiditis in the surrounding tissue, and 67 to 80 percent have thyroid antibodies.[95-98] The lymphomas are usually the non-Hodgkin's B-cell type, tend to occur in older women (50 to 80 years old), and are usually confined to the thyroid gland.[95,97] Radiotherapy alone or combined with chemotherapy results in survival rates ranging from 13 to 92 percent at five years. Patients over 65 years old with large, rapidly growing tumors of histologically high grade have the worst prognosis.[97,99]

CHRONIC AUTOIMMUNE THYROIDITIS AND PREGNANCY

Subclinical hypothyroidism has been associated with reduced fertility. The presence of thyroid antibodies alone does not affect the conception rate but has been associated with a rate of spontaneous abortion that is twice the normal rate[100] and tends to be more common in women with recurrent spontaneous abortions.[101] These findings are thought to represent

a general tendency toward the development of autoimmunity rather than a toxic effect of thyroid antibodies. About 5 percent of infants whose mothers have chronic autoimmune thyroiditis (predominantly the atrophic form) have transient neonatal hypothyroidism, which is caused by transplacental passage of thyrotropin-receptor–blocking antibodies.[102]

The most common complication of chronic autoimmune thyroiditis in pregnant women is postpartum thyroiditis. This condition, which usually occurs two to six months after delivery, is characterized clinically by hyperthyroidism with a low 24-hour radioiodine uptake, by hypothyroidism, or by hyperthyroidism followed by hypothyroidism. The condition resolves spontaneously within a year.[103] In areas with sufficient iodine, postpartum thyroiditis occurs in 35 to 85 percent of women who have positive tests for thyroid antibodies during pregnancy or in the postpartum period, as compared with 4 to 9 percent of pregnant women overall.[104-106] Despite an initial recovery, about 25 percent of women have overt hypothyroidism four or more years later.[107,108]

THERAPY

Hypothyroidism

All patients with overt hypothyroidism should be treated with thyroxine, and the dose should be adjusted to normalize the serum thyrotropin concentration. In elderly patients, particularly those with long-standing symptoms of hypothyroidism or coexistent ischemic heart disease, treatment should begin with a low dose (12.5 to 25 μg daily), with increments at intervals of four to six weeks, so that the serum thyrotropin concentration reaches a steady-state value after each change in the dose. In most women, a 25 to 50 percent increase in the dose is required during pregnancy to maintain normal serum thyrotropin concentrations.

The role of thyroxine therapy in patients with subclinical hypothyroidism is more controversial.[109] In two placebo-controlled trials of thyroxine therapy in patients with subclinical hypothyroidism, symptom scores improved. In one of these studies, however, the majority of patients had treated hyperthyroidism (and serum thyrotropin concentrations up to 39 mU per liter) rather than chronic autoimmune thyroiditis,[110] and in the other study, a fixed dose of thyroxine was given rather than titration of the dose to normalize the serum thyrotropin concentration.[111] We recommend treatment if a patient has any symptoms potentially attributable to hypothyroidism, the serum thyrotropin concentration is higher than 10 mU per liter, the patient is at high risk for progression to overt hypothyroidism (because of a strongly positive test for thyroid autoantibodies, an age over 45 years, or male sex), and heart disease is absent. If surveillance rather than treatment is planned, the se-

rum thyrotropin concentration should be measured in six months and subsequently every one to two years.

Up to 24 percent of patients with hypothyroidism caused by chronic autoimmune thyroiditis who are treated with thyroxine for more than one year remain euthyroid when the drug is withdrawn.[33,112,113] Such a remission may result from the disappearance of thyrotropin-receptor–blocking antibodies[33] (see above) or the cessation of treatment with cytokines, lithium, amiodarone, or other iodine-containing substances. Remission can be established only by reducing the dose of thyroxine or withdrawing the drug. Testing for remission should be performed if the diagnosis was made within a year after parturition or if the patient was eating foods very high or low in iodine or receiving relevant drug or cytokine therapy. In the majority of hypothyroid patients with positive thyroid-antibody tests, however, testing for remission by discontinuing thyroxine therapy is justified only if requested by the patient. Self-limited hypothyroidism may also be caused by undiagnosed silent, postpartum, or viral thyroiditis.

Goiter

Thyroxine may also be given to decrease the size of the goiter in euthyroid patients with goitrous autoimmune thyroiditis. In 50 to 90 percent of patients, the size of the goiter decreases by an average of 30 percent after treatment with thyroxine for six months, irrespective of the initial serum thyrotropin concentration.[9,114,115] Thyroid-antibody titers may also decline during therapy, and thyroid tenderness, if present, may be relieved.[116,117]

ASSOCIATIONS WITH OTHER DISEASES

Although chronic autoimmune thyroiditis is common in the general population, the prevalence rate is higher in patients with multiple endocrine neoplasia type II (70 percent), the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) (50 percent), Turner's syndrome (50 percent), Addison's disease (20 percent), and Down's syndrome (20 percent), as well as other diseases. Serum thyrotropin concentrations should be measured periodically in patients with these disorders.

CONCLUSIONS

Chronic autoimmune thyroiditis is the most common and extensively studied organ-specific autoimmune disorder in humans. The ability to detect thyroid enlargement clinically and the availability of very sensitive tests for thyroid antibodies and thyrotropin have revealed many previously unrecognized cases of subclinical disease. As in the initial cases described by Hashimoto, permanent hypothyroidism is not inevitable. Progressive disease appears to be signaled by a high titer of thyroid antibodies and elevated serum thyrotropin concentrations, especially in patients over the age of 45 years and in association with thyroid atrophy. The underlying mechanisms responsible for initiating thyroid autoimmunity and promoting the progression of the disease remain unknown.

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CORRECTION

Chronic Autoimmune Thyroiditis

Chronic Autoimmune Thyroiditis . On page 105, the first sentence under the heading ``Associations with Other Diseases´´ should have read, ``Although chronic autoimmune thyroiditis is common in the general population, the prevalence rate is higher in patients with *autoimmune polyglandular syndrome type II,´´* not ``in patients with *multiple endocrine neoplasia type II,´´* as printed.

N Engl J Med 1996;335:1079