

Thyroiditis

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Meet the Professor – “Thyroiditis”

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Overview

The term thyroiditis means inflammation of the thyroid. As an isolated word, it is meaningless. It always requires a modifying term. Several different types of thyroiditis will be discussed.

Hashimoto’s Thyroiditis

Hashimoto’s thyroiditis is also known as chronic lymphocytic thyroiditis or autoimmune thyroiditis. The prevalence of the disease is proportional to the iodide intake of the population. In experimental animals, iodine is necessary for the expression of the disease. In addition, excess iodine can precipitate hypothyroidism in euthyroid patients with Hashimoto’s thyroiditis. The prevalence of anti-thyroid antibodies (the hall-mark of this disorder) approaches 40 % in the elderly.

Diagnosis

Most patients have a **goiter**; the consistency may range from rubbery to firm to stony hard (fibrous variant). The surface is often described as bossellated. Because of the ease of palpation, many of these goiters are misdiagnosed as nodules (single or bilateral). Although discrete nodules do occur in Hashimoto’s thyroiditis they are uncommon and generally require biopsy. In rare cases the thyroid may be tender, but a **painless thyroid** is the general rule. Sudden growth of a Hashimoto’s gland raises the suspicion of thyroid lymphoma or concomitant malignancy. On **thyroid scan** the pattern of uptake may be homogeneous to spotty and uneven; scans may mimic hot or cold nodules. Note, the radioactive iodine uptake is often elevated in patients with Hashimoto’s thyroiditis at the time of TSH elevation. A thyroid scan is generally not necessary in these patients.

Anti-microsomal antibodies are positive in 95 % of patients. **Anti-thyroid peroxidase antibodies (anti TPO antibodies)** are positive in about 98%, including 50% of those with negative anti-microsomal antibodies. In some patients antibody production is confined to intrathyroidal lymphocytes. **Anti-thyroglobulin antibodies** are usually positive, particularly when newer more sensitive assays are employed. Antibodies against the sodium iodide symporter (NIS) and the TSH receptor may occur. The presence of antithyroid antibodies predicts progressive thyroid failure (Table I), subsequent development of post-partum thyroiditis and an increased risk of miscarriages. Thyroid antibody positive patients with unexplained urticaria may note improvement in hives with thyroid hormone suppressive therapy. The **perchlorate discharge test** (or iodide-perchlorate discharge test) is generally abnormal, indicating impaired iodide organification.

On **biopsy** diffuse lymphocytic infiltration with oxyphilic thyroid follicular epithelium are present. The prominent oxyphilic changes can be misinterpreted as a neoplasm. Biopsies should only be performed if a clinically suspicious area or nodule is noted.

Atrophic Thyroiditis

Some patients presenting with non-iatrogenic profound hypothyroidism demonstrate atrophy of the thyroid gland thought to be autoimmune in nature. Thyroid autoantibodies are generally present. Pathological examination may demonstrate parenchymal destruction, fibrosis and some lymphocytic infiltration. Ultrasound examination may demonstrate diffusely decreased echogenicity with reduced thyroid volume. The relation of atrophic thyroiditis to Hashimoto's is uncertain. Thyroid atrophy is not an inevitable end result of Hashimoto's thyroiditis. One study found a very high prevalence of anti-*Helicobacter pylori* antibodies in patients with autoimmune atrophic thyroiditis. Profound but occasionally reversible hypothyroidism may also occur without goiter in patients with antibodies which block the TSH receptor. Follicular cell atrophy is found in these patients.

Destructive Thyroiditis

Destructive thyroiditis is the general term for a number of disorders characterized by hyperthyroidism due to release of preformed thyroid hormone. The increased concentration of thyroid hormone suppresses serum TSH. The radioactive iodine uptake is close to nil in all cases, when hyperthyroidism is present. The duration of hyperthyroidism is limited by the amount of thyroid hormone present. It is generally no more than 2 – 3 months in duration but may be longer in cases of amiodarone induced destructive thyroiditis. The ratio of serum T3:T4 is lower in destructive thyroiditis than in Graves' disease. Hypothyroidism is common after the hypothyroidism phase. In some patients, only the hyperthyroid or hypothyroid phase is noted. Permanent hypothyroidism is common in some forms of destructive thyroiditis and rare in others. The multiple causes of destructive thyroiditis are listed in Table II.

In most cases (amiodarone destructive thyroiditis being an important exception) specific therapy is not necessary during the hyperthyroid phase. Beta blockade is often helpful. Glucocorticoids may decrease the duration of the clinical syndrome but are rarely necessary in painful or painless subacute thyroiditis. Iopanoic acid is an effective therapy to improve clinical hyperthyroidism by inhibition of peripheral T4 to T3 conversion.

Table II Hyperthyroidism secondary to destructive thyroiditis

- 1) Painful post-viral painful subacute thyroiditis (De Quervain's, granulomatous thyroiditis)
- 2) Painless lymphocytic subacute thyroiditis.
- 3) Amiodarone associated destructive thyroiditis
- 4) Palpation thyroiditis including post-surgical
- 5) Post-radiation thyroiditis
- 6) Malignant pseudothyroiditis (follicular thyroid carcinoma, anaplastic thyroid carcinoma, thyroid lymphoma, carcinoma metastatic to the thyroid)
- 7) Pneumocystis thyroiditis
- 8) Thyroid amyloidosis
- 9) Painful destructive lymphocytic thyroiditis
- 10) Painless post-viral (granulomatous thyroiditis)
- 11) Radiocontrast induced acute destructive thyroiditis

Post-viral painful subacute thyroiditis (De Quervain's or granulomatous thyroiditis)

Painful (granulomatous) subacute thyroiditis is a seasonal disorder which is attributed to a prior viral illness. Specific viruses are rarely cultured from the thyroid. A variety of viral antibody titers fall after a bout of subacute thyroiditis, thought to represent a general amnesic response to illness rather than a specific indicator of viral etiology.

The disease is thought to have a genetic predisposition with HLA-B 35 individuals at highest risk. In one study 60 - 70 % of patients with painful subacute thyroiditis were HLA-B35 positive compared with 10 - 15 % of controls. In a Japanese study HLA - B67 was more likely to be present when painful subacute thyroiditis developed in the summer or autumn whereas HLA-B35 was more common when there was no seasonal occurrence. Identical twins have been reported with the disorder. The disease is more common in females.

The **clinical picture** may be quite dramatic, with intense thyroid pain radiating to the jaw or ear, high fever, and systemic as well as hyperthyroid symptoms. Malignancy may be mimicked because of the firmness of the goiter; the disorder may present as a "fever of unknown origin" Myalgias, elevated alkaline phosphatase and anemia are relatively common. Serum thyroglobulin is markedly in contrast with factitious hyperthyroidism where the 24 hour radioiodine uptake is also nil but the serum thyroglobulin is low. Transient hypothyroidism may occur, but permanent hypothyroidism is rare, despite extensive follicular disruption seen on histological examination. Mild recurrences may occur at an annual incidence as high as 2.3 %, but full blown clinical recurrences are rare. Antithyroid antibodies are generally absent or transitory, and present in low titer. These are thought to be secondary to thyroid tissue destruction, rather than an immune attack on the thyroid. The sedimentation rate is markedly elevated and may be greater than 100 mm/hr. Pathological findings include marked follicular destruction with giant cells. Non-steroidal anti-inflammatory agents and reassurance often suffice to control the neck discomfort. Glucocorticoid therapy is rarely required.

Painless Subacute Thyroiditis ("Spontaneously resolving hyperthyroidism with lymphocytic thyroiditis") including Post-Partum Thyroiditis

The most common variant of painless subacute thyroiditis is **post-partum thyroiditis.(PPT)**. This autoimmune disorder, a variant of Hashimoto's thyroiditis, occurs in 5 - 9 % of all post-partum women in iodine sufficient areas. Patients with pre-existing Hashimoto's thyroiditis, diabetes mellitus type I and Graves' disease are particularly prone to PPT. Antithyroid antibodies are present in 75 or more percent of cases. A predilection for HLA DR3 and 5, the so-called autoimmune haplotypes, is noted. The time course of hyperthyroidism is similar to painful subacute thyroiditis.

Hypothyroidism may persist in up to 25 % of patients, and at least half of the patients with post-partum thyroiditis have persistent goiter and positive anti-thyroid antibodies two years after an episode, persistent or permanent hypothyroidism is relatively common in patients with PPT. The thyroid gland is diffusely infiltrated with lymphocytes and thyroid autoantibodies (typically anti-microsomal or anti-thyroid peroxidase [TPO] antibodies) are positive in most patients. A family history of autoimmune thyroid disease is common and female predominance is noted. I generally recommend levothyroxine therapy during the hypothyroid phase and commonly continue this therapy throughout the child bearing years. Recurrent PPT occurs in 75 % of women with subsequent pregnancies.

The etiology of **sporadic painless subacute thyroiditis** is less certain. Although many cases represent autoimmune lymphocytic subacute thyroiditis, a viral etiology has also been suggested. When patients receiving lithium become hyperthyroid they generally have painless subacute thyroiditis, presumed to be lymphocytic. Lymphocytic subacute thyroiditis is common after immunotherapy for hepatitis C whereas painful subacute thyroiditis is rare.

Atypical Subacute Thyroiditis

The presence or absence of pain in patients with destructive thyroiditis is generally considered the most important diagnostic point. Painful thyroiditis is thought to be post-viral, self limited with a granulomatous histology. Painless thyroiditis is commonly considered to be autoimmune and to require life-long surveillance.

However, there is some evidence for a viral etiology for some patients with painless Subacute thyroiditis and an autoimmune etiology for some patients with painful thyroiditis:

- 1) A husband and wife developed hyperthyroidism within a three week period of time. One had pain, the other did not. Cytological examination was not performed.
- 2) A mini-epidemic of antibody negative destructive thyroiditis occurred between July and August of 1987 in the small town of Winterswijk in the Netherlands. The authors identified 12 index cases; goiter was present in nine but was tender in only two. An additional 5 household contacts and 6 retrospectively-identified cases were noted. Clinical characteristics included low-grade fever, fatigue, headache, myalgias, and fine desquamation of palms and soles. The 20 minute ^{99m}Tc pertechnetate uptake was decreased in 10 of 11 tested. The sedimentation rate was elevated to a maximum of 68 mm/h. Only one patient expressed HLA-B35. The incubation period was estimated at 6 days; all were euthyroid after 10 months. A post-viral illness was considered likely but cytological examination of the thyroid was not performed.
- 3) Chronic autoimmune thyroiditis (Hashimoto's thyroiditis) and post-partum thyroiditis are rarely painful. However, a form of chronic autoimmune thyroiditis described in Japan is characterized by sudden thyroid pain, transient thyrotoxicosis, low radioiodine uptake and cytological evidence of chronic lymphocytic thyroiditis. Many of these patients developed permanent hypothyroidism. Age, duration of symptoms, ESR and C-reactive protein did not distinguish this group from painful post-viral subacute thyroiditis.
- 4) We recently described a mini-epidemic of likely post-viral painless subacute thyroiditis with spontaneously resolving hyperthyroidism in 10 patients, 9 of whom were men. None of 8 patients tested had positive TPO antibodies. FNA revealed multinucleated giant cells in the only patient biopsied. Although granulomatous changes in the thyroid are common without an antecedent pain history, a clinical post-viral painless syndrome characterized by nil radioiodine uptake, hyperthyroidism and granulomatous changes has only recently been described.

Amiodarone Induced Destructive Thyroiditis (Amiodarone Induced Thyrotoxicosis Type II)

Amiodarone has is an iodinated benzylfuran which contains 75 mg of iodine per 200 mg. Amiodarone inhibits T4 to T3 conversion, blocks the entry or nuclear binding of T3 and is potentially toxic to the thyroid.

Amiodarone induced thyrotoxicosis Type I is iodine induced, precipitating hyperthyroidism in patients with multinodular goiters or those with latent Graves' disease. The presence of TSAbs favors Graves' disease as does the presence of anti-TPO antibodies.

Amiodarone induced thyrotoxicosis type II (AIT II) occurs in patients with previously normal thyroid glands. This is a form of destructive thyroiditis with a relatively prolonged hyperthyroid phase, occasionally followed by transient or permanent hypothyroidism. Thyroid autoantibodies are negative. FNA is usually not helpful, as the necrosis seen on pathological specimens is quite patchy. AIT II comprises 80-90 % of amiodarone induced thyrotoxicosis cases.

The distinction between AIT II and AIT I with Graves' disease may be quite difficult. In the U.S. the 24 hour radioiodine uptake is almost uniformly nil in both groups. Italian studies suggest that a markedly elevated IL-6 concentration helps diagnose AIT II. In our own experience and the experience of Eaton in Great Britain, this test has not been valuable. Color flow doppler sonography generally reveals normal or increased blood flow in AIT I and decreased flow in AIT II, but this must be specifically requested from your ultrasound department. The most extensive experience is available in Italy. A study from Great Britain found that 20 percent of color flow studies in AIT were indeterminate. AIT II usually responds dramatically to glucocorticoid therapy. A recent prospective controlled trial found that almost all AIT II patients normalized free T4 within two weeks of prednisone therapy. When the underlying cardiac condition are precarious prompt and aggressive therapy will be necessary. This may require surgery after administration of iopanoic acid.

Therapy of AIT is summarized in Table III

Table III AIT Therapy

Type I – Nodular Goiter or Graves disease

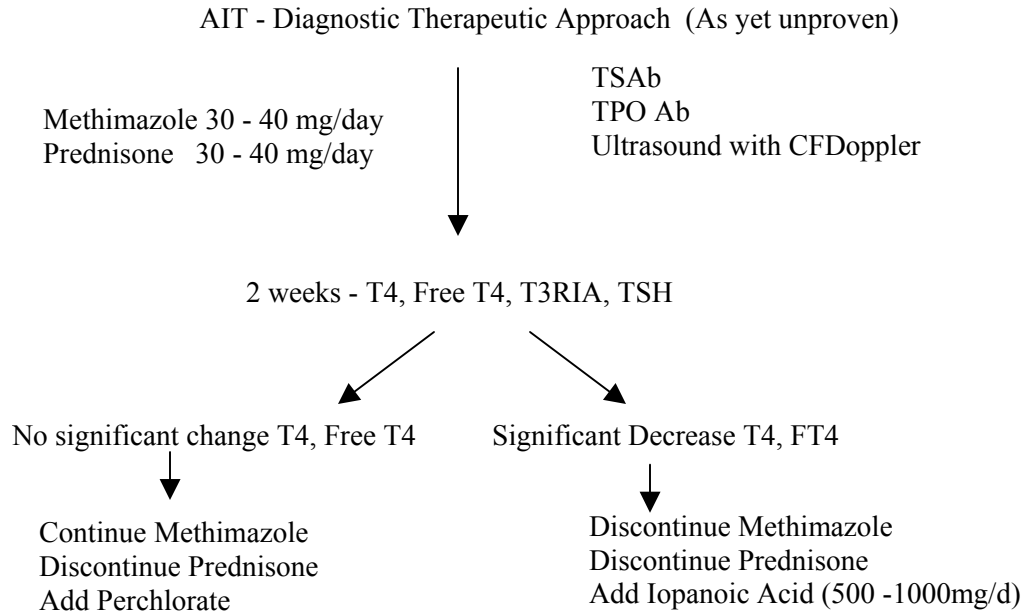
- 1) Antithyroid drugs – usually methimazole 30 – 40 mg per day.
- 2) ?Perchlorate
- 3) ? Surgery
- 4) ? Iopanoic Acid prior to surgery
- 5) ? Cholestyramine
- 6) ? Radioactive iodine eventually
- 7) Amiodarone is commonly discontinued if feasible. If not surgery becomes a more desirable option.

Type II – Destructive Thyroiditis

- 1) Glucocorticoids
- 2) ? Iopanoic Acid
- 3) ? Cholestyramine
- 4) ? Surgery ?

Uncertain if Type I or Type II

- 1) Antithyroid drugs (Methimazole 30 mg/day)
- 2) Prednisone (40 mg /day)
- 3) ?Perchlorate (0.5 gm bid)
- 4) ?Iopanoic Acid (500 - 1000 mg /day)
- 5) ?Cholestyramine (4gm 4id)
- 6) ? Surgery – after addition of Iopanoic Acid



Riedels Thyroiditis (Invasive Fibrous Thyroiditis)

Riedels thyroiditis is extremely rare disorder, characterized by invasive fibrous tissue proliferation, invasive into surround tissues. A rapidly enlarging neck mass may invade the trachea or esophagus and may mimic thyroid carcinoma or lymphoma. Hypothyroidism may occur and positive anti-thyroid antibodies have been reported. It may be accompanied by other fibro-proliferative processes, including orbital pseudotumor, mediastinal fibrosis, retroperitoneal fibrosis, sclerosing cholangitis. The condition is responsive to glucocorticoids in some patients. Tamoxifen has some efficacy in patients with retroperitoneal fibrosis and Riedel's thyroiditis.

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