

THYROIDITIS: TIME TO ENHANCE OUR UNDERSTANDING

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Thyroiditis

Thyroiditis is an inflammation of the thyroid gland. It may be painful and tender when caused by an infection or trauma, or painless when caused by an autoimmune condition or medications. Thyroiditis is most prevalent among people ages 30 to 50 and is more common in females than in males. Incidence is highest in the Appalachian region of the United States.¹

Types of Thyroiditis

There are several types of thyroiditis. These are autoimmune types (most common) includes Hashimoto's disease, painless or silent thyroiditis and postpartum thyroiditis; *sub acute or de Quervain's thyroiditis*; *drug-induced thyroiditis* (amiodarone, interferon, lithium and cytokines); radiation induced thyroiditis (post Iodine-131 or after external beam radiation therapy to neck); *acute or suppurative thyroiditis and Riedel's or fibrous thyroiditis*.

Pathogenesis of Thyroiditis

AUTOIMMUNE THYROIDITIS: The mechanism for autoimmune destruction of the thyroid involves both cellular and humoral immunity.² The anti-thyroid immune response begins with activation of thyroid antigen-specific helper T cells. This may result from infection with a virus that has a protein similar to a thyroid protein or thyroid epithelial cells present their own intracellular proteins to T cells.³ In painless postpartum thyroiditis, thyroid antigen-specific helper

T cells may be activated by the accumulation of fetal cells in the maternal thyroid gland.⁴ Activation of helper T cells induces B cells to secrete thyroid antibodies.⁵ The thyroid antibodies most frequently measured are those directed against thyroid peroxidase (anti TPO) and against thyroglobulin (anti Tg). Presence of anti-TPO antibodies tends to correlate with thyroidal damage, lymphocytic infiltration and thyroid dysfunction.⁶ The role of anti-Tg antibodies is less clear and less frequent. Anti-TSH receptors, colloid antigen, thyroid hormones and sodium iodide symporter have been detected in patients with autoimmune thyroiditis.⁷

SUB-ACUTE or de QUERVAIN'S THYROIDITIS: This was first reported in 1825, but de Quervain recorded its pathological description in 1904. It is the most common cause of a painful thyroid gland. A viral infection or a postviral inflammatory response (including coxsackie virus, Epstein-Barr, mumps, measles, adenovirus, echovirus, and influenza) is presumed to cause de Quervain's thyroiditis.⁸

Destruction of follicular epithelium and loss of follicular integrity are the primary events in the pathophysiology of de Quervain's thyroiditis.⁹ TGB, thyroid hormones, and other iodinated compounds are released into the blood, often in quantities sufficient to elevate the serum thyroxine (T4) and triiodothyronine (T3) concentrations and suppress TSH secretion. This state lasts until the stores of TGB are exhausted or until healing occurs. New hormone synthesis temporarily ceases because of the low TSH. As inflammation subsides, the thyroid follicles regenerate and thyroid hormone synthesis and secretion resume. In some patients, several months are required for thyroid hormone synthesis to return to a normal rate; during that period, clinical hypothyroidism may be evident.¹⁰

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DRUG INDUCED THYROIDITIS: Amiodarone is a type III anti-arrhythmic agent and rich in iodine. In 20% patients being treated in iodine sufficient regions, amiodarone induced hypothyroidism is observed and this is due to excess iodine. Patients with pre-existing autoimmune process are at higher risk. However, in about 23% patients in iodine deficient regions, amiodarone may induce thyrotoxicosis either due to activation of thyroid gland (more likely in patients with pre-existing thyroid disorder like nodular goiter) [Type I] or due to destruction of thyroid follicles and release of preformed thyroid hormone [Type II].¹¹

Interferon Alpha and Interleukine-2: As these agents are immunomodulator, they may cause auto-antibodies mediated destructive thyroiditis or Graves' disease caused by production of thyrotropin stimulating immunoglobulin (TSI). Reported incidence of these disorders is about 2-19%.¹²

Lithium is an effective anti-psychotic agent, known to increase the residing time of iodine in thyroid follicular cells. In 10-33% patients on long term lithium treatment, high level of anti-thyroid antibodies may induce hypothyroidism. However, destructive thyroiditis caused by direct toxic effect of lithium resulting in thyrotoxicosis has also been reported.¹³

RADIATION INDUCED THYROIDITIS: can be seen in less than 1% patients between 1-10 days after Iodine-131 ($I-^{131}$) treatment for Graves' disease or in patients after external beam radiation therapy for head and neck cancer.¹⁴ These are caused by radiation induced destruction of thyroid follicles and release of preformed hormones (thyrotoxicosis) and eventually hypothyroidism.¹⁵

ACUTE OR SUPPURATIVE THYROIDITIS: It is a rare entity as thyroid is resistant to infection due to encapsulation, rich blood and lymphatic supply and high iodine content.¹⁶ It is not uncommon in immunosuppressed individual, in patients with pre-existing thyroid disease or congenital pyriform sinus fistula. Usually caused by bacteria but fungus, mycobacterial or parasitic infection may also occur.¹⁷

RIEDEL'S OR FIBROUS THYROIDITIS: Is characterized by progressive but extensive fibrosis of thyroid gland and its bed. It is a manifestation of a systemic fibrotic process of unknown etiology.¹⁸

Symptoms and signs of Thyroiditis

There are no specific symptoms for thyroiditis but neck is usually tender in cases of de Quervain's or suppurative thyroiditis. In later case patient may be toxic depending upon the severity of infection. Hashimoto's thyroiditis is characterized by firm, rubbery and painless goiter while a rocky hard and painless goiter is the hallmark of Riedel's thyroiditis.

If thyroiditis is associated with destruction of thyroid follicles and release of stored free T₃ (FT₃) and free T₄ (FT₄) hormones, producing symptoms of thyrotoxicosis like palpitation, anxiety, fatigue, insomnia, increased appetite and weight loss. Similar symptoms are encountered in thyroiditis associated with Graves' disease or activation of thyroid gland (i.e. increased production of FT₃ and FT₄ – hyperthyroidism). Furthermore, sign and symptoms are more severe as compared to thyrotoxicosis with destructive thyroiditis. In case of destructive thyroiditis, transient phase of thyrotoxicosis is followed by sign and symptoms of hypothyroidism due to gradual depletion of stored hormones. These include weight gain, lethargy, constipation, depression, cold intolerance and dry skin. This phase may be permanent as in case of radiation induced thyroiditis, Hashimoto's or few cases of painless, subacute or postpartum thyroiditis or followed by a state of euthyroidism due to complete recovery of thyroid gland.

Laboratory Investigations for Thyroiditis

THYROID ANTIBODIES: Commonly thyroid peroxidase (TPO) and thyroglobulin antibodies are measured. TPO antibodies are closely related with thyroid destruction and overt thyroid dysfunction while role of thyroglobulin antibodies is unclear. However, serum thyroglobulin level rises earlier than FT₃ and FT₄ levels.¹⁹ Anti TPO is elevated in Hashimoto's

(90%),²⁰ painless thyroiditis (50%),²¹ postpartum thyroiditis²² and also in other types of thyroiditis where autoimmunity has a contributory role. In de Quervain's thyroiditis, thyroid antibodies are usually normal.

THYROID FUNCTION TESTS: In patients with destructive thyroiditis and release of stored hormone, serum TSH level is suppressed and FT3 and FT4 levels are elevated. It is important to note that FT4 concentration is proportionally higher than FT3, reflecting the ratio of stored hormones in thyroid. While in patients with hyperthyroidism (Graves' disease or toxic nodular goiter) FT3 is preferentially high. Hypothyroidism is most commonly seen in patients with Hashimoto's thyroiditis and less commonly in other types of autoimmune thyroiditis, and predicted by higher level of thyroid antibodies. It is also commonly encountered in radiation induced thyroiditis. In early phase of hypothyroidism, serum TSH level is elevated with normal FT4 and FT3 and this is termed as subclinical hypothyroidism.²³ But with progression of process, FT4 level starts declining and this is termed as overt hypothyroidism. Decline in serum FT3 level occurs at the advanced phase of hypothyroidism as high TSH level stimulate thyroid to release T3.

COLOR DOPPLER ULTRASOUND: May help to distinguish between thyroiditis and hyperthyroidism (Graves' disease or toxic nodular goiter). In later, gland is vascular and hyper-echogenic while in former gland is hypo-echogenic with low to normal vascularity.²⁴

¹²³IODINE THYROIDAL UPTAKE AND ^{99m}Tc THYROID SCAN: In patients with destructive thyroiditis, radiotracer (¹²³I or ^{99m}Tc) uptake is significantly reduced (less than 5% for radioiodine) and it is enhanced in patients with Graves' disease or toxic nodular goiter.

Thyroid scan (with Technetium-99m) is more commonly used to make this differentiation. In the destructive phase of thyroiditis, scan shows markedly reduced uptake over thyroid bed. As recovery is seen in majority of post-partum, painless and de Quervain's thyroiditis and it is evident by uptake of radiotracer by the regenerated thyroid parenchyma.

In acute or suppurative thyroiditis, thyroid scan shows

cold areas (focal areas of absent radiotracer compared to generalize absent uptake in destructive thyroiditis) concomitant with abscess.

FINE NEEDLE ASPIRATION/BIOPSY: Is usually not required but in nodular goiter like Hashimoto's thyroiditis, suppurative thyroiditis and Riedel's thyroiditis.

Hashimoto's thyroiditis is characterized by lymphoid follicles with germinal centre and thyroid follicle with Hurthle cell metaplasia and minimal colloid material. Painless postapartal thyroiditis contains dense lymphocytic infiltration without germinal centre, normal thyroid follicle with minimal Hurthle cell metaplasia. de Quervain's thyroiditis is characterized by mixed inflammation and fibrotic bands with residual follicles and multi nucleated giant cell.

Fine needle aspiration in acute or suppurative thyroiditis shows pus cell, necrotic material and causative organism. In Riedel's thyroiditis excisional or open biopsy shows extensive hyalinized fibrosis completely replaces the area of the gland involved, often directly infiltrates skeletal muscle cells in the immediate area and encases medium-sized veins.

MISCELLANEOUS: Markedly raised ESR, raised C-reactive protein (CRP) with normal or mildly elevated total leucocytes count (TLC) and raised FT3 and FT4 are the hallmark of de Quervain's thyroiditis.²⁵ Similarly in suppurative thyroiditis, ESR, TLC and CRP are elevated but FT3 and FT4 are usually normal

Clinical Outcome and Treatment

Hashimoto's thyroiditis is characterized by a spectrum of euthyroidism, transient thyrotoxicosis and ultimately hypothyroidism. Eighty percent (80%) of patients with painless and postpartum thyroiditis become euthyroid in 12-18 months time and 20% develops permanent hypothyroidism for which they require thyroxin replacement therapy (TRT). Ninety five percent (95%) cases of de Quervain's thyroiditis attain euthyroid status in 12-18 months and only 5% need TRT for hypothyroidism. Transient phase of thyrotoxicosis resulting from release of stored thyroid hormones is

treated by beta blocker as anti-thyroid medication has no role.

Radiation induced thyroiditis is heralded by permanent hypothyroidism and life long TRT is required. In acute stage, anti-inflammatory agents like salicylate and corticosteroid are used to control the local symptoms effectively.

In drug induced destructive thyroiditis, beta blockers and steroid are used to control symptoms of thyrotoxicosis and stabilizing the inflammatory response respectively while culprit drug is discontinued. While drug induced Graves' disease or toxic nodular goiter is treated by anti-thyroid, surgery or I-131 ablation. TRT is used to maintain euthyroid status while culprit agent is not need to discontinue in cases of drug induced hypothyroidism.

In acute or suppurative thyroiditis, anti-inflammatory agents and appropriate antibiotics are treatment of choice with incision and drainage of focal collection. In early phase of Riedel's thyroiditis, euthyroidism is seen in majority of patients while steroid and cytotoxic agents (like methotrexate) may be used to stop progressive fibrosis. However, in advanced stage patients become hypothyroid requiring life long TRT and surgical intervention for complication associated with extensive local fibrosis.

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