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REVIEW ARTICLES

THYROIDITIS – A REVIEW

AFSANA BEGUM[1], MD. SHAFIQUL BARI[2], KFM AYAZ[3], RUBINA YASMIN[4], NC RAJIB[5], MA RASHID[6], HAM NAZMUL AHASAN[7], FM SIDDIQUI[8]

Thyroiditis is a group of inflammatory thyroid disorders. Clinical presentation of different types of thyroiditis is diverse. Management of different thyroiditis depends on clear understanding of natural history of the disease and their presentation. This review will emphasize the clinical presentation along with laboratory investigations of different thyroiditis which ultimately guide their management.

Definition and classification of thyroiditis:
The term "thyroiditis" encompasses a diverse group of diseases that have inflammation, fibrosis or lymphocytic infiltration as the most prominent feature. Although classified as thyroiditis, each disease varies in etiology and natural history. The most useful classification of thyroiditis is based on the onset of signs and symptoms, duration of inflammation or cellular infiltration and persistence of thyroid pathology.

Chronic Lymphocytic Thyroiditis:
Chronic lymphocytic thyroiditis (Hashimoto's thyroiditis) was first described by the Japanese physician Hashimoto in 1912. It is the most common inflammatory condition of the thyroid gland and the most common cause of goiter in the United States.[1,2,3] It is an autoimmune condition characterized by high titers of circulating antibodies to thyroid peroxidase and thyroglobulin.[4]

Chronic lymphocytic thyroiditis is the most common cause of hypothyroidism in the United States, and euthyroid persons with Hashimoto's disease develop hypothyroidism at a rate of approximately 5 percent per year.[5] Up to 95 percent of cases of chronic lymphocytic thyroiditis occur in women, usually between 30 and 50 years of age.[6] Chronic lymphocytic thyroiditis is also the most common cause of sporadic goiter in children.[6,7] The incidence of Hashimoto's disease has risen exponentially over the past 50 years, and this increase may be related to an increased iodine content in the North American diet.[7]

A genetic predisposition to thyroid autoimmunity exists; it is inherited as a dominant trait.[8] HLA-B8 and HLA-DR5 haplotypes are most commonly found

Table-1
Classification of Thyroiditis

Histologic classification	Synonyms
Chronic lymphocytic	Chronic lymphocytic thyroiditis, Hashimoto's thyroiditis
Subacute lymphocytic	Subacute lymphocytic thyroiditis: (1) postpartum thyroiditis and (2) sporadic painless thyroiditis
Granulomatous	Subacute granulomatous thyroiditis, de Quervain's thyroiditis
Microbial inflammatory	Suppurative thyroiditis, acute thyroiditis
Invasive fibrous	Riedel's struma, Riedel's thyroiditis

1. Medicine Specialist, United Hospital.
2. Clinical Pathologist attached to Medicine Unit - White, Dhaka Medical College Hospital.
3. Master of Biomedicine, MD 2nd part course student, Dhaka Medical College, Dhaka
4. Junior Consultant, Department of Medicine, Shahid Suhrawardi Hospital.
5. Junior Consultant, Upazilla Health Complex, Sonargoan, Narayanganj
6. Assistant Professor, Department of Anatomy, Bangladesh Medical College.
7. Professor of Medicine, Dhaka Medical College.
8. Professor of Medicine, Dhaka Medical College.

in patients with chronic lymphocytic thyroiditis. Hashimoto's disease has been linked to other autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, pernicious anemia, diabetes mellitus and Sjögren's syndrome.[6]

Although Hashimoto's thyroiditis is usually asymptomatic, some patients may complain of a feeling of tightness or fullness in the neck; however, neck pain and tenderness are rare.[7,8] At the time of diagnosis, symptoms of hypothyroidism are present in 20 percent of patients.[7] Very rarely, patients may present with hyperthyroidism, although this is thought to indicate the coexistence of Graves' disease.[9] Physical examination generally reveals a firm, irregular, nontender goiter.[8] Regional lymphadenopathy may be present, or the goiter may be large enough to cause dysphagia or recurrent laryngeal nerve dysfunction.The erythrocyte sedimentation rate (ESR) and white blood cell count are normal. The definitive indicator of chronic lymphocytic thyroiditis is the presence of thyroid-specific autoantibodies in the serum. The three main targets for thyroid antibodies are thyroglobulin, thyroid microsomal antigen (also called thyroid peroxidase) and the thyroid-stimulating hormone (TSH) receptor.[8] Low levels of circulating antibodies are common in other thyroid diseases, such as multinodular goiter and thyroid malignancy. Antithyroid microsomal antibodies in titers greater than 1:6,400 or antithyroid peroxidase antibodies in excess of 200 IU per mL, however, are strongly suggestive of chronic autoimmune thyroiditis.[8] Testing of thyroid autoantibodies and measurement of serum thyroglobulin levels will confirm the diagnosis.[8] Radioactive iodine uptake (RAIU) is variable and can be depressed, normal or increased, depending on the extent of follicular destruction. Patchy uptake is common, providing little diagnostically useful information.[8] Ultrasonography shows an enlarged gland with a diffusely hypoechogenic pattern in most patients.RAIU and thyroid ultrasonography are not necessary parts of the work-up for this disease. A dominant nodule in a patient with Hashimoto's disease should prompt a fine-needle aspiration biopsy to exclude malignancy.[8]

Because thyroiditis is usually asymptomatic and the goiter is small, many patients do not require treatment.[6] When hypothyroidism is present, treatment with thyroxine (T_4) is indicated.[8] Thyroid hormone replacement therapy is also indicated in patients with a TSH level in the normal range, to reduce goiter size and prevent progression to overt hypothyroidism in high-risk patients.[8] Lifetime replacement of levothyroxine is indicated in hypothyroid patients, at a starting dosage of 25 to 50 μg per day, with gradual titration to an average daily dosage of 75 to 150 μg. A lower starting dosage (12.5 to 25 μg per day) and a more gradual titration are recommended in elderly patients and in patients with cardiovascular disease. The dosage may be increased in these patients 25 to 50 μg every four to six weeks until the TSH level is normal.[7,8]

In patients with an elevated TSH level and a normal thyroxine (T_4) level (subclinical hypothyroidism), indications for treatment are less clear. If the TSH level is greater than 20 mU per mL (20 mU per L) with a normal T_4 level, there is a high probability that the patient will develop hypothyroidism. If the TSH level is elevated but is less than 20 mU per mL and the antimicrosomal antibody titer is greater than 1:1,600, hypothyroidism will develop in 80 percent of patients.[6] Therefore, it is recommended that treatment be initiated in patients with symptoms of hypothyroidism, in patients with a serum TSH level greater than 10 mU per mL and in patients with a high risk of progression to hypothyroidism (e.g., those with high antibody titers)[9]. Because of the risk of developing hypothyroidism, patients with a history of chronic lymphocytic thyroiditis require annual assessment of thyroid function[9].

Subacute Lymphocytic Thyroiditis:

Subacute lymphocytic thyroiditis occurs most often in the postpartum period but may also occur sporadically.[8,10] Therefore, it is subdivided into two groups, postpartum thyroiditis and sporadic painless thyroiditis. Antimicrosomal antibodies are present in 50 to 80 percent of patients, while antithyroid peroxidase antibodies are present in nearly all patients.[4,7,8] A strong association also exists between these types of thyroiditis and the presence of lymphocytic infiltration on thyroid sampling (similar to that found in Hashimoto's disease or chronic lymphocytic thyroiditis) and a high prevalence of HLA-DR3, HLA-DR4 and HLA-DR5 haplotypes. Sub acute lymphocytic thyroiditis starts with an initial hyperthyroid phase, followed by subsequent hypothyroidism and, finally, a return to the euthyroid state. In the postpartum patient, thyrotoxicosis

usually develops in the first three months following delivery and lasts for one or two months. Then the patient returns to a euthyroid state or hyperthyroidism ensues for several months.[11] Patients with an initial episode of postpartum subacute lymphocytic thyroiditis have a notably high risk of recurrence in subsequent pregnancies.[1,7,12] Serum TSH testing is indicated in symptomatic patients.

There is a regional variation in the prevalence of this painless thyroiditis, with 90 percent of reported cases occurring in the Great Lakes region.[13] Outside of the Great Lakes, painless thyroiditis probably accounts for 1 to 5 percent of newly diagnosed cases of thyrotoxicosis. Postpartum thyroiditis may be found in 3.9 to 8.2 percent of patients screened four to 12 weeks after delivery.[14]

Subacute lymphocytic thyroiditis comprises 29 to 50 percent of all cases of thyroiditis[4] and occurs most often in women between 30 and 50 years of age.[7,12] There is a higher incidence of antimicrosomal antibodies in the postpartum form (80 percent) of the disease than in the sporadic form (50 percent). A family history of autoimmune thyroid disease is found in 50 percent of patients with the postpartum form of thyroiditis. The severity of the hypothyroid phase correlates directly with the antimicrosomal antibody titer. A titer of 1:1,600 or greater early in pregnancy is associated with a high risk of postpartum hypothyroidism.[15] Approximately 6 percent of patients who have the postpartum form develop chronic hypothyroidism.[7,16]

The clinical presentation of painless thyroiditis is similar to that of subacute granulomatous thyroiditis in that patients are usually between the ages of 30 and 40 years and women are more commonly affected than men (4:1 ratio).Patients usually present with acute symptoms of hyperthyroidism, such as tachycardia, palpitations, heat intolerance, nervousness and weight loss.[7,12] Postpartum depression appears to be more common in women with postpartum thyroiditis, although postpartum thyroiditis does not appear to be the cause of most cases of postpartum depression. A small painless goiter is present in 50 percent of patients.[7,12] The absence of anterior neck pain and tenderness clinically distinguishes painless thyroiditis from subacute granulomatous (painful) thyroiditis. Painless thyroiditis is more difficult to distinguish from Graves' disease, but it is imperative for the clinician to distinguish between these two diseases since important therapeutic differences exist.The ESR and white blood cell count are normal. T_4 and triiodothyronine (T_3) levels are initially elevated, with a disproportionate increase in T_4 compared with T_3.[12] RAIU is decreased in the hyperthyroid phase of the disease and is almost always less than 3 percent. This situation contrasts markedly with the elevated RAIU found in patients with Graves' disease.[4,6,11,12]

Acute symptoms of hyperthyroidism are managed primarily with beta blockers.[4,7,8,12] Antithyroid drugs, which inhibit the production of new T_4, are not indicated in the management of patients with hyperthyroidism because symptoms are caused by the release of preformed T_3 and T_4 from the damaged gland.[7,12] Replacement of thyroid hormone in the hypothyroid phase is indicated if the patient's symptoms are severe or of long duration.[8] If the hypothyroid phase lasts longer than six months, permanent hypothyroidism is likely.[17]

Subacute Granulomatous Thyroiditis:

Subacute granulomatous thyroiditis, first described by de Quervain in 1904 is the most common cause of a painful thyroid gland.[8] It is most likely caused by a viral infection and is generally preceded by an upper respiratory tract infection.[8] Numerous etiologic agents have been implicated, including mumps virus, echovirus, coxsackievirus, Epstein-Barr virus, influenza and adenovirus.[4,8] The presence of antithyroid antibodies in many patients suggests an autoimmune process during the disease course. Antibodies may be the result of T lymphocytes sensitized against thyroid antigens released during the inflammatory process. Additionally, there may be genetic factors, such as the presence of HLA-Bw35, that render an individual more susceptible to certain viral agents and the subsequent development of subacute granulomatous thyroiditis.

Women are three to five times more likely to be affected than men. The average age of onset is 30 to 50 years.[8] The disorder tends to be geographical and seasonal, occurring most often in the summer and fall.[7,8]

Subacute granulomatous thyroiditis presents clinically with acute onset of pain in the thyroid

region. The pain may be exacerbated by turning the head or swallowing, and may radiate to the jaw, ear or chest.[4,6,7] Symptoms of hypermetabolism may be present, and the ESR usually is markedly elevated.[7,8] A normal ESR essentially rules out the diagnosis of subacute granulomatous thyroiditis.[8] The thyroid is firm, nodular and exquisitely tender to palpation. The leukocyte count is normal or slightly elevated.[8] Thyrotoxicosis is present in 50 percent of patients in the acute phase, and the serum T_4 concentration is disproportionately elevated relative to the T_3 level.[8] Serum TSH concentrations are low to undetectable.[8] Thyroglobulin is elevated. A normal thyroglobulin level essentially rules out the diagnosis of subacute granulomatous thyroiditis.[7] The RAIU is notably low, often less than 2 percent at 24 hours.[8] Ultrasound examination may also be useful in establishing the diagnosis, with multiple hypoechogenic areas present in thyroid parenchyma.[18] In summary, the physical examination, an elevated ESR, an elevated thyroglobulin level and a depressed RAIU confirm the diagnosis.

The natural history of subacute granulomatous thyroiditis involves four phases that generally unfold over four to six months. The acute phase of thyroid pain and thyrotoxicosis may last three to six weeks or longer. Transient asymptomatic euthyroidism follows. Hypothyroidism often ensues and may last weeks to months or may be permanent (in up to 5 percent of patients).[6] The final phase is a recovery period, during which thyroid function tests normalize.

Therapy with antithyroid drugs is not indicated in patients with subacute granulomatous thyroiditis because this disorder is caused by the release of preformed thyroid hormone rather than synthesis of new T_3 and T_4.[7,8] Therapy with beta blockers may be indicated for the symptomatic treatment of thyrotoxicosis. Because the thyrotoxic state in subacute granulomatous thyroiditis is induced by the release of preformed T_4 and T_3 treatment with propylthiouracil and methimazole (Tapazole), which block synthesis of T_4 and T_3 is ineffective.

Nonsteroidal anti-inflammatory drugs are generally effective in reducing thyroid pain in patients with mild cases. Patients with more severe disease require a tapering dosage of prednisone (20 to 40 mg per day) given over two to four weeks.[4] Up to 20 percent of patients experience the recurrence of thyroid pain on discontinuation of prednisone.[8] RAIU can assist clinicians in determining patients at high risk for relapse. Low RAIU uptake implies ongoing inflammation, and steroid therapy should be continued.[4] If damage to the thyroid is extensive, a hypothyroid phase may occur until disrupted follicular cells fully recover. Hypothyroidism develops in about one-third of patients and persists up to several weeks. Patients with hypothyroid symptoms during this phase may benefit from thyroid hormone replacement therapy.

Overall, phases may continue over four to six months, although all patients may not exhibit all of the phases. Permanent hypothyroidism may develop in up to 5 percent of cases.[19] Many of these patients have coexistent autoimmune thyroid disease, such as chronic lymphocytic thyroiditis. Therefore, it is prudent to perform periodic thyroid hormone testing in all patients after recovery.

Microbial Inflammatory Thyroiditis:

Microbial inflammatory thyroiditis, also known as acute suppurative thyroiditis, is a rare subtype most often caused by the presence of Gram-positive bacteria in the thyroid gland. *Staphylococcus aureus* is the most common infectious agent,[8] but other organisms have also been implicated. Unusual pathogens that may infect the thyroid are Mycobacterium tuberculosis, syphilis, aspergillus, Coccidioides immitis, cytomegalovirus and Pneumocystis carinii.[20,21] This disorder is rare because of the inherent resistance of the thyroid gland to infection. Infectious agents reach the thyroid via lymphatic spread from areas of pharyngitis or mastoiditis, from hematogenous seeding from distant sites or from seeding from piriform sinus fistulas.

Microbial inflammatory thyroiditis occurs most often in women 20 to 40 years of age.[6,12] Most patients have a preexisting thyroid disorder, usually nodular goiter.[4,6,12] Anterior neck pain and tenderness are common. Other clinical features include fever, pharyngitis and dermal erythema.[6,12] The pain is typically worse during swallowing and radiates locally.[6,12,22] Tachycardia is common, along with leukocytosis and an elevated ESR level.[4,6,12,22] TSH, T_4 and T_3 levels are typically normal, while RAIU may be normal or show cold nodules in areas of abscess formation.[6,12,23] Computed tomographic (CT) scans may be useful in early diagnosis by evaluating the iodine content of the gland.[24]

Table-II
Clinical Manifestations of Thyroiditis Subtypes

Subtype	Etiology	Neck pain	RAIU	TSH	T_4	Thyroid autoantibodies
Chronic lymphocytic (Hashimoto's disease)	Autoimmune	No	Variable	Variable	Variable	Present
Subacute granulomatous	Viral	Yes	Decreased	Decreased	Increased	Absent
Subacute lymphocytic	Autoimmune	No	Decreased	Decreased	Increased	Present
Microbial inflammatory	Bacterial, fungal parasitic	Yes	Variable	Normal	Normal	Absent
Hashitoxicosis	Autoimmune	No	Decreased	Decreased	Increased	Present
Invasive fibrous	Unknown	No	Variable	Normal	Normal	Variable

The cause of infection is first determined by culture and sensitivity of samples obtained through fine-needle aspiration.

When the cause of the infection is determined, appropriate parenteral antibiotics should be prescribed.[6,12,22] Patients with abscesses require surgical drainage and, possibly, a thyroid lobectomy.[6,12,22] Heat, rest and aspirin provide symptomatic relief; steroids may offer additional benefit.[23] The disease is usually self-limited, lasting weeks to months.[23]

Invasive Fibrous Thyroiditis:
First described by Riedel in 1898, this remains the rarest type of thyroiditis. In addition to the development of dense fibrosis of the thyroid gland itself, extracervical sites of fibrosis frequently occur as inflammatory fibrosclerotic processes, including sclerosing cholangitis, retroperitoneal fibrosis and orbital pseudotumor.[12,25,26] Studies suggest that one third of patients with fibrous thyroiditis develop multifocal fibrosclerosis.[25,27] The mean age at presentation is 47.8 years, and 83 percent of all cases occur in females.[27] A stone-hard or woody mass that extends from the thyroid is common.[12,25,27] Symptoms vary according to the structures involved and most commonly result from a thyroid mass that produces dyspnea, dysphagia and, occasionally, stridor.[12,22,25,27] The thyroid mass may grow suddenly or slowly, and is usually unilateral.[25]

RAIU is decreased in affected areas of the gland.[22,26] Most patients remain euthyroid, and the ESR is frequently elevated.[6,12,25,27] Thyroid autoantibodies are present in appreciable quantities in 45 percent of patients.[6,12,25,27] Because of the similarity between fibrous thyroiditis and thyroid carcinoma, diagnosis must be made using open biopsy.[6,12,22,25] The disease is usually self-limited, with surgical wedge resection of the thyroid isthmus being the mainstay of treatment in symptomatic patients.[6,12,22,25]

Conclusion
Thyroiditis is a heterogeneous disease with several subtypes. These subtypes mimic other diseases as well as each other. Differentiation of the subtypes of thyroiditis requires an understanding of their unique clinical presentations, radiologic studies, laboratory data and indications for pharmacotherapy.

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