Thyroiditis – A Clinical Update and Review

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Review article

Thyroiditis – A Clinical Update and Review

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ABSTRACT

Purpose: Thyroiditis refers to a set of inflammatory disorders involving the destruction of normal thyroid follicular tissue. Each disorder has distinctive histology and pathology. Understanding each condition in the thyroiditis frame is crucial for physicians.

Main: This review categorizes thyroiditis into two groups based on the presence or absence of tenderness: painful and painless. This paper reviews the primary etiologies, diagnostic modalities, and treatment options for each condition. The painful thyroiditis comprises subacute, infectious, radiation, trauma-induced thyroiditis, and rarely Hashimoto's thyroiditis. The painless group consists of subacute lymphocytic thyroiditis, postpartum thyroiditis, drug-induced thyroiditis, and fibrous thyroiditis.

Findings: In the painful group, the primary etiology of subacute thyroiditis is viral, including SARS-CoV-2, which has been reported recently, and the main etiology of the infectious subgroup is bacterial infections. Symptom management and pain relief are the mainstays of treatment for painful conditions. The painless group typically progresses from transient hyperthyroidism to euthyroidism to hypothyroidism before resolving. Autoimmune and genetics, HLA-DR3, likely contribute to subacute lymphocytic thyroiditis. Certain medications, including interferon-alpha (HVC management), IL2 Tyrosine-kinase inhibitors (cancer management), amiodarone, lithium, and check-point inhibitor immunotherapy (CTLA-4 and PCD-1) are found to be related to thyroiditis. Fibrous thyroiditis is usually associated with systemic fibrous disease.

Conclusion: A comprehensive understanding of each thyroiditis condition's etiology and clinical presentation is important to accurately diagnose, appropriately manage, and counsel patients on the risk for permanent hypothyroidism that may require long-term thyroid replacement therapy.

INTRODUCTION

The term *thyroiditis* comprises a heterogeneous group of inflammatory disorders of diverse etiologies and clinical features (Table 1). All forms of thyroiditis involve the destruction of the normal follicular architecture. However, each disorder has distinctive histologic characteristics. Varying classifications of thyroid inflammatory disorders have been proposed. For this review, thyroiditis is subdivided into thyroiditis associated with pain or tenderness (painful) and thyroiditis not associated with pain (painless). The nomenclature used to describe the various thyroiditis conditions is confusing and controversial, with many conditions having multiple names. When applicable, these are included in parentheses. This review will cover the main etiologies

TABLE 1. Classification of Inflammatory Thyroid Disorders.

Painful thyroiditis	Painless thyroiditis
Infectious • Subacute viral thyroiditis (subacute granulomatous thyroiditis, subacute nonsuppurative thyroiditis, de Quervain's thyroiditis, viral thyroiditis, giant cell thyroiditis). • Infectious thyroiditis (suppurative thyroiditis, acute bacterial thyroiditis, pyogenic thyroiditis). • Opportunistic agents (e.g., *Pneumocystis carinii, Mycobacteriae, Aspergillus*). Trauma • Radiation thyroiditis. • Direct trauma (e.g., fine-needle aspiration, surgery, palpation).	Spontaneous disorders • Subacute lymphocytic thyroiditis (painless thyroiditis, silent thyroiditis). • Postpartum thyroiditis. Pharmacologic agents • Cytokines (interferon-α, interleukin-2). • Tyrosine kinase inhibitors. • Amiodarone-induced thyroiditis. • Check-point inhibitor immunotherapy. • Lithium carbonate. Fibrous thyroiditis (Riedel' thyroiditis, invasive fibrous thyroiditis)

of thyroiditis, including more recently described conditions such as thyroiditis as related to Sars-CoV-2 and checkpoint inhibitor immunotherapy. It will not discuss Hashimoto's thyroiditis or chronic lymphocytic thyroiditis, which is an entire topic of its own.

PAINFUL THYROIDITIS

Painful thyroiditis includes subacute, infectious, radiation, trauma-induced thyroiditis and very rarely Hashimoto's thyroiditis.

Subacute thyroiditis (subacute granulomatous thyroiditis, subacute nonsuppurative thyroiditis, de Quervain's thyroiditis, viral thyroiditis, giant cell thyroiditis)

The etiology of subacute thyroiditis is most likely viral in origin. Coxsackie virus, adenovirus, mumps virus, echovirus, influenza, Epstein-Barr virus, and most recently Sars-CoV-2 have all been associated with subacute thyroiditis. Clinical evidence suggesting a viral cause includes clusters of cases associated with outbreaks of viral infections, common reports of the history of an upper respiratory infection preceding thyroiditis, and a summer and fall distribution of cases [1]. Several cases of subacute thyroiditis have been described after Sars-CoV-2 infection [2], [3]. Reports of subacute thyroiditis occurring a few days after SARS-CoV-2 vaccination have also been reported [4]. Thyroid autoimmunity does not appear to play a role in subacute thyroiditis, but it is strongly associated with human leukocyte antigen (HLA)-B35 in many ethnic groups [5].

Subacute thyroiditis is relatively uncommon, with an incidence of 12.1 cases per 100,000/year. There is a predilection in women of 19.1 to 4.1 cases per 100,000/year, with the highest frequency in young adulthood, decreasing with age [6]. Clinically, subacute thyroiditis is characterized by anterior neck pain often associated with radiation of the pain to the ear or mandible with significant tenderness to palpation. Preceding the pain are myalgias, low-grade fevers, malaise, and sore throat. Symptoms of thyrotoxicosis, including tachycardia, palpitations, weight loss, tremors, diaphoresis, and increased anxiety, are often present. As the condition progresses, pain may migrate to the contralateral side. A physical exam reveals a tender, hard, ill-defined unilateral mass, although palpation is limited due to pain. The patient may be tachycardic, warm, or diaphoretic, with tremors on the exam. The thyroid inflammation and hyperthyroidism typically subside in two to eight weeks and may be followed by hypothyroidism lasting two to eight weeks. Recovery typically occurs for most patients, although 15% of patients may develop permanent hypothyroidism and require long-term treatment [6]. Recurrence has been reported in 1.6 to 4% of patients [6], [7].

Serum thyroxine (T_4) or free thyroxine (FT4) and triiodothyronine (T_3) levels are often elevated, and the serum thyrotropin (thyroid-stimulating hormone, TSH) is suppressed [8]. The severity of the thyrotoxicosis correlates with the degree of the destructive process. There tends to be a disproportionate elevation of serum (T_4) relative to serum (T_3), reflecting proportional amounts of preformed hormones released into the circulation during the active inflammatory phase. A complete blood count (CBC) usually reveals a mild normochromic-normocytic anemia and a normal total white blood cell count. However, mild leukocytosis may occur. The erythrocyte sedimentation rate (ESR) is usually >50 mm per hour. C-reactive protein (CRP) may also be elevated [9].

As stated above, thyroid autoimmunity does not appear to play a role. However, thyroid autoantibodies (anti-thyroid peroxidase [TPO] and antithyroglobulin) may be mildly elevated for several weeks after the onset of symptoms, returning to normal within a few months. The transient antibody elevation is likely a response to the release of thyroglobulin into the circulation and not an autoimmune response. The serum thyroglobulin is significantly elevated during active inflammation.

The thyroid radioactive iodine uptake (RAIU) is always suppressed during the acute phase of the illness, usually to <2% at 24 hours in the absence of recent exposure to iodine. The suppressed uptake is a result of disruption of the iodine-trapping mechanism from the inflammation and cell destruction. The RAIU test is helpful to confirm the clinical diagnosis of subacute thyroiditis and exclude other disorders associated with a painful anterior neck mass (Table 2). On ultrasound, the thyroid appears normal or enlarged and hypoechogenic. Color doppler sonography shows low flow in the hyperthyroid phase as opposed to Graves' Disease, which shows enhanced flow [10]. With recovery, the thyroid appears normal again on ultrasonography.

Subacute thyroiditis must be differentiated from both euthyroid and hyperthyroid states associated with anterior neck pain as treatment is specific to each condition (Table 2). Treatment is focused on symptom relief. Prednisone 40 mg

TABLE 2. Differential Diagnosis for Anterior Neck Pain

Subacute viral thyroiditis
Hemorrhage into thyroid cyst or nodule
Acute bacterial thyroiditis
Infected thyroglossal duct cyst
Infected branchial cleft cyst
Rapidly enlarging thyroid cancer
Painful Hashimoto's thyroiditis
Radioactive thyroiditis
Trauma-induced thyroiditis
Cellulitis of the anterior neck

per day orally is typically effective in reducing pain, often within several hours of the initial dose. If the pain does not abate quickly, the diagnosis should be questioned. After 1 to 2 weeks, the prednisone can be tapered by 5 mg every 2 to 3 days. An increase in pain may occur during steroid tapering, at which time the prednisone dosage can be increased again, and the tapering process resumed. Typically, several weeks to two months of treatment are required. Mild episodes may be treated with nonsteroidal anti-inflammatory drugs (NSAIDS). Treatment does not prevent thyroid dysfunction [6].

Symptoms of thyrotoxicosis may be controlled with the use of β-adrenergic–blocking agents. Propranolol 10-20mg every eight hours or atenolol 25 to 50mg daily may be used. Antithyroid drugs would not be of any benefit as hyperthyroidism is secondary to the release of preformed thyroid hormone and not by excess thyroid hormone synthesis.

Following the acute painful thyrotoxic phase, euthyroidism is restored as the thyroid becomes depleted of stored hormone. Patients may either remain euthyroid or progress to a hypothyroid phase. Management of hypothyroidism may not be needed because symptoms are generally mild. However, if the patient is symptomatic, levothyroxine 50 to 150mcg daily for six to twelve weeks may be given. LT_4 can then be discontinued and a serum TSH repeated in 6 to 8 weeks as the majority of patients will recover normal thyroid function.

Infectious thyroiditis (suppurative thyroiditis, acute bacterial thyroiditis, pyogenic thyroiditis)

Infectious thyroiditis is rare. Acute infections are usually caused by a bacterial pathogen, most commonly *Staphylococcus aureus, Streptococcus hemolytica, Streptococcus pneumoniae,* or anaerobic streptococcal organisms. Infection due to other bacterial pathogens, such as *Meningococcus, Salmonella, and Escherichia coli,* has been reported. Mycobacterial infections and fungal infections such as coccidioidomycosis [11] and *Pneumocystis carinii* (PCC) tend to be more chronic and occur mostly in immunocompromised individuals [12]. Infection occurs either secondarily to hematogenous or lymphatic spread, via a fistula from the piriform sinus adjacent to the larynx, common in children, or as a result of direct introduction of an infective agent by direct trauma [13]. Persistent thyroglossal duct abnormalities have also been associated with acute thyroiditis.

Clinical symptoms include fever, chills, and other systemic signs or symptoms of abscess formation. Rapid onset of anterior neck pain and swelling are usual, with pain occasionally radiating to the ear or mandible. The physical examination is notable for the presence of a tender, fluctuant mass, with erythema of the overlying skin.

Laboratory tests include a leukocytosis with a left shift. Thyroid hormone concentrations are usually within normal range [13]. However, hyperthyroxinemia has been reported likely as a result of discharge of preformed hormone. The radioactive iodine thyroid uptake and scan reveal an absence of isotope uptake in the involved area. If acute thyroiditis is suspected, fine-needle aspiration should be performed, and appropriate smears and cultures obtained.

The differential diagnosis includes any disorder associated with an acutely tender, painful anterior neck mass (Table 2). Parenteral antibiotics should be administered according to the specific pathogen identified. If fluctuance is present, incision and drainage are required. Bacterial thyroiditis must be managed early and aggressively because abscess formation can occasionally dissect downward into the mediastinum. Recurrence of the disorder is very rare, as is permanent thyroid dysfunction. If recurrence of acute thyroiditis occurs, an examination is indicated to facilitate the discovery of an undiagnosed defect, such as an internal fistula or thyroglossal duct cyst.

Radiation thyroiditis

Radiation thyroiditis caused by radiation-induced injury and necrosis of thyroid follicular cells resulting in inflammation occurs in 1% of patients after radioiodine therapy. Characterized by mild to moderate anterior neck pain and thyroid tenderness, radiation thyroiditis typically occurs approximately a week after receiving ^{131}I for thyrotoxic Graves' disease. Symptoms may last for up to one month after ^{131}I administration. There may be transient aggravation of the hyperthyroidism. NSAIDs can be used for pain relief. If pain and tenderness is significant, short-term prednisone (20 to 40 mg per day) may be used. Patients treated with ^{131}I for thyroid cancer may also develop radiation thyroiditis, especially if a significant amount of normal thyroid tissue was left remaining after thyroidectomy.

Trauma-induced thyroiditis

Thyroiditis has been associated with robust palpation of the thyroid gland during physical examination [14], manipulation of the gland during thyroid biopsy [15] or neck surgery such as parathyroid surgery) [16], and trauma (i.e., from an automobile seat belt) [17]. Patients have transient neck pain and tenderness associated with transient hyperthyroidism.

PAINLESS THYROIDITIS

Painless thyroiditis includes subacute lymphocytic thyroiditis, postpartum thyroiditis, drug-induced thyroiditis, and fibrous thyroiditis.

Subacute lymphocytic thyroiditis (painless thyroiditis, silent thyroiditis)

Subacute lymphocytic thyroiditis is characterized by transient hyperthyroidism followed by euthyroidism and hypothyroidism prior to recovery. Patients typically present with symptoms of thyrotoxicosis, elevated T_4, T_3, a suppressed serum TSH, a low RAIU, and a painless nontender goiter.

Subacute lymphocytic thyroiditis is most likely autoimmune in origin and is considered a variant of chronic autoimmune thyroiditis (Hashimoto's thyroiditis) [9]. Many patients with subacute lymphocytic thyroiditis have elevated thyroid antibodies and family history of thyroid autoimmune disease. Some will eventually develop overt chronic autoimmune thyroiditis [18]. Subacute lymphocytic thyroiditis tends to affect more women than men [9]. The condition is associated with HLA-DR3 suggesting a genetic component. However, the association is much weaker than the association between subacute thyroiditis (painful) and HLA-B35 [19].

In subacute lymphocytic thyroiditis, the thyroid follicles are damaged and large amounts of T_4 and T_3 are released into the circulation. This continues until the stores of thyroglobulin are exhausted. The new hormone is not produced due to damage to the thyroid follicular cell and inhibition of TSH from the high T_4 and T_3 concentrations. As the inflammation abates, the remaining follicular cells resume synthesis and secretion of thyroid hormone. There may be a period of increased TSH secretion before thyroid hormone secretion normalizes. In a small subset of patients, the thyroid damage is significant enough to result in permanent hypothyroidism.

Clinically 5-20% of patients with subacute lymphocytic thyroiditis will present with characteristic hyperthyroidism followed by brief euthyroidism, then hypothyroidism prior to recovery. Hyperthyroidism may last for 2-8 weeks and is associated with mild or no hyperthyroid symptoms (described above) before subsiding. The hypothyroid phase may last for 2-8 weeks and be associated with symptoms of hypothyroidism such as fatigue, cold intolerance, and constipation. Commonly, subacute lymphocytic thyroiditis is detected by routine thyroid testing. On exam, the thyroid gland may be mildly enlarged and is nontender.

The concentration of T_4 and T_3 in the circulation is the same as that in the thyroid gland compared to Graves' disease in which thyroid deiodinase is activated resulting in greater T_3 to T_4 release. As the patient progresses from the hyperthyroid phase to the hypothyroid phase, the TSH may remain low or normal due to the prior suppression of TSH secretion during the hyperthyroid phase. Antithyroid antibody concentrations are elevated in 50% of patients [9], [20]. ESR typically is normal or just slightly elevated.

The differential diagnosis is typically between subacute lymphocytic thyroiditis and Graves' disease during the hyperthyroid phase of the condition. In the absence of clinical manifestations of Graves' disease such as ophthalmopathy or large diffuse goiter with bruit, a TSH-receptor antibody (TRAb) or Thyroid -Stimulating Immunoglobulin (TSI) may be useful to distinguish initially (Table 3).

TABLE 3. Differentiation between Subacute Lymphocytic Thyroiditis and Graves' Hyperthyroidism (RAIU: radioactive iodine uptake, T_3: tri-iodothyronine, T_4: thyroxine, TRAb: TSH-receptor antibody, TSI: Thyroid-stimulating immunoglobulin)

Clinical feature	Subacute Lymphocytic thyroiditis	Graves' Disease
Onset	Abrupt	Gradual
Severity of symptoms	Mild to moderate	Moderate to marked
Duration of symptoms (usual)	< 3 months	> 3 months
Goiter	Absent or firm, diffuse, mildly enlarged	Mildly to moderately firm, diffuse, large
Thyroid bruit	Absent	Often present
Exophthalmos, dermopathy	Absent	May be present
T_4/T_3 ratio	<20:1	>20:1
RAIU	Suppressed	Elevated
TRAb/TSI	Absent	Present

The clinical course of subacute lymphocytic thyroiditis is similar to subacute thyroiditis and can be treated with beta-blockers and LT_4 as indicated.

Postpartum thyroiditis

Postpartum thyroiditis is clinically and pathologically similar to subacute lymphocytic thyroiditis except that it occurs in women within one year after delivery or spontaneous or induced abortion. Prevalence of postpartum thyroiditis is reported at 5% but varies between 1 to 18% [21]. In clinically hyperthyroid women postpartum, differential diagnosis includes postpartum onset or recurrence of Graves' disease. Women with TPO Ab are at an increased risk for developing postpartum thyroiditis [22], [23]. Women with postpartum thyroiditis are at high risk for future episodes of postpartum thyroiditis, up to 70% in one cohort [24], and at risk for permanent hypothyroidism long-term, with reported rates of 2-21% and as high as 50% [21], [25]. Patients with postpartum thyroiditis should have TSH checked prior to pregnancy and once pregnant as they are at risk for thyroid dysfunction.

Drug-induced thyroiditis is associated with interferon-alpha, interleukin-2, tyrosine kinase inhibitors, amiodarone, lithium. And check-point inhibitor immunotherapy

Interferon- alpha is used in the management of chronic hepatitis C (HCV). 5-40 percent of patients develop de novo antithyroid antibodies without clinical disease [26]. 5-10% will develop clinical thyroid disease including pain-

less thyroiditis, Hashimoto's thyroiditis, or Graves' disease [27]. Thyroid dysfunction typically occurs after 3 months of therapy but can occur as long as interferon-alpha is given. Increased risk in those with increased antithyroid antibody concentrations prior to initiation of the interferon-alpha [28], female sex, and older [29].

Interleukin-2 (IL-2) is used as adjunctive therapy in the treatment of various malignancies, including metastatic solid tumors and leukemias, and may be associated with a painless lymphocytic thyroiditis type of syndrome in a small percent of patients [30].

Tyrosine kinase inhibitors (TKIs) are used to treat various conditions such as gastrointestinal stromal tumors, renal cell carcinoma, and differentiated and medullary thyroid cancer. 50-70% of euthyroid patients with intact thyroid glands develop hypothyroidism [31]. Hypothyroidism is most frequently reported with sunitinib but occurs with other TKIs and is likely a class effect. The mechanism remains unclear. Hyperthyroidism, likely due to destructive thyroiditis can also occur followed by hypothyroidism [32]. Treatment is not generally needed for the transient thyrotoxicosis.

Amiodarone is a potent antiarrhythmic agent that contains two iodine atoms. Every 100mg of amiodarone contains 250 times the recommended daily iodine requirement [33]. Amiodarone is lipophilic, concentrating in adipose tissue, cardiac and skeletal muscle, and the thyroid with a half-life of roughly 100 days [34]. Amiodarone can cause hypothyroidism and hyperthyroidism. The risk of thyroid dysfunction varies from 2 to 30% and can depend on underlying thyroid status, dietary iodine intake, or if the subclinical disease is included [33], [35], [36]. In iodine-sufficient areas, amiodarone-induced hypothyroidism appears to be more common than hyperthyroidism while in areas of iodine-deficient regions, amiodarone-induced hyperthyroidism appears to be more common [35], [37].

There are two types of amiodarone-induced thyrotoxicosis. In type I, there is increased thyroid hormone synthesis. This is usually seen in patients with preexisting multinodular goiter or latent Graves' disease. Excessive iodine leads to enhanced thyroid hormone production [38]. In Type II there is excessive release of thyroid hormone due to a direct toxic effect of amiodarone on thyroid follicular cells resulting in destructive thyroiditis [39].

Hyperthyroidism generally occurs within a few months after beginning the drug but may have its onset at any time after initiation of treatment. Symptoms of hyperthyroidism are often lacking, probably because of the beta-blocker activity of amiodarone. However, patients are not protected from the tissue effects of thyrotoxicosis and may experience weight loss, worsening of arrhythmia, or development of congestive heart failure.

Differentiating between the two types of amiodarone-induced hyperthyroidism is important because the treatment is different for each (Table 4). The onset of Type I typically occurs earlier, around a few months after initiation of amiodarone treatment while Type II typically occurs much later with a median onset of 30 months [40]. The presence of a nodular goiter suggests iodine-induced hyperthyroidism, whereas the absence of thyroid enlargement suggests inflammatory thyroiditis. The measurement of serum interleukin-6 (IL-6) levels may occasionally allow for differentiating between the two types of amiodarone-induced hyperthyroidism, although the amount of overlap limits its usefulness. Lower levels of IL-6 associated with Type I. Color flow on Doppler thyroid ultrasound; flow is increased in patients with type 1 and decreased in patients with type II amiodarone-induced thyrotoxicosis [41], [42]. RAIU is not as useful of a diagnostic test as the iodine in amiodarone interferes with uptake. Thyroid-stimulating immunoglobin (TSI) assay can be used to distinguish as would be positive in patients suspected of having Type I and negative in those with Type II. However, the absence of TSI would not rule out the possibility of Type I [43].

TABLE 4. Differentiating Features of Amiodarone-Induced Hyperthyroidism (FT_3: free tri-iodothonine, FT_4: free thyroxine, IL-6: interleukin-6, RAIU: radioactive iodine uptake)

	Type 1 (Iodine excess)	Type II (Thyroiditis)
History of thyroid disease	Often	No
Goiter	Nodular	Small or absent
FT_4	High	High
FT_3	High	High
TSH	Suppressed	Suppressed
IL-6	Normal or slightly High	High
Thyroid RAIU	Low, Normal, occasionally High	Low
Color Doppler ultrasound	Increased flow	Decreased flow

Amiodarone does not need to be stopped if the patient develops amiodarone-induced thyroiditis. Amiodarone may be necessary to control life-threatening arrhythmia. The half-life of elimination is long so no immediate benefit to stopping treatment. Amiodarone blocks T_4 to T_3 conversion and beta-receptors, ameliorating symptoms of hyperthyroidism.

Treatment of type II amiodarone-induced hyperthyroidism consists of pharmacologic doses of glucocorticoids (e.g.,prednisone 40-60mg per day) continued for months before taper. Improvement can be seen as soon as one week. 60% of patients may be euthyroid within one month, but some may remain hyperthyroid after three months of therapy. Thionamide or antithyroid agents such as methimazole (MMI) and propylthiouracil (PTU) are not helpful, although if the diagnosis is in question, a combination of glucocorticoids and thionamide drugs (which are usually reserved for type I) may be indicated. Type II amiodarone-induced hyperthyroidism follows a course similar to that observed

with other forms of painless or lymphocytic thyroiditis with some patients developing permanent hypothyroidism requiring LT_4 therapy [39]. Patients who are refractory to glucocorticoids may be treated with thyroidectomy [44].

Lithium. Lithium can cause hypothyroidism, thyroid autoimmunity, and hyperthyroidism. In a retrospective review of 400 patients (300 with Graves' disease and 100 with painless thyroiditis) who underwent RAIU of the thyroid, the odds of lithium exposure was 4.7-fold in patients with painless thyroiditis compared with those of Graves' disease. (95% CI 1.3, 17) [45]. Because the rate of thyroid dysfunction is high in patients on lithium, thyroid function tests should be monitored every 6-12 months. Discontinuation of lithium is not typically required. Treatment of hyperthyroidism depends on the etiology (i.e., Graves' disease, toxic nodular goiter, or subacute lymphocytic thyroiditis).

Check-point inhibitor immunotherapy. Immunologic checkpoint inhibition agents targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) receptors are used to treat patients with advanced melanoma as well as other malignancies. Associated with several endocrinopathies including hypophysitis, adrenal insufficiency, and type 1 diabetes mellites, checkpoint-inhibitor therapy has been associated with hypothyroidism secondary to destructive painless thyroiditis and hyperthyroidism associated with Graves' disease [46].

Hypothyroidism from primary destruction of the thyroid gland can be distinguished from hypophysitis because TSH will be elevated in the former and low or inappropriately normal in the latter. Distinguishing between the two is important because adrenal insufficiency in hypophysitis should be treated with cortisol before the thyroid hormone is given to avoid precipitating adrenal crisis.

The incidence of hypothyroidism ranges between 3.8% to as high as 13.2% with the combination of nivolumab and ipilimumab [47]. Thyroid function tests should be monitored prior to each dose of immune checkpoint inhibitor therapy with a TSH and FT_4. A TSH alone would be insufficient to diagnose hypophysitis. Typically, thyroiditis develops within weeks to months of initiating the medication, although thyroid dysfunction has been reported to occur as soon as seven days after initiation of therapy to as late as 3 years [48].

Typically patients present with a period of transient hyperthyroidism prior to longstanding hypothyroidism [49]. Patients typically present with mild symptoms initially. However, treatment with levothyroxine is indicated in patients with hypothyroidism as severe untreated hypothyroidism has been associated with life-threatening decompensation [50]. Adverse events related to checkpoint inhibitor therapy have been associated with longer disease-free survival [51], [52].

Fibrous thyroiditis (Riedel' thyroiditis, invasive fibrous thyroiditis). Fibrous thyroiditis is an extremely rare inflammatory disorder of uncertain etiology, characterized by extensive fibrosis and macrophage and eosinophil infiltration of the thyroid gland that extends into adjacent soft tissues. Perithyroidal fibrosis can affect the parathyroids causing hypoparathyroidism [53], the recurrent laryngeal nerves causing hoarseness, the trachea leading to compression [54], the mediastinum, and the chest wall. Fibrous thyroiditis has a female-to-male prevalence of 3:1 and usually occurs between the ages of 30 and 60 years [55].

Fibrous thyroiditis may be the local manifestation of systemic disease occurring in the setting of retroperitoneal fibrosis, fibrosing mediastinitis, sclerosing cholangitis, pancreatitis, and head and neck fibrosis conditions [56]. Fibrosis thyroiditis may occur within immunoglobulin G4 (IgG4) related system disease marked by lymphoplasmacytic tissue infiltration of IgG4 positive plasma cells and small lymphocytes along with fibrosis, obliterative phlebitis, and elevated serum levels of IgG4. In these circumstances, IgG4-positive plasma cells have been found in thyroidectomy samples [57].

Clinically, patients with fibrous thyroiditis typically present with a slowly enlarging goiter. They may present with pressure symptoms, dysphagia, hoarseness, and dyspnea. On examination, a hard, "woody," immobile thyroid gland is palpated. The gland may be symmetrical or asymmetrically enlarged. The gland is fixed as the fibrosis may affect the strap muscles.

The majority of patients are euthyroid at presentation. However, anywhere from 25 to almost 70% of patients have subclinical or overt hypothyroidism due to destruction of the thyroid parenchyma by fibrosis or concurrent Hashimoto's thyroiditis [55], [58]. Thyroid antibody titers are detectable in up to 67% of patients [59].

Ultrasound of the thyroid reveals heterogeneous, hypoechoic lesions and an "invasive"-type picture, with obliteration of the normal thyroid margins and involvement of the parathyroid muscles [60]. On fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT scan, fibrosis thyroiditis is hypermetabolic [61].

Management of fibrous thyroiditis is surgical for patients in whom symptoms of obstruction occur. In general, surgery is limited to relieving the obstruction, for example excising the thyroid isthmus to relieve tracheal compression. Extensive resection is not indicated due to the risk of injury to surrounding structures.

In some patients, the condition may stabilize or regress spontaneously [56]. Mortality is generally secondary to recurrent pneumonia secondary to bronchial compression and dyspnea. Tamoxifen has been shown to be helpful in some patients. The mechanism is unknown by may be because of its inhibitory effects on growth factors [62]. Glucocorticoids are rarely effective although has been reported to reduce thyroid enlargement and soften the neck mass in a few patients [63]. However, treatment is generally long-term as disease recurrence occurs with steroid taper.

Rituximab and mycophenolate mofetil have been used for IgG4-related disease. Limited case reports have reported some benefits in patients who were not responsive to steroids or rituximab [64], [65]. Low-dose radiation therapy has been used in cases that are refractory to other treatments.

$l - T_4$ is required for the management of hypothyroidism but is not effective for goiter shrinkage or progression of fibrosclerosis.

CONCLUSION

Thyroiditis encompasses a wide range of conditions that involve the destruction of the normal thyroid follicular architecture. An understanding of the various etiologies and clinical presentations enables the clinician to make the appropriate diagnosis, manage symptoms of hyper- and hypothyroidism when indicated, and counsel patients on the risk for permanent hypothyroidism.

CONFLICTS OF INTEREST

None of the authors have conflicts of interest to declare.

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