Hyperthyroidism and Thyroiditis

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Hyperthyroidism

Hyperthyroidism is the overproduction of thyroid hormones resulting in thyrotoxicosis. Symptoms of hyperthyroidism can vary depending on the severity of thyrotoxicosis and the age of the patient. Common symptoms include nervousness, increased sweating and heat intolerance, palpitations, fatigue, weight loss, dyspnea, and weakness. These symptoms are often well tolerated in younger patients. Older patients can present with cardiovascular symptoms, depression, lethargy, and weakness (termed "apathetic hyperthyroidism") [1]. The diagnosis is made on the basis of elevated free T4 or T3 level and suppressed thyroid-stimulating hormone (TSH) level. In subclinical hyperthyroidism, the mildest form of hyperthyroidism, only the TSH is abnormal.

The most common cause of hyperthyroidism is Graves' disease, an autoimmune disease resulting in production of TSH-receptor-stimulating antibodies. Other causes include toxic adenoma, toxic multinodular goiter (TMG), postpartum thyroiditis, and subacute and rarely suppurative thyroiditis. Symptoms are similar but can vary depending on the degree of thyroiditis and patients with **Graves'** disease may have symptoms related to the nonthyroidal manifestations (exophthalmos, dermopathy, acropachy). The diagnosis is often made on clinical presentation and examination; however, studies such as iodine-123 scans (I-123), ultrasonography (US), and laboratory values are required for an accurate diagnosis. Treatment strategies are tailored to the etiology and the individual patient and can range from medical management to surgical intervention.

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Graves' Disease

Graves' disease is the most common type of thyrotoxicosis affecting approximately 2 % of women and 0.2 % of men [2, 3]. The peak incidence is in the third to fourth decades of life. In the USA, it accounts for 75 % of thyrotoxic patients [4]. In Graves' disease, the thyrotropin receptor on the follicular cells is the target for thyroid autoantibodies that bind to these receptors, stimulating them just as TSH triggers the receptor. This results in constant autonomous thyroid function, hyperthyroidism, and diffuse enlargement of the thyroid gland without focal nodules, referred to as diffuse toxic goiter. Pathologically, there is diffuse hyperplasia of the follicular epithelial cells and depletion of colloid, with increased vascularity. In addition to the autoimmune basis for Graves' disease, other factors likely play an important role. Graves' disease is likely the result of a complex interaction between autoimmune, genetic, and environmental factors.

The autoimmune basis for Graves' disease involves a group of immunoglobulin G (IgG) autoantibodies that are produced by B lymphocytes which bind and activate the thyrotropin or TSH receptor (TSHR). These IgG antibodies are variably termed thyroid-stimulating antibody (TSAb), thyroid-stimulating immunoglobulin (TSI), or thyrotropin receptor antibody (TRAb), and stimulate the thyrocyte in a similar fashion to TSH, causing secretion of T3 and T4, resulting in hyperthyroidism [5]. Serologic tests (i.e., TSI level) can help confirm the diagnosis of Graves' disease in patients with hyperthyroidism. The initiating cause for the production of the autoantibodies is still unknown. Environmental and genetic factors may play a role.

Studies of monozygotic twins have shown that Graves' disease may have a genetic component with a familial predisposition. Concordance rates of disease occurrence as high as 60 % have been reported in monozygotic twins. This is in contrast to 3–9 % in dizygotic twins and 0.2 % of the general population [6].

An environmental influence, or some sort of triggering event, has long been sought as a contributing factor to the

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Table 1 Symptoms and signs of Graves' disease

Symptoms
Nervousness
Heat intolerance
Insomnia
Anxiety
Hyperhidrosis
Weight loss
Fatigue
Muscle weakness
Decreased menstrual flow
Palpitations
Signs
Tachycardia
Ophthalmopathy
Dermopathy (pretibial myxedema)
Proximal muscle weakness
Diffuse goiter (+/− bruit)
Fine tremor
Spooning of nails

development of Graves' disease. Although bacteria, viruses, tobacco, and stress have been implicated in the pathogenesis of Graves' disease, there is no clear evidence of cause and effect.

The clinical features of Graves' disease are listed in Table 1. The hyperthyroid features of Graves' disease are nonspecific and occur with all types of thyrotoxicosis, regardless of etiology including tachycardia, widened pulse pressure, warm skin, proximal muscle weakness, and fine tremor. Unique features of Graves' disease include ophthalmopathy (proptosis) and dermopathy (pretibial myxedema).

Graves' disease is characterized by suppressed TSH level and an elevated serum-free T4. The suppressed TSH level helps exclude other conditions in which the serum T4 may be elevated, such as estrogen therapy, nonthyroidal illness, TSH-secreting pituitary adenoma, or central thyroid hormone resistance [7].

Once the diagnosis of thyrotoxicosis is established, radionuclide scintigraphy may be useful in differentiating Graves' disease from other causes of hyperthyroidism. In Graves' disease, the thyroid gland is diffusely enlarged with intense, diffuse radiotracer uptake often as high as 80 % in 24 h. The uptake is homogeneous whereas in TMG there are areas of both increased and decreased uptake. The overall uptake in TMG is not as avid as in Graves' disease. In toxic adenoma, there is focal uptake in a single nodule, often with suppression of the remaining normal glandular tissue (Table 2).

On ultrasound, patients with Graves' disease have a diffusely enlarged thyroid gland, with a smooth but lobular surface contour. The thyroid gland may range from being isoechoic to diffusely hypoechoic, and is typically homogeneous and with increased vascularity often referred to as "the thyroid inferno" [8].

Table 2 Radionuclide scanning and hyperthyroidism

Scan findings
Graves' disease intense diffuse uptake
Toxic adenoma focal uptake with suppressed adjacent tissue
Toxic multinodular goiter areas of patchy uptake

The treatment of Graves' disease is directed at decreasing the B-adrenergic symptoms by administering a B-blocking drug and inhibiting the synthesis and release of thyroid hormone thus reversing the catabolic effects. B-blocking agents such as propranolol and atenolol can quickly reduce symptoms of palpitations, nervousness, sweating, and tremor. Inhibition of thyroid hormone synthesis and release can be achieved by thionamide drugs, radioiodine (RAI) therapy, and surgery (Table 3).

The two most common thionamide drugs are methimazole (Tapazole, MMI) and propylthiouracil (PTU). Both agents are equally effective. MMI has a greater potency and longer biological half-life, whereas PTU has the theoretical advantage of a more rapid fall in serum T3 levels because of its property of inhibiting peripheral conversion of T4 to T3 [9]. Biochemical euthyroidism is usually established within 6–8 weeks and doses are adjusted accordingly. The drugs are well tolerated with minimal side effects. Approximately 20 % of patients are allergic to both agents, necessitating the use of RAI or surgery. The most serious side effect of the drugs is agranulocytosis, which is rare and can occur in 0.2–0.5 % of patients, and can be fatal. However, elevations in liver enzymes may also necessitate cessation of thionamides [10, 11].

Complete remission rates with thionamides vary considerably; however, studies have shown up to 75 % remission rate with high-dose therapy. Most relapses following cessation of thionamide therapy occur shortly after the drugs are discontinued. In some cases, relapses can occur even several years later; therefore, these patients need to be followed closely for extended periods of time. Patients who fail thionamide therapy will require definitive therapy, either RAI or total thyroidectomy.

In the USA, RAI therapy is the most common choice of therapy for Graves' disease [12]. Its benefits include general effectiveness, relatively low expense, and minimal side effects. However, RAI therapy may take months to have an effect. The most common side effect is dry mouth which may be temporary and in rare cases permanent. The most considerable side effect is hypothyroidism which is actually the intended goal of therapy. The risk of secondary malignancies from RAI therapy for Graves' disease is very small and usually not considered significant for adult patients [13, 14]. The risk of developing deleterious genetic, carcinogenic, teratogenic, and reproductive effects from RAI therapy for Graves' disease is negligible [15–17]. Contraindications for

Table 3 Hyperthyroidism and treatment options

	Thionamides	RAI	Surgery
Graves' disease	[a]	[a]	[a]
Toxic adenoma	–	[c]	[a]
Toxic multinodular goiter	–	[b]	[a]

[a] Recommended
[b] Sometimes recommended
[c] Rarely recommended
(–) Not recommended
RAI radioiodine

RAI therapy include pediatric age, pregnancy, and nursing mothers. Patients treated with RAI therapy should avoid becoming pregnant for at least 6 months [15].

Surgical management of Graves' disease is becoming more common in the USA [18]. Advantages to surgery include its high success rate, rapid onset of effect, and relative safety. Both thionamide and RAI therapy can take weeks to months to achieve euthyroidism. Thyroidectomy offers immediate therapeutic response. The risk of surgery, including hypoparathyroidism and vocal cord paralysis, is very low in high-volume surgeons [18, 19]. Unlike the high relapse rate after discontinuation of thionamides, surgery reliably provides a cure with only a small chance of recurrent hyperthyroidism.

Patients who would certainly benefit from surgery are those with large goiters likely to be resistant to RAI, patients with compressive symptoms, and those with coincidental thyroid nodules concerning for malignancy. Approximately 13% of patients with Graves' disease have thyroid nodules suspicious for carcinoma [20]. Studies have shown that the incidence of malignancy for a solid, cold nodule is the same as for a patient without the disease, 15–20%. Some studies suggest that thyroid carcinoma in patients with Graves' disease is more likely to be aggressive, with increased lymph node metastasis and local invasion [21, 22]. Multiple other studies report no difference in the prognosis of carcinoma for patients with or without Graves' disease.

Other indications for surgical management of Graves' disease include medically noncompliant patients, thyroid storm unresponsive to medical therapy, amiodarone-induced thyrotoxicosis, and thyroid-associated ophthalmopathy (TAO). TAO can be seen in up to 50% of patients with Graves' disease [23]. Some studies have shown that total thyroid ablation by surgery or RAI decreases initiation and halts progression of TAO [24–26]. Studies have also reported that RAI may worsen TAO. Of the two ablative therapies, surgery appears to be more effective than RAI.

Preoperative preparation is recommended to avoid intraoperative or postoperative thyroid storm. Many different regimens have been utilized. Most regimens consist of a combination of thionamide therapy, iodine (SSKI, Lugol's solution), and/or B-blocking agent. The choice of operation also varies based on surgeon preference and should be individualized for each patient. The three main operations are total thyroidectomy, bilateral subtotal thyroidectomy, and total lobectomy with contralateral subtotal lobectomy. The goal is to avoid hypoparathyroidism and injury to the recurrent laryngeal nerves, and at the same time minimize the chance of recurrent hyperthyroidism. Most authors recommend total thyroidectomy when possible. The other options leave remnant tissue and are associated with an increased rate of recurrent hyperthyroidism. After surgery, most patients are rendered hypothyroid and life-long thyroid hormone replacement therapy should be anticipated.

Toxic Nodular Goiter

The term toxic nodular goiter refers to two entities: toxic adenoma, implying a single lesion, and toxic multinodular goiter (TMG), in which more than one hyperfunctioning nodule exists. Toxic nodular goiter was first described as a type of thyrotoxicosis clinically distinct from Graves' disease by **Henry Plummer** in 1913. Often the term Plummer's disease is used to describe thyrotoxicosis resulting from either a single nodule or multiple autonomous nodules.

Toxic Adenoma

Toxic adenomas are discrete, solitary nodules that may occur at any age. They are most common in the third to fourth decade of life and they are rare in children [27, 28]. Toxic adenoma synthesizes and secretes thyroid hormone independent of TSH control. This results in TSH suppression, with increased T3 and T4 levels. Usually the nodule is the only functioning tissue with the extranodular tissue becoming dormant. This is highlighted in the hotspots seen with radionuclide scanning (Table 2). Toxic adenomas seem to be more prevalent in regions of iodine deficiency and recently it has been shown that a mutation of the gene for the TSHR may be associated with their development. This mutation results in the constitutive activation of the cyclic adenosine monophosphate (cAMP) cascade, causing hypersecretion of thyroid hormone and tissue growth [29–32].

Most toxic adenomas are follicular adenomas with carcinoma being very rare. Hyperthyroidism usually does not occur until the nodule is 2.5–3.0 cm in diameter. The

symptoms and signs of hyperthyroidism are milder than in Graves' disease and do not include ophthalmopathy and dermopathy. The diagnosis is usually established by a suppressed TSH and elevated free T3 or free T4 levels. In subclinical thyrotoxicosis, serum levels of T3 and T4 may be normal. Confirmation of the diagnosis may require radionuclide scanning, showing concentration of RAI in the nodule with inhibition of RAI uptake in surrounding thyroid tissue. Fine-needle aspiration biopsy of toxic adenomas is not recommended. They are rarely malignant and more importantly, cytologic features of toxic adenomas can be misleading. These lesions often exhibit cellular atypia suggestive of a follicular neoplasm or well differentiated thyroid cancer [33].

The treatment for toxic adenomas is either ablation or surgery (Table 3). Unlike Graves' disease, there is no role for thionamides in the management of toxic adenomas. Long-lasting remission rarely occurs with thionamide therapy and after therapy is stopped, the chance of recurrent hyperthyroidism is high. Radioiodine therapy can be effective but the doses required are usually higher than those used in Graves' disease. Also, complete nodule regression with RAI therapy is not common and continued surveillance is necessary. This makes RAI therapy less desirable than surgery. Sclerosing agents such as ethanol have been shown to be effective in several small series [34, 35]. However, multiple injections are often needed (3–13) and exacerbation of hyperthyroidism and temporary vocal cord paralysis have been reported with ethanol injection [36, 37].

Surgery is commonly employed in the treatment of toxic adenomas and is usually the treatment of choice. Unilateral thyroid lobectomy is the preferred procedure by most authors. It is very effective with low risk of hypothyroidism since the contralateral lobe is not removed. Surgery also provides tissue for pathologic diagnosis in the rare cases of suspected carcinoma.

Toxic Multinodular Goiter

The prevalence of TMG is significantly higher in areas of endemic goiter and iodine deficiency. In areas where iodine repletion has occurred, the prevalence of TMG has decreased [38]. A genetic predisposition and female gender also seem to play a role in the development of TMG.

TMG seems to evolve over many years from sporadic, diffuse goiter to the development of functional autonomy and eventual clinical thyrotoxicosis. The pathogenesis of TMG likely involves iodine deficiency which leads to a decreased production of thyroid hormone, resulting in an increase in TSH secretion, promoting goiter formation [39, 40]. Multiple nodules develop which in time become autonomous. Autonomous areas eventually grow large enough to secrete increased amounts of thyroid hormone and suppress TSH. Hyperthyroidism can be precipitated in nontoxic multinodular goiter both with autonomy and without autonomy and in TMG by iodides (i.e., intravenous (IV) contrast media) [41]. This is referred to as the **Jod-Basedow** phenomenon.

Due to the many years it takes to develop, TMG generally occurs in older persons. The hyperthyroidism tends to be insidious in onset, may be mild to severe, and is unaccompanied by the infiltrative ophthalmopathy and dermopathy of Graves' disease. In older patients, the hyperthyroidism may be masked and the patient may present with cardiac findings such as atrial fibrillation, tachycardia, congestive heart failure, angina, weight loss, anxiety, insomnia, or muscle wasting. Patients with TMG often have no thyromegaly on clinical examination.

The diagnosis of TMG is a clinical one, based on physical examination and laboratory confirmation. Serum levels of free T3 and free T4 are elevated with a suppressed TSH. Radionuclide scanning reveals a multinodular gland with areas of increased patchy uptake (Table 2).

The principal treatment options for TMG include RAI therapy or surgery (Table 3). Since remission does not occur with TMG, the long-term use of thionamides is not indicated unless there are contraindications to the use of RAI therapy or surgery. Patients with TMG often require multiple doses of RAI to control hyperthyroidism because of the larger gland size and lower uptake of RAI, when compared to patients with Graves' disease. Although RAI treats the hyperthyroidism, studies show that it does not significantly reduce goiter size, compressive symptoms, or substernal extension, because TMG contains areas of fibrosis, calcifications, and nonfunctioning nodules [42, 43].

Surgery is usually recommended in younger, healthier patients with large goiters and/or compressive symptoms. Either bilateral subtotal thyroidectomy or total thyroidectomy is the preferred operation. Bilateral subtotal thyroidectomy has the potential advantage of decreased hypoparathyroidism, decreased vocal cord paralysis, and decreased hypothyroidism. However, the incidence of recurrent hyperthyroidism is greater than in total thyroidectomy patients. Total thyroidectomy results in near-zero recurrence but nearly all patients are rendered hypothyroid, requiring thyroid hormone supplementation. Total thyroidectomy for patients with TMG is a safe operation in experienced hands with low rates of hypoparathyroidism and vocal cord paralysis [44].

Thyroiditis

Thyroiditis, infiltration of the thyroid gland with inflammatory cells, may be seen in a diverse group of autoimmune, inflammatory, and infectious processes. It comprises a diverse group of disorders that are among the most common endocrine abnormalities encountered. The diagnosis of thyroiditis is based on the clinical presentation and laboratory

Table 4 Different types of thyroiditis

Hashimoto's thyroiditis (chronic lymphocytic thyroiditis)
Subacute (painless) lymphocytic thyroiditis Sporadic silent thyroiditis Postpartum thyroiditis
Subacute (painful) granulomatous thyroiditis (de Quervain's thyroiditis, giant cell thyroiditis)
Acute suppurative thyroiditis
Riedel struma (Riedel's thyroiditis, invasive fibrous thyroiditis)

analysis of thyroid function. Thyroiditis can be classified as (1) chronic, which includes Hashimoto's thyroiditis and Riedel struma, (2) subacute, which includes lymphocytic and granulomatous, and (3) acute suppurative, which is rare (Table 4).

Hashimoto's Thyroiditis

Hashimoto's thyroiditis, also called chronic lymphocytic thyroiditis, is the prototypical autoimmune thyroiditis. Hashimoto's is the most common cause of goiter and hypothyroidism in the USA and affects approximately 2% of the general population [45]. **Hakaru Hashimoto** first described this disorder in 1912 and termed it "struma lymphomatosa."

Pathologically, the thyroid gland is initially enlarged and has lymphocytic and plasma-cell infiltration, follicular cell atrophy, and interlobular fibrosis, eventually leading to a shrunken fibrotic gland [46]. The normal follicular cells are altered and often replaced with pink oxyphilic or Hurthle cells. Classically, Hashimoto's thyroiditis occurs as a painless diffuse goiter in young to middle-aged women in their third and fourth decades and is frequently associated with asymptomatic hypothyroidism [47]. Hashimoto's thyroiditis has also been reported to occur with increased frequency in patients with other autoimmune disorders such as lupus, Graves' disease, and pernicious anemia [48].

The hallmarks of this disorder are high circulating titers of antibodies to thyroid peroxidase (90% of patients) and thyroglobulin (20–50% of patients). Antibodies to the TSHR have also been identified. The inciting event that triggers the development of antithyroid antibodies remains unclear. There does appear to be a genetic predisposition, with reported associations with human leukocyte antigen (HLA)-DR3, HLA-DR5, and HLA-B8 [49–51]. Viral etiologies and smoking have also been implicated. Although the exact pathogenesis is not known, it is clear that thyroid autoimmunity drives the lymphocytic collection and is responsible for thyroid epithelial cell damage. Progressive, immune-mediated thyroid cell damage leads to goiter formation and thyroid gland failure.

The clinical presentation varies, depending on the stage at the time of presentation. The patient may be completely asymptomatic or present with hypothyroid symptoms. Physical examination typically reveals a firm, bumpy, nontender goiter, often symmetric, with a palpable pyramidal lobe. Usually there are no discrete nodules. Single or dominant nodules should be evaluated and if indicated a fine-needle aspiration biopsy should be performed to exclude malignancy. Thyroid hormone levels may also vary based on time of presentation. They may be normal with a normal TSH (euthyroid), low with an elevated TSH (hypothyroid), or normal with an elevated TSH (subclinically hypothyroid). Euthyroid individuals with Hashimoto's thyroiditis develop hypothyroidism at a rate of approximately 5% per year [52]. Mild thyrotoxicosis ("Hashitoxicosis") has been reported to be the initial presentation in up to 5% of patients with Hashimoto's thyroiditis [53]. The clinical course for Hashimoto's thyroiditis is variable. Up to 50% of patients can become subclinically hypothyroid and 5–40% can become clinically hypothyroid, emphasizing the importance of following thyroid function tests in these patients [54].

Imaging studies for Hashimoto's thyroiditis are not particularly useful. Radionuclide scanning usually reveals patchy nonspecific uptake with minimal clinical significance. Ultrasound reveals marked hypoechogenicity with coarse echogenic bands. If a dominant nodule is found, then follow-up with repeat sonography and/or fine-needle biopsy may be warranted. Patients with Hashimoto's thyroiditis can be at increased risk of developing B-cell lymphoma, and as such, rapid growth in the setting of Hashimoto's thyroiditis should raise concern about the possibility of thyroid lymphoma [55, 56].

The treatment of Hashimoto's thyroiditis consists of thyroid hormone replacement for hypothyroidism. Levothyroxine is the hormone of choice for replacement therapy because of its consistent potency and prolonged duration of action. In patients who remain symptomatic on levothyroxine alone, combination therapy with liothyronine may be beneficial. Surgery is indicated only for large symptomatic goiters or persistent painful Hashimoto's thyroiditis.

Subacute (Painless) Lymphocytic Thyroiditis

There are two forms of painless thyroiditis, sporadic silent and postpartum, both sharing very similar features. It is characterized by destruction of the thyroid gland by lymphocytes (destruction-induced thyroiditis), absence of pain, and temporary thyroid dysfunction. Sporadic silent thyroiditis and postpartum thyroiditis are probably variants of the same disorder, distinguished only by their relationship to pregnancy.

The etiology is unclear, but the immune system is likely involved because it has been found in patients with a wide variety of autoimmune diseases. HLA-DR3 is present in increased frequency in both sporadic and postpartum thyroiditis [57]. HLA-DR5 is also increased in frequency in postpartum thyroiditis [57]. Histopathology shows extensive lymphocytic infiltration, collapsed follicles, and degeneration of follicular cells [58, 59]. The changes can be either focal or diffuse, with lymphoid follicles being present in about half of the patients [59]. Unlike Hashimoto's thyroiditis, there is usually no stromal fibrosis, oxyphilic changes, or germinal centers.

Clinically, the patient typically passes through four phases: thyrotoxic, euthyroid, hypothyroid, and euthyroid, although not all phases are seen in all patients. The initial thyrotoxicosis is caused by a release of preformed hormone and not because of sustained overproduction of the hormone and therefore is not true hyperthyroidism [60]. The thyrotoxicosis typically lasts from 3 to 6 months but can persist up to a year. Postpartum thyroiditis typically occurs 4–6 weeks following delivery. It occurs in up to 5% of postpartum women and may recur with subsequent pregnancy [61]. The process usually resolves after transient hypothyroidism; however, some patients (20%) progress to chronic lymphocytic thyroiditis.

Symptoms are generally mild; however, in certain cases they can be severe. The initial thyrotoxic phase in postpartum thyroiditis is usually milder than in sporadic silent thyroiditis. The thyroid is symmetrical, slightly enlarged, and painless. The erythrocyte sedimentation rate (ESR) is usually normal. Because the hyperthyroid phase is usually transient and mild, most patients do not require treatment.

Subacute (Painful) Granulomatous Thyroiditis

Subacute granulomatous thyroiditis is also referred to as de Quervain's thyroiditis, giant cell thyroiditis, pseudogranulomatous thyroiditis, and subacute painful thyroiditis. The pathology of this disorder was first described by **Fritz de Quervain** in 1904 [62]. He showed giant cells and granulomatous changes in the thyroid gland of affected patients.

Like sporadic silent and postpartum thyroiditis, subacute granulomatous thyroiditis is a spontaneous, remitting, inflammatory disorder that may last for weeks to months. As with other thyroid disorders, subacute granulomatous thyroiditis is more common in women, with a peak incidence in the fourth and fifth decades of life and is rarely seen in children or the elderly [62].

The pathogenesis of subacute granulomatous thyroiditis is unclear. It does not seem to be an autoimmune disease. A viral etiology has been implicated; however, the evidence is largely indirect [63–65]. Subacute thyroiditis has been associated with adenovirus, Coxsackie, Epstein–Barr, and influenza viruses [66, 67]. Subacute granulomatous thyroiditis often follows an upper respiratory tract infection and occasionally includes a prodromal phase of muscular aches, pains, fever, and malaise. The primary events in the pathology of subacute granulomatous thyroiditis are destruction of the follicular epithelium and loss of follicular integrity; however, the histopathological changes are distinct from those found in Hashimoto's thyroiditis. The characteristic follicular lesion is a central core of colloid surrounded by multinucleate giant cells. These lesions progress to form granulomas [68, 69].

The most prominent physical finding is an enlarged thyroid gland that is exquisitely tender to palpation. The pain is usually constant, gradual to sudden in onset, and often severe, involving the entire thyroid gland. Pain is often aggravated by turning the head or swallowing and may radiate to the jaw, ear, or occiput on the ipsilateral side. Frequently, patients present with tachycardia and hyperpyrexia, with temperatures elevated up to 102 °F. Unlike subacute (painless) lymphocytic thyroiditis, the ESR is consistently high and the white blood cell count may be elevated. Thyroid function tests may be normal, elevated, or low depending on the stage of the disease at the time of presentation. The clinical course of subacute granulomatous thyroiditis is self-limited and is similar to painless thyroiditis. Similar to painless thyroiditis, patients go through the initial phases of thyrotoxicosis for a few months. The thyrotoxicosis is a result of the release of stored thyroid hormones from acute destruction of the thyroid parenchyma. Subsequent to that, they become euthyroid. In rare, severe cases, patients can then develop hypothyroidism which is usually transient with 90% of the patients returning to a euthyroid state.

Salicylates and nonsteroidal anti-inflammatory drugs are often adequate to decrease pain in mild to moderate cases. In more severe cases, oral glucocorticoids may provide dramatic relief of pain and swelling.

Acute Suppurative Thyroiditis

This rare entity usually occurs from a bacterial infection and rarely from nonbacterial infections of the thyroid [70]. This disease tends to affect younger patients and typically occurs in the 30s to 40s. The pathogenesis primarily involves decreased resistance of the thyroid gland to infection. Infection may reach the gland via blood, lymphatics, or directly through a persistent thyroglossal duct or a nearby internal fistula such as a piriform sinus fistula [71]. Bacterial thyroiditis is often preceded by an upper respiratory infection.

Treatment of acute bacterial thyroiditis requires admission to the hospital, drainage of any abscess and parenteral antimicrobial therapy aimed at the causative agent. Since a

piriform sinus fistula is a very common route of infection in bacterial thyroiditis, a barium swallow, computed tomography (CT), or magnetic resonance imaging (MRI), and possibly hypopharynx endoscopy should be performed to look for communicating fistulas in most patients with their first episode and in all patients with recurrent episodes. Such fistulas must be surgically excised for definitive cure and prevention of recurrent infection [72, 73]. In the adult, *Staphylococcus aureus* and *Streptococcus pyogenes* are the offending pathogens in approximately 80% of patients [70]. Mortality has markedly improved for acute bacterial thyroiditis, from 25% down to 8.6% in recent years [70]. However, the mortality is close to 100% if the diagnosis is delayed and antimicrobial therapy not initiated [70].

Nonbacterial infection of the thyroid gland is very rare. Known causes are *Aspergillus, Coccidioides immitis, and Candida*. The treatment consists of appropriate antimicrobial therapy and analgesics.

Riedel Struma

Also known as invasive fibrous thyroiditis or Riedel's thyroiditis, it is a very rare disorder of unknown etiology which is characterized by intense infiltration of the thyroid parenchyma by inflammatory cells and subsequent replacement by dense fibrosis and collagen [74]. This disorder results in an extremely fibrotic thyroid gland. Riedel's thyroiditis is not a primary disorder of the thyroid but involves the thyroid and represents a systemic disease. This disease may involve other sites such as the mediastinum, orbit, retroperitoneum, and biliary tract. It is named after Bernhard Riedel, who initially described this entity in 1893. Riedel struma affects mainly women in their fourth to fifth decade of life.

The clinical presentation is a painless goiter which is firm, fixed, and "woody" in texture [74]. The extensive, progressive fibrosis may eventually cause compression of the trachea and esophagus. Most patients are euthyroid, but may progress to hypothyroidism when the gland is sufficiently replaced by the fibroid tissue. The clinical presentation may be confused with an aggressive thyroid malignancy such as anaplastic carcinoma. Imaging studies and fine-needle aspiration or open biopsy can help differentiate the two. Unlike the CT findings of locally advanced thyroid malignancies, in Riedel struma the infiltrative mass is isodense with the neck muscles, hypodense with the normal thyroid tissue, and does not enhance with contrast [75, 76].

This condition is benign and usually self-limiting. Nonetheless, surgery may be warranted to alleviate compression symptoms. Extensive resection is often impossible, but wedge resections, especially over the isthmus, to relieve tracheal compression, can be very effective [77]. Recurrent obstruction after resection is rare. Medical therapy, especially if started early, may be successful in preventing compressive symptoms. Effective agents include corticosteroids, tamoxifen, and methotrexate [78–81].

Key Summary Points

- The most common cause of hyperthyroidism is Graves' disease.
- Graves' disease is an autoimmune disease.
- Graves' disease may have nonthyroidal symptoms such as exophthalmos and dermopathy.
- Surgery can be performed safely with excellent results for patients with Graves' disease and toxic nodular goiter.
- Thyroiditis comprises a diverse group of disorders ranging from chronic, subacute, and acute.
- Hashimoto's thyroiditis is the most common cause of goiter and hypothyroidism in the USA.
- Treatment for thyroiditis is focused on relieving the symptoms and correcting thyroid hormone levels.

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