Diagnosis and Management of Thyroiditis: Hashimoto, de Quervain, Riedel

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Contents

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Case Presentation

A 47-year-old woman presented with progressively enlarging thyroid goiter, which had developed over the previous 6-month period. She reported dysphagia to liquids and solids and dyspnea when lying flat. Physical examination revealed firm enlargement of the thyroid. Ultrasound demonstrated symmetric enlargement (approximately 5 × 9 × 4 cm for each lobe) with heterogenous hypoechogenicity and no distinct nodules or increased vascularity (Fig. 4.1). TSH was elevated at 5.74 mIU/mL (normal range 0.37–4.42 mIU/mL) and TPO-Abs were elevated at >1300 U/mL. A diagnosis of Hashimoto's thyroiditis (HT) was rendered, and she was started on LT_4 with a plan to monitor her thyroid enlargement. She was lost to follow-up and returned 1 year later with complaints of persistent compressive symptoms. TSH was found to be elevated to 24.22 mIU/mL, and she acknowledged poor compliance with LT_4 therapy. A repeat US was performed, which showed enlargement of the heterogeneous and hypoechoic thyroid gland compared to 1 year prior (now approximately 7 × 9 × 5 cm for each lobe). The goiter also had a deep retrosternal component. Although the ultrasound did not reveal discrete nodules, an FNA was obtained due to the size and firmness of the thyroid as well as increase in size over 1 year. Pathology showed lymphocytes and bland follicular epithelial cells, felt be consistent with a diagnosis of chronic lymphocytic thyroiditis. However, given the firm and relatively rapid enlargement of the thyroid, Riedel's thyroiditis (RT) and primary thyroid lymphoma (PTL) remained under consideration. To further characterize the thyroid, an MRI was obtained, which showed a markedly enlarged thyroid with T1- and T2-hypointensity and moderate contrast enhancement, displacing but not encasing the great vessels (Fig. 4.2). She was subsequently recommended to undergo thyroid isthmusectomy for histologic characterization. Intraoperatively, the isthmus was noted to be markedly fibrotic and firm but not adherent to surrounding tissues. Pathology showed chronic inflammatory cells, germinal centers, and dense fibrosis, which did not appear to extend outside the thyroid capsule (Fig. 4.3). Abundant IgG4+ plasma cells were noted, up to 30 per high power field. Together these findings suggested IgG4-related variant of HT. Serum IgG4 levels were normal. She was started on high-dose prednisone, which was continued for 4 months. During this time, she reported improvement in dysphagia symptoms, though no change in size of the thyroid was appreciated on physical examination. She was weaned off steroid treatment over the ensuing year. A follow-up US obtained 2 years after treatment showed no change in size or characteristics of the thyroid. At the present time, she has remained on LT_4 therapy for 3 years with stable thyromegaly and no progression of symptoms.

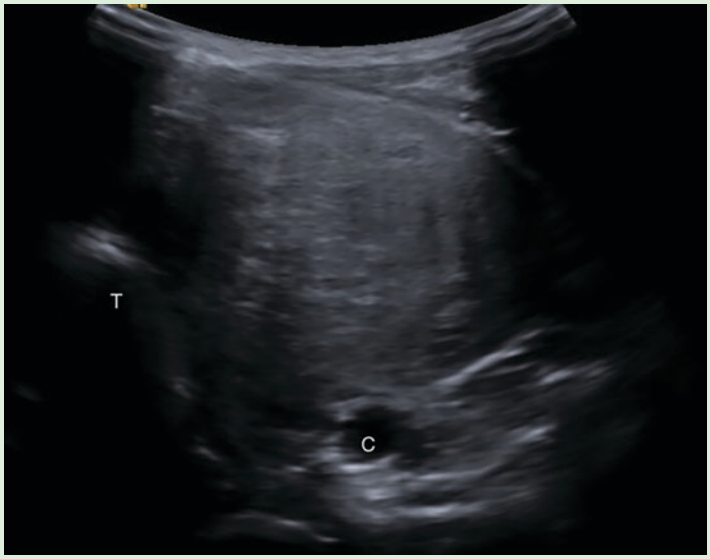

Fig. 4.1 Ultrasound image in axial view demonstrating an enlarged and heterogenous left thyroid lobe without distinct nodules (C = carotid artery, T = trachea)

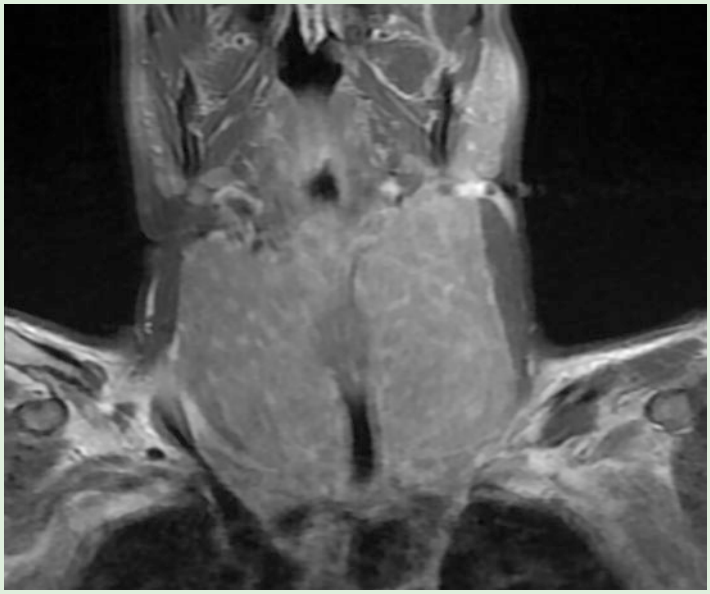

Fig. 4.2 Contrast-enhanced MRI in coronal view demonstrating marked diffuse enlargement of the thyroid

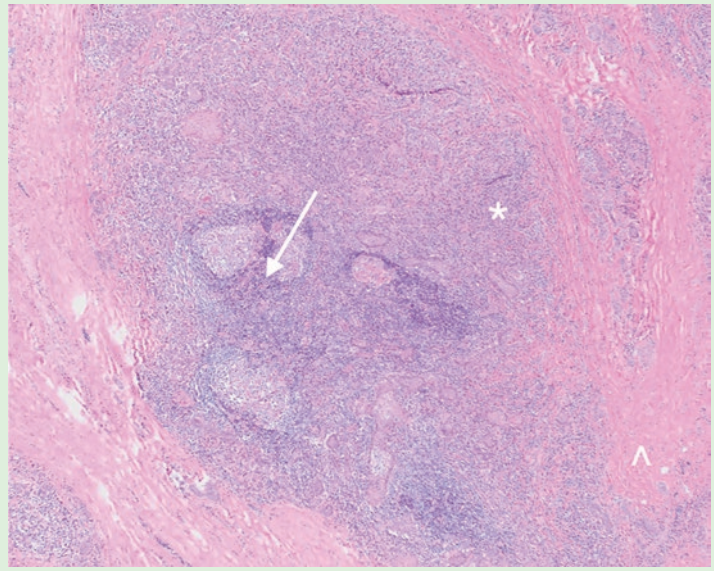

Fig. 4.3 Histologic appearance of IgG4-related Hashimoto's thyroiditis, including chronic inflammatory cells (*) and germinal centers (arrow) in a background of fibrosis (^)

Questions

1. Which of the following can be presenting features of Hashimoto's thyroiditis?
   1. Painless enlargement of the thyroid
   2. Atrophic thyroid gland
   3. Thyroid toxicosis
   4. Hypothyroidism with elevated thyroperoxidase levels
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (1) and (2) and (4) are correct.
      (c) Only (1) and (3) and (4) are correct.
      (d) Only (2) and (3) and (4) are correct.
      (e) All are correct.
2. During the thyrotoxic phase of subacute thyroiditis, what pattern of radioactive iodine uptake would be expected?
   1. Diffuse increased uptake
   2. Focal increased uptake
   3. Focal decreased uptake
   4. Diffuse decreased uptake
      (a) Only (1) is correct.
      (b) Only (4) is correct.
      (c) Only (1) and (2) are correct.
      (d) Only (3) and (4) are correct.
      (e) All are correct.

3. Which of these treatment or supportive options are reasonable for patients presenting with de Quervain's thyroiditis?
   1. Beta-blocker
   2. Levothyroxine
   3. Corticosteroids
   4. Nonsteroidal anti-inflammatory drugs
   5. Methimazole or other antithyroid medications
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (1) and (3) and (5) are correct.
      (c) Only (1) and (3) and (4) are correct.
      (d) Only (2) and (3) and (4) are correct.
      (e) All are correct.
4. Which of the following are features that can be found on ultrasound in patients with Hashimoto's thyroiditis?
   1. Pseudonodules
   2. Heterogeneity with ill-defined areas of hypoechogenicity
   3. Atrophied gland with "honeycomb" appearance
   4. Prominent central neck adenopathy
      (a) Only (1) is correct.
      (b) Only (4) is correct.
      (c) Only (1) and (2) are correct.
      (d) Only (3) and (4) are correct.
      (e) All are correct.
5. Which of these antibodies are often found to be positive in patients with Hashimoto's thyroiditis?
   1. Thyroperoxidase antibodies (TPO)
   2. Thyroglobulin antibodies (Tg)
   3. Thyrotropin receptor antibodies (TRAB)
   4. Thyroid-stimulating immunoglobulin (TSI)
      (a) Only (1) is correct.
      (b) Only (4) is correct.
      (c) Only (1) and (2) are correct.
      (d) Only (3) and (4) are correct.
      (e) All are correct.
6. Which of these statements are true regarding interpretation of ultrasonographic findings in patients with coexistent Hashimoto's thyroiditis (HT) and differentiated thyroid cancer?
   1. Benign central neck nodes are frequently encountered in patients with HT and one must not reflexively characterize prominent neck nodes as metastatic disease.
   2. Sensitivity of ultrasound for detecting central compartment lymphadenopathy is higher when thyroid is present.
   3. Atrophy of the thyroid gland in later HT limits detection of central neck lymphadenopathy.

4. Metastatic central neck lymph nodes are frequently encountered in patients with HT and prominent central nodes should be biopsied.
   (a) Only (1) is correct.
   (b) Only (4) is correct.
   (c) Only (1) and (2) are correct.
   (d) Only (3) and (4) are correct.
   (e) All are correct.

7. Which of the following statements are true regarding the association between Hashimoto's thyroiditis (HT) and papillary thyroid cancer (PTC)?
   1. Chronic inflammation in HT may facilitate malignant transformation.
   2. HT is associated with aggressive PTC including increased rates of metastasis and recurrence.
   3. HT may be an immune response to the tumor.
   4. Patients with HT have lower TSH levels from levothyroxine treatment, which contributes to thyroid epithelial cell proliferation.
   5. Increased expression of the (PI3K)/Akt pathway has been shown in thyroid tissue of those with HT.
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (1) and (3) and (5) are correct.
      (c) Only (1) and (3) and (4) are correct.
      (d) Only (2) and (3) and (4) are correct.
      (e) All are correct.
8. Which of these statements are true regarding postpartum thyroiditis?
   1. Onset of postpartum thyroiditis typically occurs within 2–6 months after delivery.
   2. Postpartum thyroiditis is often transient with return to normal thyroid function within a year.
   3. Postpartum thyroiditis may manifest as mild hyperthyroidism.
   4. Postpartum thyroiditis results in development of permanent hypothyroidism.
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (3) and (4) are correct.
      (c) Only (1) and (3) and (4) are correct.
      (d) Only (2) and (3) and (4) are correct.
      (e) All are correct.
9. In which of the following scenarios are FNAs likely to have pitfalls, either with nondiagnostic samples, low sensitivity, or low positive predictive value?
   1. A patient with thyroid tenderness following an upper respiratory illness
   2. A patient with a rapidly enlarging hypoechoic thyroid mass with variable edge characteristics, homogeneous echotexture without calcifications, and absence of necrosis

3. A patient with firm enlargement of the thyroid associated with compressive symptoms, with sclerotic thyroid, which is hypointense on MRI T1- and T2- weight images
4. A patient with Hashimoto's thyroiditis and a thyroid nodule rich in Hürthle cells
   (a) Only (1) and (2) and (3) are correct.
   (b) Only (3) and (4) are correct.
   (c) Only (1) and (3) and (4) are correct.
   (d) Only (2) and (3) and (4) are correct.
   (e) All are correct.

10. What are some pitfalls of cytologic evaluation of nodules in setting of Hashimoto's thyroiditis (HT)?
    1. Structural or nuclear features of papillary thyroid cancer, including papillary or microfollicular pattern and nuclear groves, can be present in HT without malignancy.
    2. Nondiagnostic samples are commonly encountered in HT due to atrophic thyroid tissue.
    3. Aspirates interpreted as "suspicious for follicular neoplasm, Hürthle cell type" may have low positive predictive value (PPV) for malignancy in those with HT.
    4. Molecular testing platforms such as the Afirma™ gene sequencing classifier (GSC) demonstrate poor performance for samples rich in Hürthle cells.
       (a) Only (1) and (2) and (3) are correct.
       (b) Only (3) and (4) are correct.
       (c) Only (1) and (3) are correct.
       (d) Only (2) and (3) and (4) are correct.
       (e) All are correct.
11. Which of these statements are correct regarding surgical treatment for Riedel thyroiditis?
    1. Complete surgical excision has higher likelihood of success compared to partial thyroid surgery.
    2. Isthmusectomy alone could be considered as treatment to relieve pressure symptoms.
    3. Thyroidectomy is challenging due to obliteration of normal tissue planes.
    4. Significant risk of complications such as temporary and permanent vocal cord paralysis and rates of temporary and permanent hypoparathyroidism may be associated with thyroidectomy.
       (a) Only (1) and (2) and (3) are correct.
       (b) Only (3) and (4) are correct.
       (c) Only (1) and (3) and (4) are correct.
       (d) Only (2) and (3) and (4) are correct.
       (e) All are correct.
12. Which of these are possible medical treatment options for Riedel's thyroiditis?
    1. Corticosteroids
    2. Tamoxifen

3. Mycophenolate mofetil
4. Levothyroxine
5. Methimazole

(a) Only (1) and (2) and (3) and (4) are correct.
(b) Only (3) and (4) are correct.
(c) Only (1) and (3) and (4) are correct.
(d) Only (2) and (3) and (4) are correct.
(e) All are correct.

4

4.1 Introduction

The term "thyroiditis' encompasses a broad spectrum of clinical conditions characterized by inflammation of the thyroid gland with varying causation and clinical manifestations. Both autoimmune and infectious etiologies have been implicated in thyroiditis. These clinical entities may present as isolated disease states or may be coexistent with thyroid nodules or malignancy. Indeed, Hashimoto's thyroiditis (HT) is associated with an increased risk of developing thyroid lymphoma, and a linkage between HT and papillary thyroid carcinoma (PTC) has been proposed [1, 2].

Several thyroiditis syndromes have been described, many sharing overlap in their clinical features [2]. This chapter will address the diagnosis and management of three thyroiditis types: Hashimoto, de Quervain, and Riedel. A summary of clinical characteristics and treatment recommendations discussed in this chapter is presented in Table 4.1.

While medical management of thyroiditis is paramount, surgical treatment for compressive symptoms or coexistent nodules or malignancy is often indicated. To this end, the surgeon should be familiar with surgical considerations specific to these conditions. It also is important to understand the impact of thyroid inflammation on the assessment of thyroid nodules and malignancy in order to make sound clinical decisions regarding surgical management.

4.2 Clinical Presentation and Diagnosis

4.2.1 Hashimoto's Thyroiditis

Hashimoto's thyroiditis (HT), also called chronic lymphocytic thyroiditis or autoimmune thyroiditis, is the most common autoimmune condition [3] and the leading cause of hypothyroidism in iodine-replete areas of the world [4]. The worldwide incidence is estimated to be 0.3 to 1.5 per 1000 [1]. Women are 8–10 times more likely to suffer from HT than men, with a peak age of onset between 30 and 50 years of age [2, 4]. There is increasing evidence to suggest that genetic susceptibility and

Table 4.1 Characteristics and treatment of thyroiditis syndromes

Syndrome	Hashimoto	de Quervain	Riedel
Etiology	Autoimmune	Infectious	Unknown
Clinical presentation	Symmetric thyroid enlargement; later stages with thyroid atrophy	Thyroid pain/tenderness preceded by viral prodrome or upper respiratory illness	Firm enlargement of thyroid, may include compressive symptoms, hypoparathyroidism, or hoarseness
Thyroid hormone status	Initial hyperthyroidism ("hashitoxicosis") or euthyroid status, progressing to subclinical and overt hypothyroidism	Initial thyrotoxicosis followed by euthyroidism or hypothyroidism; majority return to euthyroid state	Initially may be euthyroid, progressing to hypothyroidism
Thyroid antibodies	High titers of anti-TPO (>90%), anti-Tg (~50%)	Absent, low titers or transient anti-TPO	+/– anti-TPO, +/– anti-Tg
US features	Diffuse heterogeneity with ill-defined areas of hypoechogenicity and "pseudonodules"; atrophied with "honeycomb" appearance in later stages	Patchy, poorly defined areas of hypoechogenicity with decreased vascularity	Heterogeneous hypoechogenicity with decreased vascularity
Histology	Interstitial lymphocytic infiltrate with plasma cells, macrophages; lymphoid follicles with or without germinal centers; hyperplastic or atrophied thyroid follicles with Hürthle cell change; fibrosis	Noncaseating granulomas; disrupted follicles; interstitial inflammatory infiltrate containing lymphocytes and multinucleated giant cells; fibrosis	Diffuse fibrosis extending outside thyroid capsule
Medical treatment	Thyroid hormone replacement	NSAIDs, corticosteroids	Corticosteroids, tamoxifen, mycophenolate mofetil
Surgical indications (excluding coexistent thyroid pathology)	Compressive symptoms, persistent systemic symptoms	Recurrent thyroiditis	Compressive symptoms (isthmusectomy recommended)

environmental triggers contribute to the loss of immune tolerance [5]; nutritional factors, including high iodine intake and dietary deficiencies of selenium and iron, have been implicated in its development [6, 7]. For reasons that are not clear, smoking appears to have a protective effect against levels of autoantibodies and development of hypothyroidism in HT [8, 9].

Hashimoto first described this condition in 1912 as "struma lymphomatosa," based on histopathologic examination of 4 goitrous thyroidectomy specimens from middle-aged women showing diffuse lymphocytic infiltration with formation of lymphoid follicles and degeneration of thyroid follicles [10]. Several variants of thyroiditis along the same clinical and histopathologic spectrum have since been described, including

fibrous variant, IgG4-related variant, juvenile form, and painless/postpartum thyroiditis. The defining feature in each of these entities is profound lymphocytic infiltration of the thyroid gland [11].

Classically, HT presents with painless, gradual enlargement of the thyroid, though morphology of the thyroid gland may vary, depending on the timing and circumstances of clinical detection. Patients who present later in the disease process may demonstrate thyroid atrophy resulting from destruction and fibrosis of thyroid parenchyma [5, 12]. Elevated levels of antibodies to thyroperoxidase (TPO) are present in nearly all patients, and antibodies to thyroglobulin (Tg) are present in up to half of patients with HT [11, 13]. Mild hyperthyroidism or so-called Hashitoxicosis, resulting from destruction of follicular cells and release of hormone, has been described as a presenting feature [11, 14], though thyroid function is frequently normal at presentation. While subclinical hypothyroidism may persist for a period of time, most eventually develop overt hypothyroidism [11].

In patients in whom the diagnosis of HT is considered, the presence of anti-TPO and Tg antibodies can be helpful. Notably, ultrasound findings suggestive of HT may precede evidence of elevated antithyroid antibodies in a subset of cases [15]. The characteristic ultrasonographic appearance of HT is of diffuse heterogeneity with ill-defined areas of hypoechogenicity resulting from accumulation of lymphoid tissue. Parenchymal destruction and fibrosis distort thyroid architecture and give the appearance of "pseudonodules." The term "pseudonodule" refers to an area within the thyroid that appears to represent a nodule in one imaging plane but loses its demarcation as such in another plane; this finding is especially marked in the fibrosing variant of Hashimoto's, where dense fibrous bands appear as hyperechoic septations, generating the false appearance of distinct nodules. Vascularity may be increased early in the disease course and decreased as disease progresses. In later stages, the atrophied gland appears shrunken and imparts a "honeycomb" appearance. Central neck adenopathy may be prominent, reflective of increased local immune activity [11, 16, 17].

Histologically, HT shows interstitial lymphocytic infiltrates containing plasma cells and macrophages; lymphoid follicles containing occasional germinal centers are seen. Thyroid follicles range from hyperplastic to atrophic with minimal colloid. Hürthle cell change is often observed, and variable degrees of fibrosis are present. The fibrosing variant of HT, which clinically presents with a large, firm, and nodular thyroid, is characterized by a predominance of fibrosis replacing thyroid parenchyma. This entity must be distinguished from Riedel's thyroiditis (discussed below), which shows a similar extent of fibrosis, but which progresses outside of the thyroid capsule. The IgG4 variant of HT also shows dense stromal fibrosis but with the hallmark finding of increased number of IgG4-

producing plasma cells. This latter disease is clinically characterized by earlier age of onset, decrease in the ratio of women to men, higher levels of circulating antithyroid antibodies, and a more rapid and progressive clinical course [11, 18].

Painless sporadic (silent) thyroiditis and postpartum thyroiditis are autoimmune conditions, which demonstrate similar histologic findings of lymphocytic infiltration and may be considered variants of HT. Contrasting findings include an absence of germinal centers, less extensive fibrosis, minimal Hürthle cell metaplasia, and lack of follicular atrophy [2, 11, 19]. Clinically, silent thyroiditis and postpartum thyroiditis are felt to represent the same disease process, distinguished only by the association of postpartum thyroiditis with pregnancy [2, 11]. The onset of postpartum thyroiditis occurs typically within 2 to 6 months after delivery. Both conditions initially manifest as mild hyperthyroidism caused by destruction of follicular cells and release of thyroid hormone. In some, a brief period of euthyroidism follows before development of hypothyroidism. In about 80% of cases, the disease is transient and normal thyroid function returns within a year [20].

The increased utilization of immunotherapy in oncologic diseases has led to the recognition of checkpoint inhibitor–mediated thyroiditis as another variant of autoimmune thyroiditis. The prevalence of thyroiditis with checkpoint inhibitor treatment (such as nivolumab, ipilimumab, and pembrolizumab) ranges from 6% to 20%. Thyroiditis can present with a thyrotoxic phase lasting an average of 6 weeks, followed by development of hypothyroidism [21]. Histological findings include lymphocytic inflammation and nonnecrotizing colloid granulomas [22].

4.2.2 de Quervain's Thyroiditis

Also known as subacute thyroiditis (SAT) or granulomatous thyroiditis, de Quervain's thyroiditis is a self-limited inflammatory disorder thought to be a sequela of viral infection. The incidence varies geographically but is noted to be higher in women in the fifth and sixth decades of life [23, 24]. Clinical presentation is characterized by a viral prodrome or upper respiratory illness preceding development of fever and thyroid pain or tenderness. Thyrocyte destruction results in thyrotoxicosis, which resolves over a period of several weeks. Hypothyroidism sometimes follows and resolves spontaneously over several months. Approximately 5% experience persistent hypothyroidism; recurrence of subacute thyroiditis has been reported in 2–9% [23–26].

The diagnosis of SAT is primarily clinical. In most patients, the findings of thyroid tenderness, a viral prodrome, and a self-limiting course are enough to establish the diagnosis. If the diagnosis is uncertain, an elevated erythrocyte sedimentation

rate (ESR) or C-reactive protein (CRP) may help establish the diagnosis. Antithyroid antibodies are typically absent but may be present transiently or in low levels and may predict development of future hypothyroidism [2]. Extreme tenderness of the thyroid with palpation is characteristic. During the thyrotoxic phase, thyroid-stimulating hormone (TSH) is suppressed and uptake of radioactive iodine on nuclear imaging is low; uptake may be increased during the recovery phase when TSH is elevated [24, 27]. Ultrasonographic findings include patchy, poorly defined areas of hypoechogenicity with decreased vascularity; diffuse heterogeneity may also be seen [28]. Tissue sampling is not required for diagnosis, though cytologic findings reveal noncaseating granulomatous inflammation with disrupted follicles, interstitial inflammatory infiltrate with lymphocytes and multinucleated giant cells, and interfollicular fibrosis [29].

4.2.3 Riedel's Thyroiditis

Riedel's thyroiditis (RT) is a rare form of chronic thyroiditis characterized by dense progressive fibrosis extending outside the thyroid capsule to surrounding tissues. The true incidence is not known but is estimated to be 1.06 per 100,000 based on a large population study [30]. The etiology of RT is unclear, though it has been linked to a generalized fibroinflammatory disorder based on concurrent presentation with other inflammatory conditions, including idiopathic retroperitoneal fibrosis, sclerosing cholangitis, fibrosing mediastinitis, inflammatory pseudotumor, and Tolosa-Hunt syndrome [31–34]. This constellation of findings shares overlapping features with IgG4-related systemic disease, a systemic sclerosing process characterized by infiltration of IgG-4-bearing plasma cells, leading some to suggest they are the same clinical entity [35, 36]. The IgG4 variant of HT also shares similar clinicopathologic characteristics [37–39].

The clinical presentation of RT includes firm enlargement of the thyroid, often associated with compressive symptoms, which worsen as extrathyroidal involvement progresses. Hypoparathyroidism may be a presenting symptom, resulting from extension of fibrosis to the parathyroid glands [40, 41]. Vocal cord paralysis related to involvement of the recurrent laryngeal nerve was reported in 29% in one series [32]. Thyroid function may be normal at presentation though hypothyroidism is frequent, occurring up to 80% [42]. On ultrasonographic examination, the thyroid appears heterogeneously hypoechoic with decreased vascularity; tracheal narrowing or encasement of the carotid artery or jugular vein may be seen. Computed tomography (CT) shows hypodense enlargement of the thyroid with relative lack of contrast enhancement; evidence of extrathyroidal extension can be readily appreciated, along with

carotid artery or jugular vein encasement [32, 42]. On magnetic resonance imaging (MRI), the sclerotic thyroid appears hypointense on T1- and T2-weighted images with modest enhancement following administration of gadolinium contrast [43]. Elevated levels of circulating thyroid autoantibodies (anti-Tg, anti-TPO) are commonly encountered in RT, though it is not clear whether this represents a causative element or a reaction to thyroid degeneration [42]. The clinical course of RT is often progressive but may be stabilize over time [32].

The presence of a firm, fixed mass along with clinical and radiographic evidence of extrathyroidal involvement may raise concern for malignancy. Fine-needle aspiration (FNA) biopsy is often nondiagnostic owing to a pauci-cellular sample obtained from densely fibrous tissue [32, 42, 44]. A diagnosis of Riedel's thyroiditis is confirmed by open biopsy with histopathology showing a fibroinflammatory process extending outside the thyroid. Inflammatory infiltrate without the presence of giant cells, lymphoid follicles, oncocytic cells, or granulomas differentiates this condition from other inflammatory disorders, including the fibrous variant of HT and de Quervain's thyroiditis [38, 44, 45].

4.3 Treatment

4.3.1 Hashimoto's Thyroiditis

HT is primarily a medical disease, with thyroidectomy uncommonly indicated as treatment (discussed below). Medical therapy involves levothyroxine (LT_4) administration for patients with thyroid hypofunction. Patients initially require low doses of LT_4, but with gradual loss of thyroid function, full thyroid hormone replacement with LT_4 (1.6 to 1.8 μg per kg of body weight) may ultimately be required [11]. Thyroid hormone replacement may also be effective in reducing thyroid enlargement associated with HT [46, 47]. Selenium (Se) supplementation has been studied as an adjunctive treatment to LT_4. A systematic review and meta-analysis showed reduction in TPO-Ab titers and improvement in mood-related symptoms associated with 3 months of Se supplementation [48], though benefit has not been consistently demonstrated [49]. Corticosteroid treatment may be beneficial in the IgG-4 variant of HT, as IgG-4-related disease is shown to be steroid-responsive [11, 36].

4.3.2 de Quervain's Thyroiditis

Treatment of de Quervain's thyroiditis is supportive and directed at pain relief with administration of nonsteroidal anti-inflammatory drugs (NSAIDS). Caution is advised with use of

salicylates, which may increase levels of free thyroid hormone [27, 50]. Corticosteroids may be offered for more severe cases. Dosing of prednisone is 20–40 mg daily, tapered over several weeks to avoid relapse of symptoms [27, 32]. Treatment of hyperthyroidism with antithyroid medications is ineffective, as increased thyroid hormone results from destruction of thyrocytes and release of stored thyroid hormone and not increased production; as such, beta-blockade should be used for treatment of systemic effects. LT_4 therapy is indicated for prolonged or symptomatic hypothyroidism.

4.3.3 Riedel's Thyroiditis

Thyroid isthmusectomy allows for diagnosis of RT and may provide relief of compressive symptoms, but thyroidectomy is associated with increased risk, especially in later stages where invasion may be extensive. As such, medical management is generally advocated, with treatment directed at inhibiting the fibroinflammatory process. Treatment with corticosteroids may reduce thyroid size and improve compressive symptoms. Hypothyroidism in IgG4-related disease has been shown to respond to corticosteroid therapy [36]. Tamoxifen, believed to inhibit fibroblast proliferation through stimulation of transforming growth factor (TGF)-β1, has been used with reports of success in some patients [32, 43, 51–53]. Recommended dosing of tamoxifen is 10–20 mg per day, with or without prednisone therapy [27]. Mycophenolate mofetil, an immune modulator shown to be beneficial in the treatment of fibrotic disorders, has been reported to be effective in treatment of steroid- and tamoxifen-resistant RT [31, 37], and treatment with Rituximab has also been described [54].

4.4 Surgical Indications and Outcomes

4.4.1 Hashimoto's Thyroiditis

Surgical treatment in HT is most commonly recommended for management of coexistent thyroid nodules or malignancy. Thyroidectomy as a treatment for HT alone is not frequently undertaken, but may be indicated in patients with goiters to treat local compressive symptoms or address cosmesis [55]. Several case series have shown thyroid surgery to be effective for relieving compressive symptoms such as dysphagia, dyspnea, and neck discomfort or tightness [55–58]. Heggie et al. [59] compared the resected gland weight for thyroidectomies performed to treat compressive symptoms in HT versus goiter and found lighter gland weights in the HT group, suggesting that thyroid stiffening in HT contributes to pressure symptoms, even without significant gland enlargement.

Thyroidectomy has been explored for some patients who experience systemic symptoms of HT, including fatigue and joint or muscle tenderness, despite normalization of thyroid hormone status. A study of HT patients randomized to total thyroidectomy and hormone replacement versus hormone replacement alone found improved health survey and fatigue scores in the thyroidectomy group at 18 months follow-up, with no significant changes in the medical management group. The authors hypothesize that the improvements were related to normalization of TPO-Ab levels, which declined sharply in the thyroidectomy group but decreased only modestly in the hormone replacement group [60]. This remains a controversial area as the trial was nonblinded and concerns remain regarding whether the findings were placebo-driven.

Potential benefits from thyroid surgery should be considered in the context of surgical risk. Increased risk of recurrent laryngeal nerve or parathyroid injury related to inflammatory changes and adherence of the thyroid to surrounding structures have been raised by many as a concern. A large prospective multicenter study published by Thomusch et al. [61] examined complication rates in 18,955 patients undergoing surgery for autoimmune thyroid disease or multinodular goiter (MNG) without known malignancy. Preoperative and postoperative laryngoscopy was performed for all patients. Among the 1266 patients who underwent thyroid surgery for HT, 67% received total thyroidectomy. No difference was seen in rates of transient and permanent vocal cord paralysis (VCP) between surgery for HT and surgery for MNG. However, rates of transient and permanent hypoparathyroidism were slightly increased for HT compared with MNG (15.3 vs. 12.9% for temporary, 1.1 vs. 0.9% for permanent, $p < 0.001$).

4.4.2 de Quervain's Thyroiditis

Thyroidectomy for SAT is rarely indicated, as the disease is typically self-limiting. However, for the rare cases in which there is repeated recurrence, thyroidectomy may be considered. Despite this uncommon indication, 69 cases of thyroid surgery for SAT were included in the Thomusch et al. study [61], with over half receiving total thyroidectomy. Rates of temporary and permanent VCP were not different than for MNG, though rates of temporary and permanent hypoparathyroidism were higher than for MNG, at 14% and 7%, respectively.

4.4.3 Riedel's Thyroiditis

Thyroidectomy for RT is regarded as challenging due to obliteration of normal tissue planes and may be associated with significant risk of complications. Fatourechi et al. [32] reported a

series of 21 patients with RT treated over a 30-year period at the Mayo Clinic, including 18 patients who underwent at least partial thyroid surgery (isthmusectomy, lobectomy, or subtotal thyroidectomy). Complete surgical excision was deemed impossible in all cases. Seven patients (39%) experienced surgical complications involving the recurrent laryngeal nerve or parathyroid glands. Isthmusectomy alone was recommended as treatment to relieve pressure symptoms. By contrast, 10 cases of RT were reported in the large multicenter study described above [61], with 5 receiving total thyroidectomy. Rates of temporary and permanent VCP were 6.7% and 0%, respectively, and rates of temporary and permanent hypoparathyroidism were 16.7% and 0%, respectively. It is not clear whether these disparate findings are the result of selection bias, with patients in the latter study receiving surgery at an earlier stage of disease when fibrosis is less extensive.

4.5 Association with Malignancy

A link between HT and the development of thyroid malignancy has been long surmised [1]. Patients with HT have a 67–80-fold higher risk of developing primary thyroid lymphoma (PTL) [62, 63], though overall, the rate of occurrence in this population is just 0.5% [64]. The pathogenic mechanism underlying this epidemiologic association is not clear; however, the high prevalence of thyroid autoantibodies in cases of PTL suggests autoimmune stimulation plays a role [63, 65, 66]. The most common type of lymphoma occurring in the thyroid is large diffuse B-cell lymphoma, which can present with rapid thyroid enlargement, hoarseness, and dysphagia, and must be differentiated from anaplastic thyroid carcinoma [65]. The ultrasonographic appearance of thyroid lymphoma is a solid hypoechoic mass with variable edge characteristics (well defined to poorly defined) and increased vascularity [67]. Homogenous echotexture without calcifications and absence of necrosis or cystic degeneration can help distinguish its appearance from anaplastic carcinoma [68]. Core needle biopsy has better sensitivity and accuracy than fine-needle aspiration (FNA) in the diagnosis of thyroid lymphoma [67, 69] and should be employed when PTL is suspected.

An association between HT and PTC has also been observed, though the linkage appears inconsistent and a causal relationship has not been established [1]. Whether co-occurrence of HT and PTC is simply coincidental, HT triggers the development of PTC, or HT represents an immune response to tumor remains controversial. A systematic review conducted by Jankovic et al. [70] examined the coexistence of PTC with HT and noted a statistically positive correlation in studies of thyroidectomy specimens (27.2% prevalence of PTC in specimens with HT), but no association in studies of FNA specimens (1.2% preva-

lence of PTC in FNAs of subjects with HT). Notably, thyroidectomy studies are subject to selection bias; population studies of FNA are more representative of patients with HT but are limited by absence of histologic examination [1, 70]. Despite these challenges, several hypotheses have been proposed to explain a linkage, including chronic inflammation facilitating malignant transformation and elevated TSH levels in hypothyroid patients stimulating thyroid epithelial proliferation [1, 71]. Various molecular mechanisms supporting a linkage have been explored. Larson et al. [72] examined expression of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway in thyroidectomy specimens of patients with HT and PTC and found increased expression in regions of HT and PTC compared with normal thyroid tissue. RET/PTC rearrangement has been implicated as an early oncogenic event in patients with lymphocytic thyroiditis [73, 74], and differential expression of various genes, including CD98 and p63, appears to support a linkage [75, 76]. Several studies have found that PTC coexisting with HT exhibits less aggressive clinicopathologic features and is associated with more favorable outcomes, including decreased rate of metastases, lower recurrence rates, and improved overall and disease-specific survival [77–80].

The diagnostic performance of FNA in the evaluation of thyroid nodules coexisting with HT has been examined in several studies. Overall, the positive predictive value (PPV) of FNA for malignancy is high at 97–99%, with sensitivity of 65–99% and specificity of 72–100% [81]. However, various pitfalls have been described for cytologic evaluation of nodules in the setting of HT, with risk of both false-negatives and false-positives [82, 83]. Structural and nuclear features of PTC, including a papillary or microfollicular pattern and nuclear grooves, can be present in HT without malignancy [82–84]. Furthermore, the frequent presence of Hürthle cells in HT can complicate interpretation of FNA, with aspirates rich in Hürthle cells being interpreted as "suspicious for follicular neoplasm, Hürthle cell type" (Bethesda IV category) [85]. One study found this cytologic designation had a PPV for malignancy of just 9.5% when HT was coexistent, versus 25.2% without HT, though this difference did not meet statistical significance [86]. The presence of Hürthle cells was also found to impact the diagnostic accuracy of early molecular testing platforms, with the Afirma™ gene expression classifier (GEC) disproportionately assigning "suspicious" results to samples rich with Hürthle cells [87–90]. The more recently developed Afirma™ gene sequencing classifier (GSC) addressed this problem by incorporating new classifier algorithms with improved performance for Hürthle cell samples [91, 92].

HT coexistent with PTC should inform the interpretation of ultrasonographic findings, especially as it relates to the presence of lymph nodes in the central compartment. Overall, the sensitivity of ultrasound for detecting central compartment

lymphadenopathy is limited when the thyroid is present [93]. However, atrophy of the gland, as occurs in later stages of HT, may allow for improved detection of central neck lymphadenopathy. Benign central neck nodes are frequently encountered in HT, with one study demonstrating a sensitivity of 93.4% in the diagnosis of autoimmune thyroiditis [94]. As such, when evaluating thyroid malignancy coexistent with HT, the clinician must be careful to not reflexively characterize prominent central neck nodes as metastatic disease. Indeed, it has been suggested that an explanation for the finding of decreased central neck metastases in PTC coexistent with HT is increased sampling of benign nodes brought to clinical attention as a result of HT [77].

Answers

1. (e); 2. (b); 3. (c); 4. (e); 5. (c); 6. (a); 7. (b); 8. (a); 9. (d); 10. (c); 11. (d); 12. (a)

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