IgG4-Related Fibrous Thyroiditis (Riedel’s Thyroiditis): A Case Report

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Conflict of interest: None declared

Patient: Female, 69-year-old

Final Diagnosis: Riedel thyroiditis

Symptoms: Dysphagia • goiter

Medication: —

Clinical Procedure: —

Specialty: Endocrinology and Metabolic

Objective: Rare disease

Background: Riedel’s thyroiditis is a rare form of immunoglobulin G (IgG) 4-related invasive fibrosis of the thyroid gland; given its scarce incidence, standardized therapeutic guidelines are unavailable. Although complications are unusual, obstructive symptoms produced by the stony-hard goiter may put patients’ lives at risk. The diagnosis must be biopsy-proven, and treatment consists of thyroid hormone replacement and anti-inflammatory drugs, although sometimes thyroidectomy may be required.

Case Report: A 69-year-old woman presented with a 7-month history of progressive hypothyroidism and obstructive dysphagia. On physical examination, she had a large, stony-hard goiter. A Doppler ultrasound study revealed a massive, avascular enlargement of the thyroid gland. A computed tomography scan failed to demonstrate any extrathyroidal extension of the abnormal tissue. A Tru-Cut biopsy of the thyroid was performed. Extensive replacement of thyroid follicles by prominent bands of fibrous tissue was observed, with follicular obliteration and mild focal occlusive phlebitis. A lymphoplasmacytic infiltrate was clearly identified; no oxyphilic nor giant cells were found. On immunohistochemistry, the immunoglobulin G (IgG) 4/IgG ratio in the plasma cell infiltrate was 40%; increased serum IgG4 levels were also found, supporting the diagnosis of Riedel’s thyroiditis. The patient was successfully treated with levothyroxine replacement and tamoxifen with prompt resolution of obstructive symptoms.

Conclusions: Fibrous thyroiditis should be considered in the differential diagnosis of primary hypothyroidism in a patient with a stony-hard goiter. Although steroids are often used as a therapeutic strategy for this disease, our patient had an excellent therapeutic response to tamoxifen, avoiding adverse effects associated with steroid therapy, the higher cost of monoclonal antibody therapy, and surgery-associated risks.

MeSH Keywords: Fibrosis • Goiter • Immunoglobulin G

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/928046
**Background**

Riedel's thyroiditis is an exceedingly rare disease of the thyroid, originally described in 1894 by the German surgeon Bernhard Moritz Carl Ludwig Riedel [1]. Thyroid parenchyma replacement by fibrous tissue results in progressive thyroid enlargement [1,2] and permanent destruction of thyroid epithelial tissue, leading to primary hypothyroidism [2,3]. In spite of the nonmalignant, inflammatory nature of Riedel's thyroiditis, the affected gland may lead to obstruction of vital structures in the neck, causing dysphagia and dyspnea [2,4]. Fibrous tissue may extend outside of the thyroid capsule and has been reported to destroy the parathyroid glands and cause hypoparathyroidism [3].

Riedel's thyroiditis is considered a generalized immune disorder involving B lymphocytes and immunoglobulin G (IgG) 4-secreting plasma cells. Its systemic nature is clearly manifested by its association with mediastinal and retroperitoneal fibrosis, and sclerosing cholangitis [1,5]. Fibrous thyroiditis should be considered in the differential diagnosis of stony-hard goiters, which includes the fibrous variant of Hashimoto’s disease, anaplastic carcinoma of the thyroid, lymphoma of the thyroid, and thyroid fibrosis resulting from previous radioiodine treatment [1,6]. Because Riedel's thyroiditis is so rare, management of patients with it can be challenging, given the lack of available information about this disease.

**Case Report**

We report the case of a 69-year-old woman who came to the Endocrinology Clinic with a 7-month history of progressive hypothyroidism and an enlargement at the base of her neck. The family history included primary hypothyroidism in the woman's daughter. The patient's personal history included osteoporosis and a well-controlled seizure disorder diagnosed as inactive neurocysticercosis. She did not report currently or previously smoking tobacco. She had noted progressive difficulty in swallowing solid food.

On physical examination, the patient was found to have profound hypothyroidism (thyroid-stimulating hormone 107.3 µU/mL) and a stony-hard goiter (estimated to be 5 times the normal size). Laboratory results included: 25-hydroxy D3 8 ng/µU/mL (reference range 30–50 ng/mL); serum PTH 129.9 pg/mL (reference range 31.4–90 pg/mL); calcium 10.0 mg/dL (reference range 8.4–10.2 mg/dL); phosphorus 2.61 mg/dL (reference range 2.20–4.50 mg/dL); erythrocyte sedimentation rate 34 mm/h (reference range 0–15 mm/h); antithyroglobulin antibodies >9000 IU/mL (negative <100 IU/mL); and anti-peroxidase antibodies >3000 IU/mL (negative <50 IU/mL). Serum range for immunoglobulin G (IgG) subclasses were as follows: IgG1 790 mg/dL (reference range 405-1011 mg/dL); IgG2 966 mg/dL (reference range 169–786 mg/dL); IgG3 15 mg/dL (reference range 11–85 mg/dL); and IgG4 621 mg/dL (reference range 3–201 mg/dL).

A Doppler ultrasound study of the woman's neck revealed a massive avascular thyroid enlargement (Figure 1A). We observed a considerable diffuse increase in elastographic tissue rigidity (Figure 1B), without nodules or evident extension of abnormal tissue outside of the thyroid capsule. A thoracoabdominal computed tomography (CT) scan ruled out mediastinal or retroperitoneal involvement. The thyroid gland was very large, with estimated volumes on ultrasound and CT scan of 36.3 cc and 35.14 cc, respectively.

Considering the low expected yield of fine-needle aspiration, we performed an ultrasound-guided Tru-Cut biopsy of the thyroid under local anesthesia, which provided a single tissue cylinder sample measuring 8×1 mm. On microscopic examination, extensive fibrosis replacing the thyroid follicles was observed, with follicular obliteration and mild focal occlusive phlebitis. A prominent lymphoplasmacytic infiltrate was clearly identified. No oxyphilic or giant cells were observed. Masson's trichrome staining confirmed the destruction and replacement of thyroid parenchyma with collagen-rich, keloid-like fibrous bands (Figure 2). A few hardly recognizable colloid-centered thyroid follicles were observed among the fibrous tissue.

Our tissue sample allowed for microscopic demonstration of extension of the fibrotic process to the extrathyroidal connective tissue. Thyroglobulin-positive cells could be identified among the thyroid follicular epithelium remnants (Figure 3A). On immunostaining, the IgG4/IgG ratio in the plasma cell infiltrate was 40% (Figure 3B).

The patient was successfully treated with oral levothyroxine replacement (100 µg per day) and oral tamoxifen (20 mg per day) for 1 to 2 months. On follow-up, her dysphagia and hypothyroidism both had resolved. In light of these findings, no further imaging studies were considered necessary and no surgery was planned.

**Discussion**

Riedel's thyroiditis is an extremely rare disease with a reported incidence of approximately 1 in 100,000, with a higher incidence in women (female/male ratio of 3:5:1) [1,7]. It is more common in middle-aged adults (30-50 years of age) [1,7] and should be considered in the differential diagnosis of primary hypothyroidism after excluding more common etiologies, particularly in patients in which a stony-hard goiter is evident. Although Riedel's thyroiditis is a benign, inflammatory condition, it can become an emergency due to airway obstruction.
A Doppler ultrasound study is very useful in diagnosis of the condition because it can identify the nonvascular nature of the disease, enabling exclusion of the usual hypervascular ultrasonographic pattern of Hashimoto’s thyroiditis [8]. As in the present case, elastography usually shows the very increased tissue rigidity typical of collagen deposition. Because fibrous thyroiditis is considered a systemic IgG4-related disease, it can be associated with other disease entities characterized by excessive deposits of collagen, such as retroperitoneal fibrosis, fibrosing mediastinitis, sclerosing cholangitis, lacrimal and parotid gland fibrosis (Mikulicz syndrome), orbital pseudotumor, and other entities [1]. CT or magnetic resonance imaging is required to exclude extrathyroidal extension of fibrosis to the mediastinum or to the retroperitoneal space.

**Figure 1.** Doppler ultrasound of the thyroid gland. (A) Diffuse, nonvascular enlargement of both thyroid lobules can be seen with discrete pseudonodule structures. (B) Strain elastography demonstrates a severe diffuse increase in thyroid tissue rigidity (mean 4.99, reference value 1).

**Figure 2.** 20× Masson’s Trichrome. The thyroid parenchyma is almost completely replaced by blue collagen fibers in keloid-like bands (left arrow). Residual colloid follicles are present (right arrow).
Thyroid fibrosis also can be seen in other thyroid disease entities, such as the fibrous variant of Hashimoto’s thyroiditis, in the late-stage thyroid tissue inflammation associated with previous radioiodine therapy [6], and even in patients with recurrent subacute thyroiditis [1]. In our patient, there was no history of radioiodine therapy nor any clinical features of subacute thyroiditis.

Clinical and pathological features of Riedel’s thyroiditis overlap with those of the fibrous variant of Hashimoto’s thyroiditis [9–11]. High titers of antithyroglobulin and anti-peroxidase antibodies are frequently seen in both entities. Although no definitive test exists with which we could have excluded the fibrous variant of Hashimoto’s disease in our patient, we believe that the weight of evidence favors Riedel’s thyroiditis, particularly in light of the high IgG4/IgG plasma cell infiltrate, the very high level of serum IgG4, and most of the histopathological features, as well as the microscopic demonstration of extension of fibrous tissue outside the thyroid capsule. In our case, we ruled out hypoparathyroidism as a possible complication of extrathyroidal fibrosis.

The diagnosis of Riedel’s thyroiditis should be biopsy-proven; thyroid tissue can be obtained with an ultrasound-guided Tru-Cut needle or during open surgery. Biopsy specimens should be stained with hematoxylin and eosin as well as the Masson’s trichrome technique. Normal thyroid parenchyma is replaced by abundant collagen fibers that take on the appearance of keloid bands. An inflammatory infiltrate that consists mainly of lymphocytes and plasma cells is readily apparent in Riedel’s thyroiditis [7,12].

Even though the etiology of Riedel’s thyroiditis currently remains unknown, some authors have found an increased expression of phosphoinositide 3-kinase (PI3K)/Akt in a patient with this diagnosis. PI3K/Akt is a well-known signaling mediator of fibroblast growth factor. Gain-of-function mutations in PI3K also have been associated with some thyroid cancers and with chronic autoimmune thyroiditis [13].

The low incidence of Riedel’s thyroiditis has precluded the establishment of clear-cut treatment criteria for it. In retrospective thyroid surgical specimens, Mayo Clinic reported 37 [14] and 21 [15] cases of Riedel’s thyroiditis during an interval of 64 and 32 years, respectively. Although many reports of individual cases having been published, the largest series reported included only 6 patients [2], making it impossible to standardize treatment. Decompressive surgery could be useful as a way to relieve airway obstruction. Thyroidectomy might be indicated in some patients, although the presence of fibrous tissue in the neck may increase the rate of morbidity associated with it [3]. Steroids are among the most accessible therapeutic options [2,3], although at the cost of their long-term adverse effects. The antiestrogen tamoxifen is an interesting option as well; this drug has been found to increase tumor growth factor-β, a well-known inhibitor of cell proliferation [16]. In our case, considering the patient’s advanced age, the immunosuppression associated with steroids posed a significant risk. Therefore, we decided that tamoxifen was the most suitable option in this specific scenario. Although Riedel’s thyroiditis is more common in women, no association with estrogen receptors has been demonstrated. The monoclonal antibody rituximab [17] and the immunosuppressant mycophenolate also have been used in isolated patients in whom steroids failed [2,14].

In line with observations by other authors [2], in our case, we believe that the use of tamoxifen clearly was successful, based on the clinical outcome. In light of our patient’s complete relief from symptoms and full recovery, we considered further immediate imaging studies and use of steroids, other drugs, or surgery unnecessary.
Conclusions

Riedel's thyroiditis is a very rare form of fibrous destruction of thyroid parenchyma, which leads to thyroid dysfunction and progressive airway and digestive tract obstruction. The immunologic nature of this disease is underscored by the B-cell lineage infiltrate found in the thyroid gland, as well as the involvement of an IgG4 subclass that can be demonstrated in tissue samples. Abnormal fibrotic processes may also be found in extrathyroidal tissues. The diagnosis is based on the disease's characteristic histopathological features, supported by immunostaining for IgG4 and thyroglobulin or thyroid transcription factor 1. Treatment currently recommended for Riedel's thyroiditis includes anti-inflammatory and immunosuppressant drugs, when possible. In some cases, surgery may have to be considered as a viable option. Although there is not enough published information about management of patients with Riedel's thyroiditis, taking into account an individual's unique characteristics in conjunction with suggestions in recent literature may dictate the best therapeutic course of action.

Conflicts of interest

None.

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