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Case History

An Unusual Form of Riedel's Thyroiditis: A Case Report and Review of the Literature

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We report the case of a 36-year old woman with a history of long-term fever associated with a biologic inflammatory syndrome that was not corrected by several courses of corticosteroid treatment. The only remarkable result during previous investigations was the presence of a positive Epstein-Barr virus (EBV) serology. Clinical examination revealed an heterogenous thyroid with a nodule on the right lobe. Serum thyrotropin (TSH) concentration was normal. The levels of antiperoxidase antibodies and thyrocalcitonin were normal. Ultrasound examination of the neck showed a 3-cm hypoechogenous nodule in the right lobe of the thyroid. A total thyroidectomy was performed. Histopathologic findings led to the diagnosis of Riedel's thyroiditis. We observed a dramatic improvement after surgery with absence of fever and normalization of inflammatory parameters. The role of EBV infection in the process of this unusual form of Riedel's thyroiditis is discussed.

Introduction

RIEDEL'S THYROIDITIS is a rare form of thyroiditis that can be associated with polymorphic clinical and biologic data. The diagnosis can be difficult to assess prior to surgical removal of the thyroid, and histopathologic examination of the resected thyroid is necessary for a definite diagnosis. Several contributing factors (inflammatory, autoimmune, thrombotic, or infectious) are likely to be involved in the constitution of the extensive fibrosing process within the thyroid gland, but the pathophysiology of Riedel's thyroiditis remains controversial (1).

Case Report

A 36-year-old female presented initially with a 4-month history of unexplained febrile syndrome. Continuous fever with acute episodes (39°–40°C) was associated with physical weakness and diffuse muscular pain. The initial clinical examination was normal. Chest x-ray and computed tomography (CT) scan of the chest and abdomen were normal. Biologic investigations showed the following abnormalities: increased erythrocyte sedimentation rate (ESR) (83 mm/hr) and C-reactive protein (CRP) level (120 mg/L), nonregenerative anemia (hemoglobin = 9.4 g/dL) and microcytosis (78 fL) with a normal white blood cell count (6600/mm^3), hyper-α2-globulinemia and polyclonal hyper-γ-globulinemia, no monoclonal gammapathy, positive Epstein Barr virus (EBV) serology (immunoglobulin M [IgM]), hyperplastic bone marrow (myelogram and osteo-medullar biopsy). Screening for all other infectious diseases (BK, serologies for CMV, HIV, viral hepatitis, Brucella, Coxiella, Bartonella) and immunologic investigations (antinuclear, anti-DNA antibodies, ANCA) found no abnormalities. A diagnosis of infectious mononucleosis was presumed. Treatment with glucocorticosteroids (prednisone 1 mg/kg per day) led to clinical improvement with apyrexia, but there was persistence of the biologic inflammatory syndrome (ESR 68 mm/hr). The patient was treated with glucocorticoids for short periods (on average 1-month duration) over a total of 2 years. During this period, several attempts to withdraw glucocorticosteroids resulted in reappearance of fever, and her ESR and CRP levels remained elevated (78 mm and 62 mg/L, respectively).

The woman was then referred for new evaluation. Questioning revealed a 2-year history of cervical discomfort, with no pain or compression symptoms. Palpation showed an enlarged, heterogenous, and stony thyroid, with clinical perception of a nodule in the right lobe. Biologic findings were unchanged (ESR 60 mm/hr; CRP 48 mg/L). At that time, significantly high levels of antinuclear antibodies (640 IU,

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normal range, <80 IU/mL) and antiphospholipid (41 IU; normal range, <15 IU/mL) antibodies were found. Other serologic and immunologic examinations did not yield additional information. The levels of thyrotropin (TSH; 2.24 mIU/L) and thyrocalcitonin (<2 pg/mL) were normal. The level of antithyroperoxidase (anti-TPO) antibodies was not significantly elevated (33 U/mL; normal range, <60 U/mL). Ultrasound examination of the neck confirmed the clinical findings and showed a 3-cm hypoechogenic nodule in the lower part of the right lobe of the thyroid. In addition, a few 1-cm lateral neck lymphadenopathies were detected.

Total thyroidectomy was performed, followed by histopathologic examination. During surgery, the surgeon found major inflammatory alterations of the thyroid gland that was adhesive to adjacent structures including the neck vessels, trachea, esophagus, parathyroid glands, and recurrent laryngeal nerve, making dissection very difficult. Extemporaneous examination of the right lobe of the thyroid showed lymphocytic thyroiditis in part of the thyroid tissue and fibro-inflammatory lesions with lymphoid follicles in paratracheal tissue. Histologic examination of the excised thyroid tissue revealed polymorphic infiltrates including eosinophilic polynuclear white blood cells, plasmocytes and lymphocytes, some of them organized as lymphoid follicles. A few epitheliod granulomas containing rare giant cells were also found (Figs. 1 and 2). Few vascular thromboses were observed. Immunocytochemical study with markers for B- and T-lymphocytes enabled us to rule out the diagnosis of MALT (mucosae-associated lymphoid tissue) lymphoma. Mutilating fibrosis invaded the tissues surrounding the thyroid parenchyma and infiltrated the thyroid tissue, which contained only a few remaining thyroid follicles. All these histopathologic findings led to the diagnosis of Riedel's thyroiditis.

Postoperatively, the patient was treated with levothyroxine, 75 μg per day (Lévothyrox*, Lab. Lipha, Lyon, France).

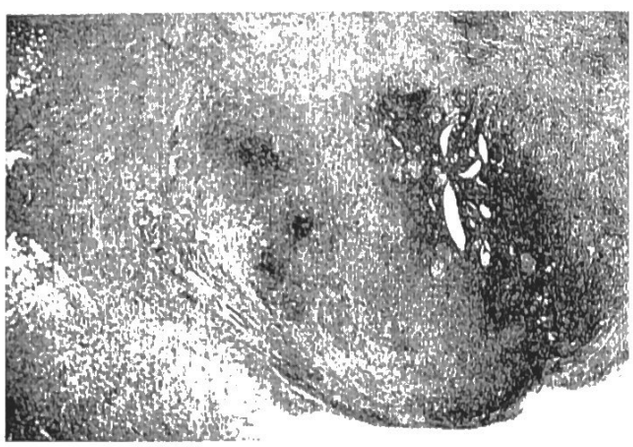

FIG. 1. The normal thyroid architecture is totally destroyed by a fibro-inflammatory process. On the right side of the cut, one finds a remain of disorganized thyroid tissue. The rest of the gland is replaced by fibrosis. The limit of the inflammatory process crosses the thyroid capsule. The soft perithyroid tissues are invaded by fibrosis (some groups of fatty cells are seen on the left side of the cut). In the center, the presence of epithelioid granulomas containing giant cells can be observed.

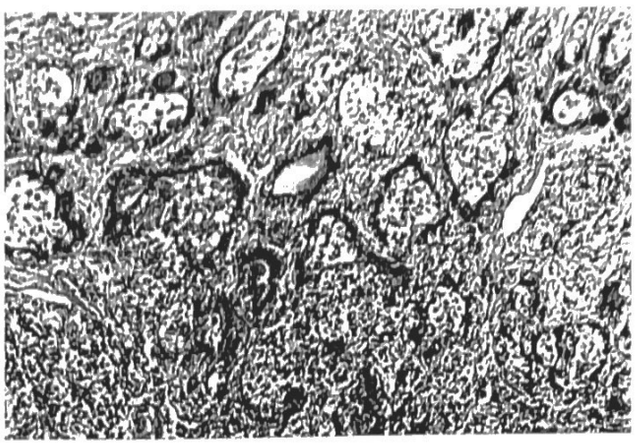

FIG. 2. Thyroid residual islets disorganized by inflammation and fibrosis.

Her condition improved dramatically, and her fever resolved. At 1-year follow-up, her laboratory results were normal: TSH, 0.58 mIU/L; ESR, 15 mm/hr; CRP, <5 mg/L.

Discussion

Riedel's thyroiditis is a rare thyroid disease. It is found in 0.05% of all thyroidectomies (2). Its prevalence is greater in women (gender ratio 3:1), and the average age for diagnosis is 50 years. Patients with Riedel's thyroiditis frequently demonstrate thyroid dystrophic enlargement, with mild heterogeneity generally without clinical evidence of thyroid nodules. On clinical examination, the entire thyroid gland has a hard or stony consistency. Symptoms of regional compression might progressively appear. Few cases of hypoparathyroidism (3), as well as of bitonal voice caused by recurrent laryngeal nerve paralysis (4,5) have been reported. In such patients, Riedel's thyroiditis is often difficult to differenciate from anaplastic thyroid carcinoma before thyroid surgery. However, the clinical presentation of Riedel's thyroiditis is polymorphic and might comprise cases with a total lack of thyroid-related symptoms. In our patient with fever and cervical discomfort, histopathologic examination led to the diagnosis of Riedel's thyroiditis, based on the following criteria previously reported in the literature: extensive mutilating fibrosis crossing the thyroid capsule and invading the adjacent tissues, disorganization of the normal thyroid architecture and near-total disappearance of thyroid follicles, which are replaced by an inflammatory infiltration, predominant fibrosis with a very small number of cells. Histopathological examination ruled out the diagnosis of thyroid carcinoma and lymphoma.

The pathophysiology of Riedel's thyroiditis remains controversial. First, the role of autoimmunity in the process leading to Riedel's thyroiditis has been widely discussed. A link between Hashimoto's autoimmune thyroiditis and Riedel's thyroiditis has been suggested. It has been shown that significant levels of thyroid antibodies (anti-TPO and anti-Tg antibodies) are present in 45% of sera from patients with Riedel's thyroiditis (6,7). On the other hand, Riedel's thyroiditis might be a rare outcome of lymphocytic thyroiditis. Moreover, several patients with typical Graves' disease with hyperthyroidism, ophthalmopathy, and positive anti-TSH

receptor antibodies, may present with extensive thyroid fibrosis and the final histopathologic diagnosis being Riedel's thyroiditis (8). Such previous reports on Riedel's thyroiditis do not argue to the conclusion that an autoimmune process of lymphocytic thyroiditis is the sole mechanism leading to Riedel's thyroiditis. To date, the actual role of the autoimmune process in the pathophysiology of Riedel's thyroiditis remains unknown. In our patient, the lack of anti-TPO antibodies does not provide evidence for the hypothesis of a preexisting Hashimoto's thyroiditis. In addition, it should be noted that histopathologic examination found only scarce areas of lymphocytic thyroiditis in comparison with the large areas of extensive fibrosis without any cellular infiltrate. Although a few adhesions can be found in the fibrous variant of Hashimoto's thyroiditis, grossly the capsule is clearly demarcated from surrounding structures. The fibrous changes are confined to the thyroid. By contrast, in Riedel's disease, the thyroid is a stony mass fixed to surrounding structures. This extension of the fibrosis beyond the thyroid gland is characteristic of Riedel's disease. In the fibrous variant of Hashimoto's thyroiditis, the gland lobulation is preserved and noted at low power magnification. This feature serves in distinguishing this lesion from carcinoma or from Riedel's disease, where the gland is destroyed and replaced by fibrous tissue.

Thyroid lymphoma and Riedel's thyroiditis seem also to be very similar with regard to several histopathologic findings, but they are likely to be unrelated to each other with respect to the pathophysiologic processes involved. In our patient, histopathologic examination excluded the diagnosis of thyroid lymphoma: the small number of cells and the almost total lack of B lymphocytes labeling with immunofluorescent techniques argued against the diagnosis of thyroid lymphoma (including that of MALT lymphoma).

Second, in cases of Riedel's thyroiditis associated with multilocular fibrosis (retroperitoneal, mediastinal, hepatic and, even orbital) (9), thyroid involvement may appear as one of the localizations of a general inflammatory disease (10). In such systemic forms, occurrence of venous thrombosis has been reported. The possible role of tissue ischaemia resulting from such vascular occlusions remains to be determined (11). The possible role of antiphospholipid antibodies has also been discussed. In our patient, the presence of antiphospholipid antibodies was not considered to be of pathophysiological significance, because no clinical antiphospholipid syndrome was observed, and small number of vascular thrombosis were seen histopathologically in the thyroid tissue.

Third, the role of infection in the process leading to Riedel's thyroiditis has been considered. Moderate inflammatory syndrome (slightly increased ESR and CRP) is observed in 65% of patient with Riedel thyroiditis (5). During the initial phase of the disease, our patient experienced an important inflammatory syndrome which was more severe that is usually observed in patients with Riedel's thyroiditis. This clinical and biochemical inflammatory syndrome suggest the possibility of recurrent subacute thyroiditis occurring before the development of the extensive fibrosis which led to the diagnosis of Riedel's thyroiditis. In two previous reports (12,13), recurrent subacute non autoimmune thyroiditis resulted in extensive fibrosis and Riedel's thyroiditis. In our patient, the time course of the process is very similar to that observed in those patients. The extensive thyroid fibrosis might be related to the numerous recurrences of the local inflammatory process involved in subacute thyroiditis. However, most cases of subacute thyroiditis, even if recurrent, do not result in Riedel's thyroiditis.

To our knowledge, no previous reports of an association between Riedel's thyroiditis and EBV infection has been reported. Nevertheless, EBV infection can be linked to several processes possibly involved in the pathophysiology of Riedel's thyroiditis, namely, lymphocytic thyroiditis (14), thyroid lymphoma (15), or subacute thyroiditis (16). With regard to the possible link between EBV infection and lymphocytic thyroiditis, there is serologic evidence that EBV infection is found more frequently in patients with autoimmune thyroiditis than in the general population. EBV could activate T4 lymphocytes and increase the autoimmune response. The role of EBV in triggering a process of subacute thyroiditis has already been reported, and it is well documented that subacute thyroiditis can follow infectious mononucleosis. Therefore, the possible initial phenomenon could be the EBV infection, triggering a recurrent process of inflammatory subacute thyroiditis being followed itself by the constitution of Riedel's thyroiditis. For the reported patient, such succession of pathologic events should be considered, because it could explain initial features of the disease and for the disappearance of the inflammatory syndrome after total thyroidectomy.

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