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CASE REPORT

A case of Riedel's thyroiditis with pleural and pericardial effusions

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Abstract Riedel's thyroiditis (RT) is a rare type of chronic thyroiditis of unproven etiology and definite treatment. It can be associated with retroperitoneal, mediastinal, orbital, and hepatic fibrosis. Symptoms arise mainly due to compression of neighboring structures. Surgery is usually required for a definite diagnosis and decompression to relieve the symptoms. Glucocorticoids and tamoxifen are commonly used agents for the pharmacotherapy. We hereby describe the development of pleural and pericardial effusions during the clinical course of an RT case. A 39-year-old woman suffering from neck compression symptoms was admitted to the hospital. After a decompression isthmectomy, RT was diagnosed. She responded well to glucocorticoid therapy after surgery. However, symptoms reoccurred shortly after glucocorticoid withdrawal and the disease process extended to the mediastinum. Tamoxifen was started and the neck and mediastinal mass regressed and her symptoms disappeared considerably for more than 6 months. However, she was re-admitted with severe dyspnea and chest pain. Further investigation revealed an exudative pleural and pericardial effusion and mediastinal enlargement. A thorough evaluation of the patient's effusions did not disclose any specific etiological insult. The patient was symptom-free with a considerable reduction of the soft tissue mass and no effusions, and treated successfully with colchicine, azathioprine, and glucocorticoids. To the best of our knowledge, this is the first case reported in the literature as an RT presenting with pleuropericardial effusions.

Keywords Riedel's thyroiditis · Riedel's struma · Invasive fibrous thyroiditis · Pleural effusion · Pericardial effusion · Tamoxifen · Raloxifen · Glucocorticoid · Colchicine

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Introduction

Riedel's thyroiditis (RT), also known as invasive fibrous thyroiditis or Riedel's struma, is a rare type of chronic thyroiditis of uncertain etiology. It is characterized by fibrosis of the thyroid gland and adjacent structures [1, 2]. The disease was initially described by Riedel in 1896 [3]. Occurring mainly in middle-aged women, it can be associated with fibrosis in retroperitoneum, mediastinum, orbita, liver (i.e., sclerosing cholangitis). Symptoms arise chiefly due to compression of neighboring structures including trachea, esophagus, carotid and jugular vessels, and recurrent laryngeal nerves. The hard consistency of the thyroid gland and invasion of the local structures may suggest malignancy and usually creates a diagnostic

dilemma. Hypothyroidism and hypoparathyroidism may occur during follow-up and might be enhanced by surgery [1, 2].

Diagnosis and treatment are usually problematic. Surgery is generally required for a definite diagnosis and for decompression to relieve the symptoms [1, 4]. Glucocorticoids and tamoxifen are the two most commonly used agents which have been reported to be beneficial in several case reports [4, 5].

In this report, we describe the development of pleural and pericardial effusions in the clinical course of a case with RT treated with surgery followed by medical therapy including glucocorticoids, colchicine, and azathioprine.

Case report

A 39-year-old woman suffering from a fast growing neck mass and neck pain was admitted to the hospital. She was on levothyroxine (L-T4) replacement therapy with the diagnosis Hashimoto's thyroiditis (HT) for 8 years. She had pallor, a grade 2 goiter with quite hard in consistency and palpable nodules of about 2.5 cm on both lobes, and her neck veins were prominent in physical exam.

Thyroid function tests showed the following; serum thyroid stimulating hormone (sTSH): 0.42 mIU/ml (0.30–4.50), free T4: 23.0 pmol/l (10–23), free T3: 5.28 pmol/l (2.8–7), anti-thyroglobulin antibody: 150 IU/ml (10–115), anti-microsomal antibody: 17 IU/ml (5–34). Erythrocyte sedimentation rate was 77 mm/h. Thyroid ultrasonography (USG) revealed diffuse hyperplasia with extremely heterogeneous parenchyma, multiple 2–3 cm-sized nodules with irregular macrocalcifications. Computerized tomography (CT) imaging of thorax demonstrated an enlarged thyroid gland surrounding the main vascular structures and compressing the trachea, and continuing through the superior mediastinum down to the arcus aorta (Fig. 1a, b). A fine needle aspiration biopsy (FNAB) was not diagnostic.

She was operated for her large compressive goiter and undiagnostic FNAB results. During surgery, it was noted that the thyroid tissue was stony hard in consistency, adherent to the surrounding structures, and its anatomy was completely destroyed. A decompression thyroidectomy, which included only isthmectomy, could be performed. Histopathology revealed proliferation of connective tissue elements and inflammatory cell infiltration of the thyroid gland and surrounding soft tissues of the neck predominantly by lymphocytes and plasma cells, partly destructing the gland, and RT was diagnosed (Fig. 2).

Glucocorticoid therapy was started and continued for about 2 months; she responded well initially. However, symptoms reoccurred in a few months after withdrawal, and tamoxifen 20 mg/day was launched. Her symptoms disappeared considerably with tamoxifen and follow-up CT images showed the prominent regression of neck and mediastinal soft tissue masses for more than 6 months.

About 6 months later, she presented with severe dyspnea and chest pain prominent especially on exertion while she was on tamoxifen.

The chest X-ray followed by CT of thorax revealed that she had a considerable right-sided pleural and pericardial effusions (Fig. 3). CT also revealed a soft tissue density in the neck and mediastinum surrounding vascular structures, trachea, and reaching subcardinal region. There were also several lymphadenopathies in the neck.

The echocardiography detected high amount of fluid around the heart's chambers that created systolic and diastolic collapse. This was consistent with pericardial tamponade. Therapeutic and diagnostic thoracentesis and pericardiocentesis together with biopsies were performed and 1500 cc fluid was withdrawn from each space.

A thorough evaluation of the fluids included direct microscopy, specific stains, i.e., tuberculous bacilli, biochemistry, cultivation, cytology, and did not disclose any specific etiological insult. The fluid was exudative and the only microscopic finding was a mixed inflammatory cell infiltrate. The pleural biopsy showed a chronic pleuritic

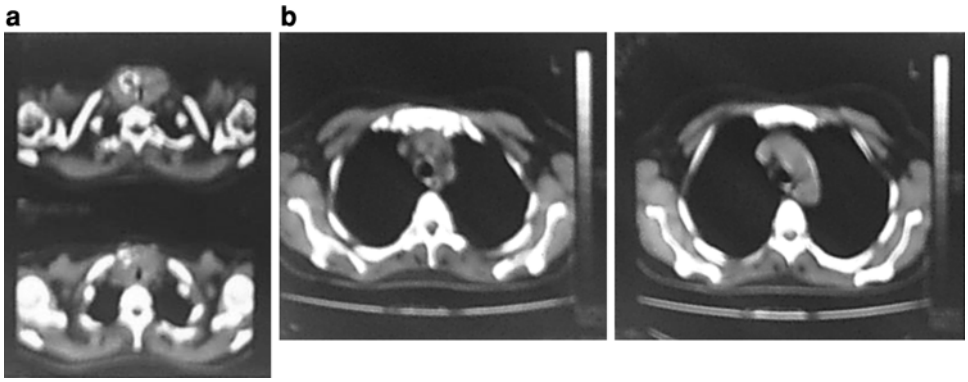

Fig. 1 CT images of the case at first presentation; **a** neck region, showing the diffuse enlargement of the thyroid gland tightly constricting the trachea, **b** thorax (mediastinal window), demonstrating mediastinal extension of the process down to aortic arc

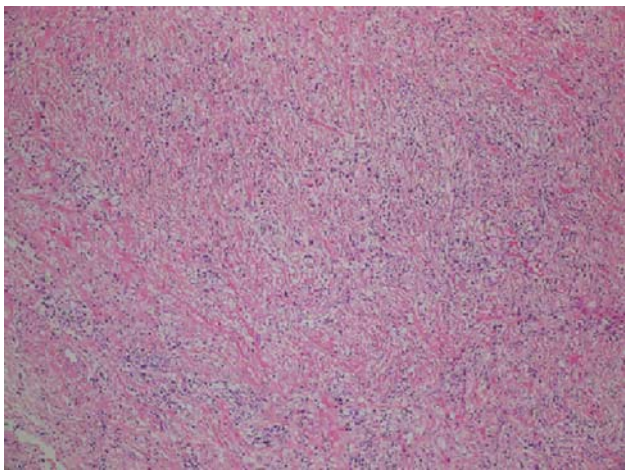

Fig. 2 Fibrous tissue effacing normal thyroid tissue, hematoxylen and eosin

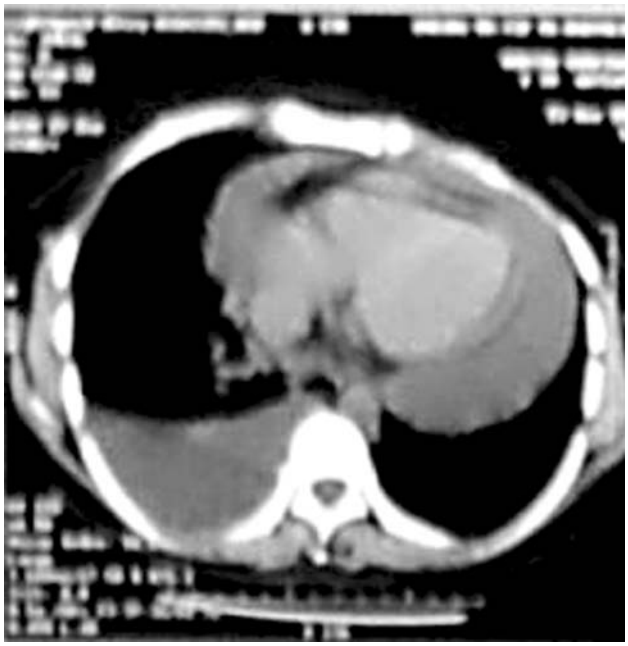

Fig. 3 Thorax CT of the patient showing the massive right-sided pleural effusion and the huge pericardial effusion

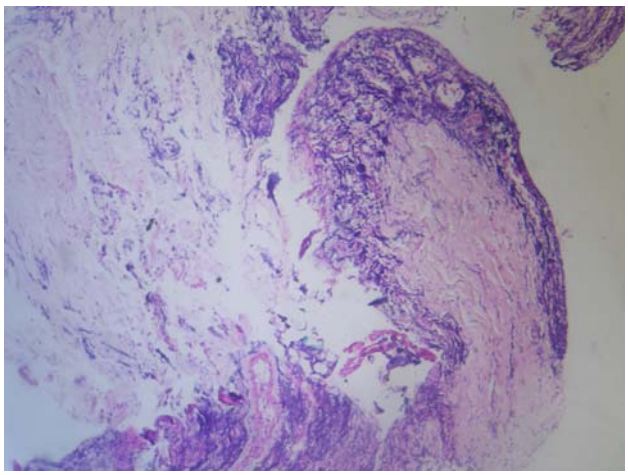

Fig. 4 Prominent, predominantly lymphocytic infiltration in pleura, hematoxylen and eosin

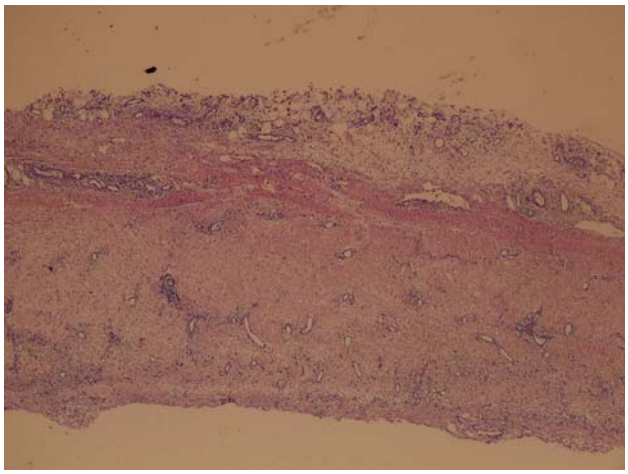

Fig. 5 Thickened pericardium with vascular proliferation and inflammation, hematoxylen and eosin

reaction with predominantly lymphocytic infiltration (Fig. 4) and fibrosis. The pericardial biopsy including immunohistochemical evaluation yielded active chronic fibrinous pericarditis with prominent mesothelial cell proliferation (Fig. 5).

Other aspects of the etiological evaluation of the effusions included investigation in the blood of hepatitis B surface antigen, hepatitis C virus antibody, human immunodeficiency virus antibodies, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and toxoplasma IgM, and they were all negative. Quantitative immunoglobulins (IgG, A, M) and complement levels (C3, C4) were within normal ranges. Rheumatoid factor, anti-nuclear antibody, anti-centromere antibody, anti-mitochondrial antibody, anti-smooth muscle antibody, anti-cardiolipin antibodies, anti-nuclear cytoplasmic antibody were all negative. She was euthyroid under L-T4 replacement therapy. An abdominal USG and CT showed no abnormality, i.e., no retroperitoneal fibrosis.

Tamoxifen was stopped and raloxifen 60 mg b.i.d. was started together with ibuprofen 600 mg t.i.d. The patient was followed with monthly serial pleural and pericardial taps especially due to pericardial recollections for four more months. Adding colchicine tb 0.5 mg b.i.d. did not change the course effectively. Otherwise, repeat thorax CT revealed re-regression of the mediastinal masses.

Glucocorticoid therapy was restarted as methylprednisolone 1 mg/kg/day. The patient was doing better with this, effusions decreased; however, she could not tolerate

tapering the dose down. Colchicine dose was increased to 0.5 mg q.i.d. Later on, azathioprine 50 mg/day was added to therapy and increased to 125 mg/day, which enabled glucocorticoid tapering in 6 months. A trial of withdrawal of glucocorticoid therapy resulted in recollection of effusions. The patient is now on L-thyroxine 150 mcg/day, azathioprine 125 mg/day, colchicine 2 mg/day, methylprednisolone 4 mg/day, and the last CT seen shows almost cure.

Discussion

RT is a rare type of thyroiditis [6]. Women are more commonly affected than men and the disease occurs usually between 30 and 50 years of age [7]. The classical clinical presentation is a stony hard, painless neck mass often extending into surrounding structures. Frequent compressive symptoms include dyspnea, stridor, dysphagia, and hoarseness [8].

There are no specific laboratory findings for RT. Sedimentation rate is usually moderately elevated. Patients are mostly euthyroid, hypothyroidism is a less frequent finding; hyperthyroidism is very rare [9, 10]. Anti-thyroid antibodies are usually positive at a wide range of frequency [9]. For an exact diagnosis; a neoplasm should be excluded histopathologically, and a fibroinflammatory process involving the entire or part of the gland and extension into nearby structures should be described grossly and histologically. Also, a granulomatous reaction should be ruled out [7, 9]. The diagnosis is not achieved most of the time by FNAB and usually a surgical biopsy is needed. However, there are a few reports declaring the diagnostic use of FNAB in RT [8, 11].

There is a continuing debate on whether RT is primarily a fibrotic disease or an autoimmune one. Strong histological evidence of cellular infiltration of lymphocytes, plasma cells, neutrophils, eosinophils, and sometimes phlebitis besides fibrosis exists supporting both views [9]. The reported reasonable therapeutic responses to glucocorticoids and accumulating data about successful response to tamoxifen and raloxifen further complicate the matter. Tamoxifen is thought to have anti-fibrotic properties through stimulation of TGF-β production [8, 12, 13]. The opinion that RT is a local expression of a systemic fibrotic disease, i.e., idiopathic multifocal fibrosclerosis is widely accepted [14]. Many RT cases with extracervical manifestations such as retroperitoneal and mediastinal fibrosis, sclerosing cholangitis, orbital pseudotumor have been reported [4, 10, 12, 15, 16].

Another complex issue is the relation between RT and HT. Although the fibrous variant of HT is among the differential diagnosis of RT as there are clear-cut differences between them, there are a few reports suggesting that RT is a variant of HT or it may follow HT; these may also coexist [8, 10, 16–18].

Overall prognosis is generally favorable, but might not be so, and rarely, spontaneous regression of the disease is reported [19].

The clinical course of our case was that of a classical RT patient; the initial diagnosis was HT and she was under L-T4 replacement therapy for about 8 years. The initial presentation leading to surgery (Fig. 1a, b), the gross appearance in surgery and decompression of the trachea was typical for RT. She was well shortly after glucocorticoid therapy as stated in most of the literature data [2, 4, 8, 14, 15, 19], but her symptoms reoccurred soon after the withdrawal. Relapse after withdrawal of glucocorticoid therapy is likely in these patients [15, 20].

The long-term good responses to the patient's following medication and tamoxifen are worth mentioning. She was symptom-free for about 6 months and the serial CT images revealed that her neck and mediastinal masses decreased in size by the time. Similar course after tamoxifen has been reported in a limited number of cases [5, 13, 20]. Raloxifen, a selective estrogen receptor modulator, has also been reported to be effective in a few RT cases [21]. Thus, we tried to switch to raloxifen when the patient relapsed under tamoxifen, but it was not helpful.

A thorough investigation of the patient's pleural and pericardial effusions did not disclose any specific etiological insult, and their coexistence suggests a common inflammatory reaction. To the best of our knowledge, this is the first case of RT in the English literature, relapsing with third space effusions in the thorax (Fig. 3). We have encountered one case report in German reporting a pleural effusion in an RT case [22].

The differential diagnosis of exudative pleural and pericardial effusions includes infections, malignancy, pulmonary embolization, gastrointestinal diseases, collagen vascular diseases, uremia, sarcoidosis, Meigs' syndrome, drugs, radiation therapy, trauma, pericardial disease, chylothorax [23, 24]. Almost normal levels of fluid glucose (>60 mg/dl) and amylase (data not elevated) were determined; no pneumonic and malignant infiltrations or images reflecting pulmonary embolus were detected in the CT scan. Cytological examination of the fluids and the tissue biopsies were negative for malignancy, and fluid cultivation and tuberculosis investigation including PCR were also negative. These findings effectively ruled out a bacterial infection, malignancy, pulmonary embolism, and gastrointestinal disease. Viral serology excluded the few known viruses which may cause this clinical picture. These results with autoimmune and other immunological markers within normal limits eliminated any collagen vascular disease. The patient's history did not reveal any possible drugs or trauma as an etiological factor.

The patient's pleural biopsy disclosed fibrotic and hyalinized pleural tissue infiltrated with diffuse mononuclear cells (Fig. 4). This finding together with a mixed population of lymphocytes and polymorphonuclear leucocytes determined in differential cell count of the pleural fluid strongly suggested that the effusions are the manifestations of the primary disease process, i.e., RT.

The course of the pericardial pathology was initially that of an acute effusive pericarditis [23]. However, it turned out to become a chronic effusive pericarditis with frequent massive collections. Pericardial fluid cytology demonstrated abundant lymphocytes and mesothelial cells and the biopsy resulted as active chronic fibrinous pericarditis with prominent mesothelial cell proliferation (Fig. 5). These may reflect a comparable expression of RT.

The only argument against our thesis could be an acute idiopathic pericarditis. This is mostly a diagnosis of exclusion, but is a frequent cause of pericardial inflammation. It is usually associated with pleural effusions, sometimes may become a chronic effusive pericarditis [24–26]. But tamponade is highly unusual in this form of pericarditis. The most common causes of tamponade are malignant conditions and uremia, which we had excluded.

Non-steroidal anti-inflammatory drugs, colchicine, and/or glucocorticoids usually respond well in acute idiopathic pericarditis. Colchicine might also avoid recurrences. Glucocorticoids are usually reserved for resistant or drug-intolerant patients [24–26]. Considering this possibility, we used these drugs in order but the response was not satisfactory, as the patient could not tolerate tapering steroid therapy and needed further drainage of the recollections.

The therapeutic approach for patients resistant to these drugs (NSAID, colchicine) or requiring high doses of glucocorticoids in the long run would be a trial of other immunosuppressive agents such as azathioprine. Another option would be switching to surgical methods, namely pericardiectomy or construction of a pericardiopleural window for drug-resistant cases. Development of constrictive findings in the pericardium, which is a rare complication of recurrent effusions, will probably require a pericardiectomy, if it ever occurs [25, 26]. For the moment, the patient is doing well with azathioprine, with a lowest dose glucocorticoid and other anti-inflammatory agents.

To conclude, we have reported a case of RT developing pleuropericardial effusions in the clinical course, for the first time in the literature to the best of our knowledge. This is most likely to be another reflection of the systemic inflammatory nature of the disease.

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