Presentación de caso

Riedel´s thyroiditis: treatment with raloxifene

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Summary
We report a case of Riedel's thyroiditis (RT) and its response to raloxifene and glucocorticoids. A hypothyroid woman, under T4 treatment, developed spontaneously a 10 x 8 cm painful mass in the anterior lateral neck, infiltrating adjacent muscle and soft tissues. Surgical attempt was unsuccessful. Biopsy revealed RT. Despite 12 mg/day prednisone, CT showed tumor growth extending to the left side. Tamoxifen 40 mg/day was added. After 6 months there was a reduction in tumor size and significant amelioration of symptoms. Since gynecological ultrasound disclosed endometrial hyperplasia, tamoxifen was switched to raloxifene 240 mg/day. During the following 6 months, the patient remained asymptomatic and CT showed a great reduction (72%) in the mass, allowing decrease steroid dose. However, she stopped raloxifene on her own. One month later appeared a 2-cm painful nodule in the right lobe. With restoration of raloxifene the pain ameliorated but the nodule remained unchanged. Raloxifene could act as a modulator of the transforming growth factor, and therefore an inhibitor of fibroblastic proliferation.This is the first report on the use of raloxifene as therapy for RT. We propose its use given the excellent results in our case and to prevent the side effects of tamoxifen.
Key words: *Riedel's thyroiditis, raloxifene, fibrosis, TGF*

Resumen
TIROIDITIS DE RIEDEL: TRATAMIENTO CON RALOXIFENO
Presentamos un caso de Tiroiditis de Riedel y su respuesta al raloxifeno y corticoides. Una mujer hipotiroidea que, bajo tratamiento con T4, desarrolló espontáneamente una tumoración dolorosa en la región anterolateral derecha del cuello, que infiltraba músculo y tejidos blandos adyacentes. La excéresis quirúrgica fue imposible. La biopsia reveló Tiroiditis de Riedel. La masa se extendió hacia el lado izquierdo a pesar de 12 mg/d de prednisona. Tamoxifeno 40 mg/dia fue adicionado. Seis meses después disminuyó el tamaño tumoral y mejoraron los síntomas. Una ecografía ginecológica reveló hiperplasia endometrial y tamoxifeno fue cambiado por raloxifeno 240 mg/día. Durante los 6 meses siguientes, ella permaneció asintomática y la TAC mostró franca reducción (72%) del tumor, permitiendo reducir la dosis de corticoides. Ella suspendió el raloxifeno por cuenta propia. Un mes después apareció un nódulo de 2 cm doloroso en el lóbulo derecho. Al reinstaurar el raloxifeno el dolor mejoró sin modificación del nódulo. Raloxifeno podría actuar como un modulador del factor de crecimiento transformante beta (TGF), e inhibir la proliferación fibroblástica. Este es el primer reporte del uso del raloxifeno en Tiroiditis de Riedel. Nosotros proponemos su uso dado el excelente resultado obtenido y para prevenir los efectos adversos del tamoxifeno.
Palabras claves: *Tiroiditis de Riedel, raloxifeno, fibrosis, TGF*

Introduction

Riedel's thyroiditis (RT) is a rare chronic inflammatory disease of the thyroid gland, characterized by an invasive dense fibrosis that tends to progress and destroy the gland. It may involve adjacent structures in the neck causing symptoms such as airway obstruction, dysphagia, recurrent laryngeal nerve paralysis, hypothyroidism and hypoparathyroidism. The etiology is unknown, and the disorder is frequently associated with manifestations of extracervical fibrosis, which may occur in the mediastinum, the retroperitoneum, the biliary tract, parathyroid, lacrimal and parotid glands. The characteristic histological pattern is an infiltrate of eosinophils and mononuclear cells, such as activated T lym-

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phocytes, macrophages, and aggregates of B lymphocytes, between dense fibrous bands[1-4]. Thyroid antibodies have been found in 45 per cent of patients[5]. Diagnosis is established by surgical excision and pathological examination. Surgical treatment is usually unsatisfactory and glucocorticoids have been used with variable results. Previous reports have shown that tamoxifen is effective for managing abnormal proliferation of connective tissue, including RT[6-9].

We present a patient with RT who received combined treatment with steroids and tamoxifen showing amelioration of symptoms. To prevent side effects of tamoxifen, as endometrial hyperplasia, we switched to raloxifene with better clinical and radiological response. This is the first report of successful treatment of RT with raloxifene.

Case report

A 57-year-old woman with a 7-year history of subclinical hypothyroidism due to autoimmune thyroiditis, while being treated with tyroxine, developed in January 1999 a painful swelling in the right anterior region of the neck. The tumor progressed quickly to a large, stony hard mass involving the thyroid gland and extending beyond the sternocleidomastoid muscle and surrounding tissues, measuring 10 x 8 cm. A computed tomographic (CT) scan revealed an isodense mass located at the right antero-inferior aspect of the neck with displacement of the tracheal lumen.

Despite initial improvement with ibuprofen and prednisone 12 mg/day, 6 months later she experienced dysphagia to solid meals. A new CT scan showed enlargement of the tumor (176%) that expanded to the left side of the neck (Fig. 1).

A surgical attempt to remove the mass was unsuccessful. Biopsy disclosed the typical histological pattern of Riedel's thyroiditis (Fig. 2). An abdominal CT scan showed no evidence of retroperitoneal fibrosis.

After a normal gynecologic control, Tamoxifen (20 mg twice daily) was added to the treatment in November 1999. After 2 months, there was a reduction in mass size (47.8%) and a dramatic amelioration of symptoms. Alternative withdrawal of steroids (10 days) and tamoxifen (20 days) led to reappearance of pain and dysphagia, and a slight increase in tumor size, so that combined therapy was required. By 6 months after initiation of tamoxifen, the volume of the cervical mass continued to decrease (59.6%) and it was less firm, allowing lateral tracheal movement. At that time she started with decreasing doses of prednisone.

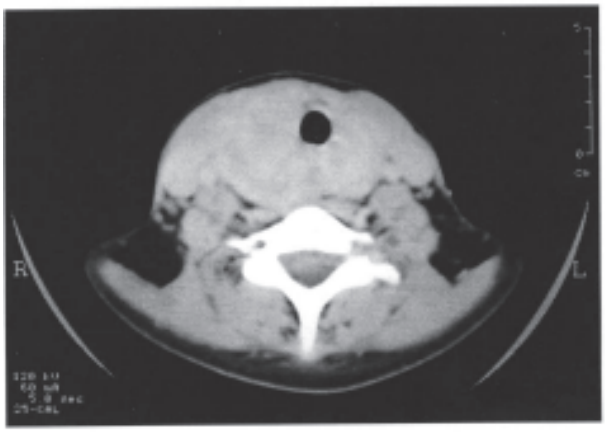

Figure 1. Computed tomographic (CT) scan of neck after 6 months of corticoid treatment, showing a large isodense mass that surrounds and displaces the trachea, expanding to both sides.

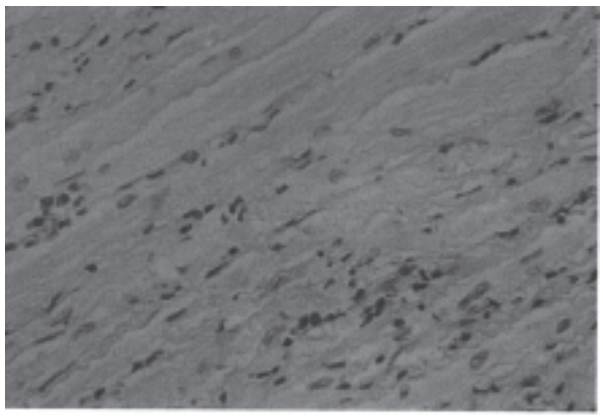

Figure 2. Histological pattern showing fragments of skeletal muscle with disrupted fibers due to dense fibrous proliferation and chronic inflammatory infiltrate consisting of lymphocytes, plasma cells and eosinophilic granulocytes. Fibers showed cytoplasmic eosinophilia and focal multinucleation. There was lymphoid infiltration without perivascular germinal centers. No evidence of malignancy, lymphoma or the presence of thyroid follicular cells was observed.

In October 2000, a gynecological ultrasound showed endometrial hyperplasia, so that tamoxifen was switched to raloxifene 120 mg/day, while keeping the patient on prednisone 4 mg/day. Since slight cervical discomfort reappeared,

raloxifene dose was raised to 240 mg/day and she became asymptomatic.

In January 2001, a new CT scan showed a great shrinkage in tumor volume (72.4%) from baseline (Fig. 3). Physical examination at that time revealed a thyroid gland of normal size, slightly irregular in the right lobe.

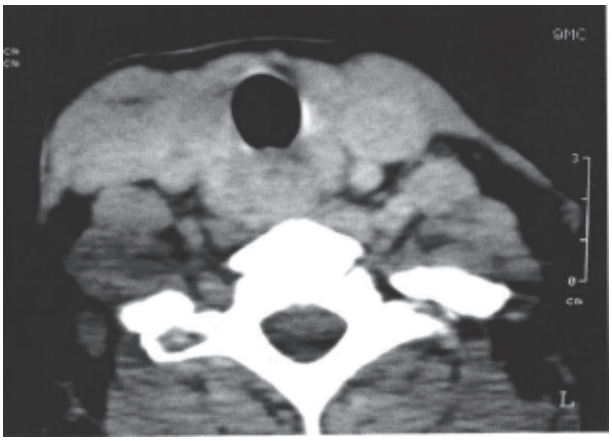

Figure 3. CT scan of neck. Note great shrinkage in tumor size and increase in tracheal diameter.

In February 2002, the patient discontinued raloxifene on her own, and within a month returned to consultation with a painful tumor of 2 cm in the right upper region of the neck. A CT scan showed that the tumor was part of the thyroid gland. Fine needle aspiration disclosed a lack of follicular cells, without evidence of malignancy. On resuming treatment, the pain was less intense, but tumor size remained undiminished.

Currently, after 4 years on glucocorticoids and 28 months on raloxifene, she achieved a dramatic reduction in lesion mass, attaining an almost palpably normal thyroid gland, although the small tumor in the upper right lobe remained stable for the last year (Fig. 4).

Discussion

Riedel's thyroiditis may be seen in isolation or as a part of a fibrotic multisystem disorder, that may involve various organs.

The thyroid gland is replaced by a progressive inflammatory fibrotic process extending into adjacent structures[10]. The fibrosis typically continues beyond the thyroid capsule, invading in some cases most of the neighboring neck tissues. The inflammatory infiltrate is a mixed population of mononuclear cells, as activated T and B lymphocytes, and macrophages. There may be associated phlebitis and thrombosis. Eosinophil infiltration and extracellular major basic protein deposition have been documented in surgical biopsy specimens from 16 patients with RT[11]. Eosinophils have been found to express genes for various cytokines including transforming growth factor (TGF)[12], a multifunctional protein believed to play a role in the pathogenesis of chronic inflammation and fibrosis. These features in RT and other associated fibrosclerotic conditions[13], but not in other forms of thyroiditis, suggest the participation of eosinophils and their products in propagating the fibrogenesis seen in RT. It is not unlikely that the inflammatory and destructive process in RT is directed against thyroid connective tissue rather than thyroid epithelial cells and represents an extension of a cervical fibrotic process into the thyroid[11].

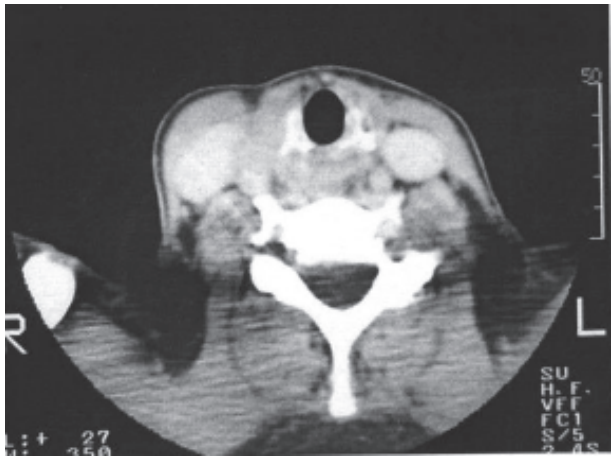

Figure 4. Contrast-enhanced CT scan of neck after 11 months of tamoxifen followed by 28 months of raloxifene showing a small right mass that partially surrounds the carotid artery and impinges upon the right jugular vein.

On occasion, coexistence of Hashimoto's and Riedel's thyroiditis in the same patient has been demonstrated, and for many years it was debated whether both entities represent different stages of the same disease or whether they are unrelated conditions. Aggressive fibrosis with extension beyond the thyroid into adjacent tissues contrasts with the diffuse, though intracapsular fibrosis of Hashimoto's thyroiditis. Although an unknown immunological etiology is

postulated for both diseases, most current studies question the possibility of progression from a highly fibrosing form of Hashimoto's thyroiditis to a RT[14-16].

Circulating thyroid antibodies have been reported in over half of patients[17]. One explanation for the existence of these antibodies is that they are generated by antigens released by damaged thyroid cells, subsequent to the extension of an initial injury in the thyroid connective tissue.

Another possibility is the simultaneous occurrence of Hashimoto's and Riedel's thyroiditis.

However, the development of both diseases in a patient is probably coincidental.

Surgical treatment is generally ineffective given the extensive invasion of neck structures.

Glucocorticoids have been used in almost all cases[18-21]. Variable doses (15-100 mg/day)

have been promptly effective in ameliorating symptoms. However, some patients relapsed after treatment was withdrawn, whether in the same organ or at another site[4, 22, 23]. A few patients with prolonged symptomatic disease failed to respond to corticosteroid therapy, suggesting that glucocorticoids may be mainly effective in early stages of disease.

Alternatively, other drugs such as cyclophosphamide have been used[24]. The response to immunosuppressive therapy supports the belief that an autoimmune mechanism plays a major role in the pathogenesis of RT.

There are several reports of successful treatment with tamoxifen, a selective estrogen receptor modulator (SERM), in fibrotic processes, including RT[6-9]. The mechanism of action of tamoxifen in these fibrosclerotic entities is unclear. Favorable response to tamoxifen in fibrotic disease seems unrelated to its action on the estrogen receptor (ER), because fibrotic masses seen in retroperitoneal and mediastinal fibrosis are estrogen receptor negative[8]. Instead, a probable effect as modulator of TGF is postulated. *In vivo* studies of fibroblastic lesions suggest that tamoxifen decreases fibroblast function and downregulates TGF, a growth factor known to promote extracellular matrix production and fibrosis[25, 26]. In disagreement, some reports based on human fetal fibroblast and breast cancer cell studies, have claimed that tamoxifen effectiveness is attributable to the stimulation of TGF production[6, 8, 9, 27, 28].

Although not fully understood, these findings suggest that the action of tamoxifen in the treatment of fibrotic disorders could be through TGF modulation and resultant inhibition of fibroblast production[6]. In breast cancer, the clinical efficacy of tamoxifen has also been ascribed to additional non-ER mediated apoptotic mechanisms. These include modulation of various signaling proteins, such as protein kinase C, calmodulin, TGF and proto-oncogene cmyc.

These mechanisms should not be ruled out as possible molecular actions of tamoxifen in fibrotic disease[29].

We decided start the treatment with tamoxifen 20 mg twice daily following the good results in a group of patients with RT[6]. The autors reported disease regresion ranging from 50 to 100% in 4 patients with RT who had failed previous attempts to treatment. They do not report significant side effects on the course of more than 3 years of therapy. In our patient, tamoxifen was interrupted because she presented endometrial hyperplasia. We switched to another SERM, raloxifene, a newly developed molecule devoid of this side effect. The response to raloxifene was successful and after almost 3 years of raloxifene combined with reduced doses of steroids, she showed a 70% reduction in thyroid mass. No studies on the effect of raloxifene on pathological fibrosis are available in the literature. Another SERM, toremifene, has demonstrated reduced *in vitro* TGF1 autocrine and paracrine secretion by fibroma fibroblasts[30]. Studies in osteoclasts from ovariectomized rats have shown that raloxifene modulates TGF3 with inhibition of osteoclast differentiation and activity[31, 32]. In mesangial cells *in vitro*, SERMs suppress type I and type IV collagen synthesis[33]. These effects of raloxifene seem to be estrogen receptor mediated. Moreover, raloxifene, as tamoxifen, decreased the *in vitro* rate of the cell cycle and proved proapoptotic in breast cancer cells[34].

It may therefore be speculated that raloxifene is a modulator of TGF and of its fibrogenic properties. However, so far it is unknown whether these effects are estrogen receptor mediated,

so that further studies are required to elucidate the true mechanism of raloxifene in fibrotic process including RT.

This is the first case of successful treatment of RT with raloxifene. Despite that a multicenter clinical trial would be interesting to support its use, we propose the use of raloxifene as an alternative treatment of RT, given the excellent results obtained and to prevent the side effects of tamoxifen in susceptible patients.

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