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Clinical and Pathological Features of Riedel's Thyroiditis

Lin Lu¹, Feng Gu^{1*}, Wei-xin Dai¹, Wu-yi Li², Jie Chen³,
Yu Xiao³, and Zheng-pei Zeng¹

¹Department of Endocrinology, Key Laboratory of Endocrine and Metabolic Diseases of Ministry of Health, ²Department of Otorhinolaryngology,

³Department of Pathology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China

Key words: Riedel's thyroiditis; chronic fibrous thyroiditis; Hashimoto's thyroiditis; differential diagnosis; pathological features

Objective To evaluate the clinical and pathological features of Riedel's thyroiditis (RT), and current diagnostic and treatment methods for that disease.

Methods Five RT cases identified by surgery and pathological examinations at Peking Union Medical College Hospital from 1985 to 2009 were analyzed and compared with the cases reported in the literature in terms of clinical and pathological features. Immunohistochemical staining of kappa and lambda light chains was carried out for RT tissues from all the five patients.

Results All the five cases were females, aged 45-55 years. Elevation of serum thyroid autoantibodies was found in only one patient, who had longer disease duration than the others. Pathological examination revealed invasive fibrosclerosis of the thyroid follicles, thyroid capsule, and the surrounding tissues. In RT tissues, the number of cells containing lambda chains was a little higher than those containing kappa chains.

Conclusions RT is a rare disease which might be more common in middle-aged females than in other populations. Pathological features include the destruction of thyroid follicle, extension into surrounding tissues by inflammatory cells and fibrous tissues. Immunohistochemical staining of kappa and lambda chains could help diagnose RT.

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RIEDEL'S thyroiditis (RT), also called chronic fibrous thyroiditis or woody thyroiditis, was first described by Bernhard Riedel in 1896, characterized by extension of fibrous tissue and destruction of normal thyroid tissue. RT typically presents with

solid enlargement of the thyroid gland (described as stone-hard consistency), and is often tightly adhered to surrounding tissues, causing dyspnea, dysphagia, repetitive recurrent laryngeal nerve paralysis, and hypothyroidism.¹ The etiology of this disease is still elusive, and it is often difficult to differentiate RT from undifferentiated thyroid carcinoma, lymphoma, or fibrous variant of Hashimoto's thyroiditis (HT) in physical examination.²⁻⁴ In addition, this disease has rarely been reported, with one of the largest relevant studies

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*Corresponding author Tel: 86-10-65295070, E-mail: gufeng1025@yahoo.com.cn

having found only 37 RT cases in 57 000 thyroidectomies reviewed.⁵ Women are four times more likely to be affected than men, and RT most commonly occurs in population between 30 and 50 years of age.⁶ In this study, we reviewed five RT cases and the relevant literature to identify the clinical and pathological features of this rare disease.

PATIENTS AND METHODS

Patients' data collection

We retrospectively search the term "chronic fibrous thyroiditis", "Riedel's thyroiditis", or "woody thyroiditis" in the database of Peking Union Medical College Hospital which was introduced in 1985. From the data between 1985 and 2009, five cases of RT were identified based on the findings from surgery and pathological examinations in the hospital. The clinical and pathological features of the five cases were compared with those reported in literature.

Immunohistochemical staining

It has been suggested that immunohistochemical profiles of RT has unique features,^{7,8} which is helpful in distinguishing RT from other thyroiditis. For instance, the ratio of kappa to lambda light chain in fibrous variant of HT is similar to that in normal circulation (2 : 1), while in RT tissue the proportion of lambda-containing cells is markedly higher. Therefore, the tissues from the 5 cases were processed by immunohistochemical staining of kappa and lambda light chains. The experiments were performed using the labeled streptavidin-biotin-peroxidase complex method with DAB as chromogen. Four- μ m-thick sections of each formalin-fixed, paraffin-embedded tissue block was deparaffinized by dimethylbenzene, and then incubated in 3% H₂O₂ ethanol to block endogenous peroxidase activity. After washing in phosphate buffered saline (PBS), the sections were incubated with the primary antibody to kappa chain (1 : 200, Dako, Denmark) or lambda chain (1 : 200, Dako) for 30 minutes at room temperature. It was followed by incubation with goat anti-rabbit serum for 30 minutes at room temperature. The sections were counterstained with hematoxylin. As a control for the immunostaining, PBS was used instead of the primary antibody. Three samples were examined for each tissue of all the cases.

RESULTS

Clinical features

The identified five patients were all middle-aged (45-55 years) females with enlarged thyroid glands (grade II-III) and a disease course ranging from 0.5 to 30 months. The

cases were numbered in sequence of the date of their hospitalization. Serious neck pain accompanying tracheal compression occurred in two patients (cases 2 and 3), and recurrent laryngeal nerve paralysis and dysphagia were evident in one patient (case 3). Notably, case 3 exhibited hypothyroidism prior to surgery and received oral thyroxin.

Serum levels of antithyroid antibodies were normal in four patients (cases 1, 2, 4, and 5) while elevated in case 3. In the two patients (cases 1 and 3) who underwent thyroid iodine uptake examinations, the uptake rate was found decreased. In the three patients (cases 1, 3, and 4) who received thyroid Tc99 scanning, single or multiple cold nodules were detected.

Partial thyroidectomy was carried out in all the 5 patients to identify the diagnosis or to relieve compressive symptoms. One patient (case 3) was found hypothyroid whereas the other four were euthyroid before surgery. Only one patient (case 3) was detected with moderately elevated antithyroglobulin (TGA) and antimicrosomal antibodies (TMA). No fibrous sclerosis was observed beyond the thyroid in any of the 5 patients. In all the five patients, we found that leucocytes in peripheral circulation were at normal levels and erythrocyte sedimentation rate was mildly elevated.

The general information and results of examinations are listed in Table 1. Pathological findings identified the diagnosis of RT in all the 5 cases.

Pathological features

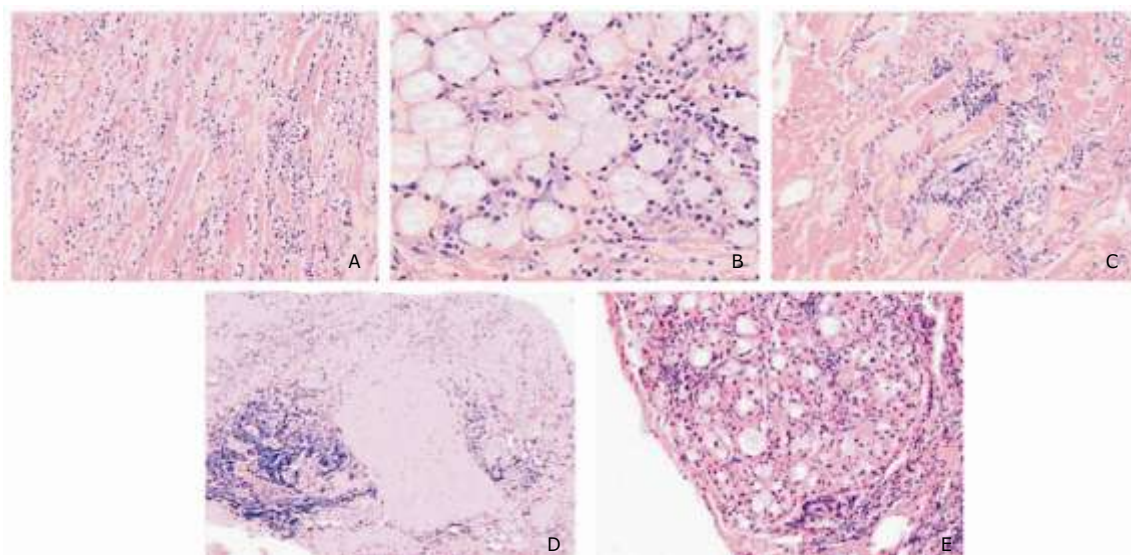
Microscopic evidence of RT included destruction of thyroid follicles, hyperplasia of fibrous connective tissue, and infiltration of lymphocytes. It was also found that inflammatory cells and fibrous tissue extended into surrounding fatty tissue, skeletal muscle, and nervous tissue, resulting in occlusive vasculitis (Figs. 1A-D). For comparison, the most common pathological features of HT, as shown in Figure 1E, include small/atrophic thyroid follicles, dense or absent colloid tissue, and lymphoplasmacytic infiltration, with well-developed germinal centers in nodules and atrophic follicles, and variable degrees of interlobular fibrosis. In addition, mononuclear cells aggregated in the perivascular spaces in the HT tissue. As the clinical symptoms were more prominent in case 3, we compared her pathological features with the other 4 patients. More occlusive vasculitis and more organizing vasculitis were found in the RT tissue of case 3, indicating the particularity of her pathological features and severity of her condition.

The result of immunohistochemical staining showed that an average of 16.4% cells contained kappa chains and

Table 1. Clinical features of the five Riedel's thyroiditis cases

Clinical data	Case 1	Case 2	Case 3	Case 4	Case 5
General features					
Sex	Female	Female	Female	Female	Female
Age (yr)	45	50	48	55	47
Course of disease (mons)	3	2	30	0.5	12
Symptoms					
Neck pain	None	Serious	Serious	None	None
Tracheal compression	None	Trachea displaced to the right	Trachea displaced to the right	None	None
Recurrent laryngeal nerve paralysis	None	None	Yes	None	None
Dysphagia	None	None	Yes	None	None
Hypocalcemia-induced tetany	None	None	None	None	None
Physical signs					
Grade of goiter	II	II	III	II	II
Thyroid quality	Fleshy	Hard	Hard	Fleshy	Fleshy
Adhesion	Mild	High	High	Mild	Mild
Laboratory examinations					
White blood cell	Normal	Normal	Normal	Normal	Normal
ESR (mm/h)	27	30	36	28	32
Preoperative thyroid function	Euthyroid	Euthyroid	Hypothyroidism	Euthyroid	Euthyroid
Postoperative thyroid function	Euthyroid	Hypothyroidism	Hypothyroidism	Euthyroid	Euthyroid
TGAb and TMAb levels	Normal	Normal	Moderately increased	Normal	Normal
Thyroid ultrasound	Multiple nodules	Single nodule	Diffuse inflammatory changes	Single nodule	Multiple nodules
Thyroid iodine uptake	Decreased	ND	Decreased	ND	ND
Thyroid Tc99 scanning	Single cold nodule	ND	Multiple cold nodules	Single cold nodule	ND
Treatment	Partial thyroidectomy	Partial thyroidectomy	Partial thyroidectomy+ prednisone	Partial thyroidectomy	Partial thyroidectomy
Fibrous lesion beyond the thyroid	No	No	Soft tissue surrounding the thyroid	No	No

ESR: erythrocyte sedimentation rate; TGAb: antithyroglobulin antibodies; TMAb: antimicrosomal antibodies; ND: not done.

**Figure 1.** Microscopic pictures of Riedel's thyroiditis (A-D) and Hashimoto's thyroiditis (E). HE staining

- A. Abundant fibrous tissue and rare normal tissue in Riedel's thyroiditis; $\times 100$
- B. Inflammatory cells extending to fatty tissue surrounding the thyroid gland; $\times 200$
- C. Inflammatory cells extending to striated muscle surrounding the thyroid gland; $\times 100$
- D. Inflammatory cells extending to nervous tissue surrounding the thyroid gland; $\times 40$
- E. Integral capsule and acidophilic staining in the thyroid gland with Hashimoto's thyroiditis. $\times 200$

30.8% cells contained lambda chains in RT tissues, the latter proportion moderately increased (Fig. 2).

Treatment and follow-up

All the five patients received partial thyroidectomy. The neck pain in two patients (cases 2 and 3) was alleviated immediately after surgery. Case 2 developed hypothyroidism after surgery while the preoperative hypothyroidism in case 3 persisted after surgery. Moreover, neck pain recurred in case 3 and several nodules were found 2 months after surgery. These symptoms were obviously mitigated after prednisone treatment (30 mg/d) for 2 weeks with a follow-up period of 36 months. Up to December, 2009, no malignant thyroid lesions were observed in the follow-up period of the 5 cases.

DISCUSSION

RT is a rare type of thyroid disease with an estimated incidence of 0.06%, the etiology of which has not been clarified yet. It has been suggested that an autoimmune mechanism is involved in the etiology of RT.⁹ It was shown in a quantitative immunohistochemical study that the cells containing lambda chains outnumbered kappa chain-containing cells (71% vs. 29%), and that the number of IgG-containing cells was comparable to IgA-containing cells (53% vs. 47%) in tissues of RT.¹⁰ The similar result in kappa and lambda chains was observed in our study, though showing only slight difference (30.8% vs. 16.4%). It was also reported that the total counts of heavy and light chains per field were much higher in HT than those in RT, with a ratio of 6 : 1 for the heavy chains combined and 5 : 1 for the light chains combined.¹¹ The differences between HT and RT in the proportions of various immunoglobulin-containing cell types raise the possibility that an autoimmune mechanism, different from that seen in the former thyroiditis, may be relevant to the etiology of RT.

As RT is sometimes associated with mediastinal and retroperitoneal fibrosis as well as and sclerosing cholangitis,

it is now believed that RT is probably a local manifestation of idiopathic multifocal fibrosclerosis.^{12,13} Although no multifocal fibrosclerosis were found beyond the thyroid in our group of patients, further follow-up is still needed to clarify the existence or absence of other fibrosis foci.

A previous report identified a patient series with a mean age of 47.8 years and a female preponderance of 83%,⁷ similar as the age and sex structure of the patient group in our study. The course of RT may range from months to years, and the patients typically present with painless thyroid mass.¹⁴ Two of our patients (cases 2 and 3) had neck pain and local tenderness, but no fever on physical examination. The neck pain was relieved immediately after partial thyroidectomy, indicating that RT, not subacute thyroiditis, accounted for that symptom in those two patients.

Schwaegerle et al⁷ reviewed 178 previously reported cases, of which 64% presented with euthyroidism, 32% with hypothyroidism, and 4% with hyperthyroidism, similar with the proportion in the present study. In addition, the serum levels of TGAb and TMAb in RT patients were reported to be either normal or slightly elevated,¹⁵ the same as we observed in the present study. The high percentage of euthyroidism as well as the normal levels of TGAb and TMAb in RT form a contrast with HT. Concurrent HT and RT were reported for several times in the literature.^{16,17} Pathological features of this rare coincidence demonstrated extensive replacement of the thyroid parenchyma with dense keloidal fibrosis, intermixed well-developed lymphoid follicles, scattered lymphocytes and plasma cells. The fibrotic process extended into the perithyroidal soft tissues and skeletal muscle with complete obliteration of the thyroid capsule. Based on those previous observations, case 3 in this study could not be considered as concurrent RT and fibrous variant of HT, as intact or well-developed follicles were not seen in diffuse fibrosis.

RT in the early stage was difficult to differentiate from other chronic thyroiditis; on the other hand, RT in the late stage may develop compressive symptoms such as

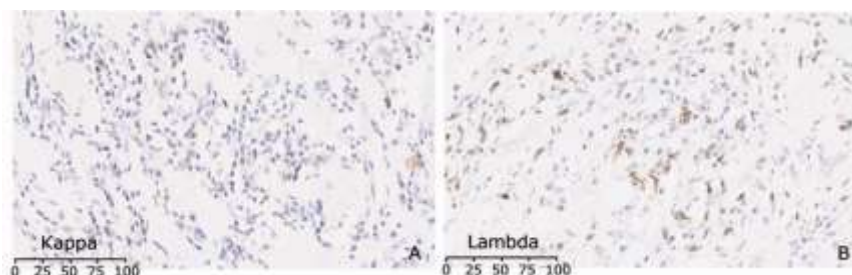


Figure 2. Immunostaining of kappa (A) and lambda chains (B) in Riedel's thyroiditis. DAB $\times 400$
The number of lambda-containing cells exceeds that of cells containing kappa chains.

dyspnea, dysphagia, and vocal cord paralysis due to extension of inflammatory cells into surrounding tissues and adhesion of the thyroid gland to adjacent tissues, imposing difficulty on clinical differentiation from malignancy.¹⁸ Of the five patients in this study, only one patient (case 3) was distinguished based on her typical symptoms after long disease duration (30 months). The other 4 patients with shorter disease duration did not have such typical manifestations. Before surgery, none of the five cases in this study were diagnosed as RT solely based on the clinical manifestations. Because fine needle aspiration was not widely applied in our hospital until 2003, the diagnosis of RT in the present study was confirmed by pathological findings after surgery. The well accepted and established pathological criteria for RT include: (1) gross description of a visible fibro-inflammatory process involving all or a portion of the thyroid gland; (2) gross and/or histological evidence of extension into adjacent structures; (3) absence of granulomatous reaction; and (4) absence of neoplasm.⁶ In addition, histological examination of RT often reveals invasion of collagen-rich fibrous bands into shrinking or disappearing damaged follicles. Apart from the existence of shrinking or atrophic follicles, another histological indicator distinguishing RT from the fibrous variant form of HT is the extension of fibrosis into structures beyond thyroid. For confirmation, pathological examination is necessary to identify the property of thyroid nodules.

In treating RT, high dose of glucocorticoids was recommended as the first-line therapy for patients with confirmed diagnosis.¹⁹ Our findings also proved the effectiveness of prednisone. Tamoxifen has also been proved effective for some patients resistant to glucocorticoids or prohibited to use them, possibly through stimulating production of transforming growth factor-beta and inhibiting fibroblastic proliferation.^{20,21} However, in the case of suspected carcinoma and serious compressive symptoms, surgical treatment should also be considered to both confirm diagnosis and relieve symptoms.²²

In conclusion, RT is a rare chronic thyroiditis, which manifests euthyroidism, and normal levels of TGAb and TMAb in most cases. Differentiation from other chronic thyroiditis in the early stage and thyroid malignancies in the end stage is difficult if given only clinical signs and laboratory results. Hence we suggest that for middle-aged female patients presenting with a hard thyroid mass, especially those with accompanying compressive neck symptoms, pathological examinations of the thyroid and advanced examinations with emphasis on extensive fibrosis may help in diagnosis. When confirmed, glucocorticoid could be prescribed as the first-line medication, or replaced

by tamoxifen in the case of resistance or contraindication. For serious compression or suspected carcinoma, surgical procedure could be provided. Careful long-term follow-up is necessary to prevent recurrence, subsequent complications, and thyroid malignancies.

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