

Riedel's Thyroiditis and Multifocal Fibrosclerosis Are Part of the IgG4-Related Systemic Disease Spectrum

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Objective. Riedel's thyroiditis is a chronic fibrosing disorder of unknown etiology often associated with "multifocal fibrosclerosis." IgG4-related systemic disease is characterized by IgG4+ plasma cell infiltration and fibrosis throughout many organs. We hypothesized that Riedel's thyroiditis is part of the IgG4-related systemic disease spectrum.

Methods. We searched our institution's pathology database using the terms "Riedel's," "struma," "thyroid," and "fibrosis," and identified 3 cases of Riedel's thyroiditis. Riedel's thyroiditis was diagnosed if there was a fibroinflammatory process involving all or a portion of the thyroid gland, with evidence of extension of the process into surrounding tissues. Immunohistochemical stains for IgG4 and IgG were performed. The histopathologic and immunohistochemical features of each involved organ were evaluated. The clinical features of one patient with multiple organ system disease were described.

Results. All 3 thyroidectomy samples stained positively for IgG4-bearing plasma cells. One patient had extensive extrathyroidal involvement diagnostic of IgG4-related systemic disease, including cholangitis, pseudotumors of both the lung and lacrimal gland, and a lymph node contiguous to the thyroid that stained intensely for IgG4+ plasma cells. The histologic features of all organs involved were consistent with IgG4-related systemic disease. Patient 3 had 10 IgG4+ plasma cells per high-power field initially, but rebiopsy 2 years later demonstrated no IgG4+ plasma cells. That patient's second biopsy, characterized by fibrosis and minimal residual inflammation, further solidifies the link between IgG4-bearing plasma cells in tissue and the histologic evolution to Riedel's thyroiditis.

Conclusion. Riedel's thyroiditis is part of the IgG4-related systemic disease spectrum. In many cases, multifocal fibrosclerosis and IgG4-related systemic disease are probably the same entity.

INTRODUCTION

More than 100 years ago, Riedel described 3 cases of a peculiarly hard, infiltrative lesion of the thyroid gland (1–3). On the basis of physical examinations and intraoperative findings, all 3 patients were believed to have thyroid malignancies. However, histologic examination revealed a chronic inflammatory process in each case. Riedel commented on "collections of round cells interspersed among normal thyroid tissue, whereby the latter

(becomes). . .destroyed" (4). This unusual and poorly understood thyroid disorder became known as Riedel's thyroiditis.

Riedel's thyroiditis is associated with global or partial fibrosis of the thyroid gland, destruction of the thyroid follicle architecture, obliterative phlebitis, and a mixed infiltrate of lymphocytes, eosinophils, and plasma cells (5–8). The fibrosis that characterizes this disease typically extends beyond the thyroid capsule and into surrounding tissues, particularly the trachea and the infrahyoid ("strap") muscles (9,10). The diagnostic evaluation for Riedel's thyroiditis usually involves imaging studies and needle biopsies, but the diagnosis is generally confirmed at thyroidectomy. The indication for thyroidectomy is usually to exclude malignancy or to alleviate compressive symptoms (10).

In a review of 57,000 thyroidectomies performed at the Mayo Clinic between 1920 and 1984, 37 cases of Riedel's thyroiditis were identified, with an estimated incidence of 1.06 cases per 100,000 outpatients (11). A Cleveland Clinic review described 6 cases identified over a 40-year period

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Submitted for publication December 15, 2009; accepted in revised form March 31, 2010.

Table 1. Demographic, clinical, and pathologic features of patients with Riedel's thyroiditis

Patient	Age, years	Sex	Indication for thyroidectomy	Fibrosis intraoperatively	Pathology	Thyroid IgG4/IgG
1	39	Female	Compressive symptoms	Yes	Fibroinflammatory infiltrate with extrathyroidal extension	0.8
2	43	Female	Rule out thyroid carcinoma	Yes	Fibroinflammatory infiltrate with extrathyroidal extension and phlebitis	0.56
3	37	Female	Compressive symptoms	Yes	Left thyroid: fibroinflammatory infiltrate with extrathyroidal extension Right thyroid: dense hyalinizing type of fibrosis with extrathyroidal extension	0.20

(8). The rarity of Riedel's thyroiditis has made treatment studies difficult, but many patients respond to glucocorticoids (12). Tamoxifen has also been employed in some patients in an attempt to treat the fibrosis characteristic of Riedel's thyroiditis and to minimize glucocorticoid toxicity (13,14).

Riedel's thyroiditis has long been linked to a generalized fibroinflammatory process termed "multifocal fibrosclerosis" (MFS) (15,16). One-third of patients with Riedel's thyroiditis develop fibrosing disorders in other organs over a 10-year period (11,17). Riedel's thyroiditis frequently occurs in close temporal association with sclerosing cholangitis; retroperitoneal or mediastinal fibrosis; or fibrosis of the lung, parotid, or lacrimal glands (18,19). Beyond case reports and case series, however, little has been written about MFS; its basis has remained obscure.

IgG4-related systemic disease is an emerging multiple organ system condition that is defined by the infiltration of IgG4+ plasma cells and fibrosis (20–22). IgG4-related systemic disease is known to affect the pancreas, biliary tree, salivary glands, the periorbital tissues and ocular adnexa, kidneys, lungs, lymph nodes, meninges, aorta, breast, colon, and prostate gland (23). The histologic findings in IgG4-related systemic disease include a lymphoplasmacytic infiltrate, storiform fibrosis, an abundance of eosinophils, and obliterative phlebitis (22). Up to 95% of patients have elevated serum IgG4 concentrations, which can be more than 25 times the upper limit of normal (24,25). However, estimates as low as 54% have also been reported for serum IgG4 concentrations (26). Recent reports suggest an association between MFS and IgG4-related systemic disease (27,28).

Riedel's thyroiditis and IgG4-related systemic disease share the histopathologic features of fibrosis, lymphoplasmacytic infiltration, tissue eosinophilia, and obliterative phlebitis (22). Moreover, IgG4-related systemic disease and MFS have similar patterns of multiple organ involvement: both have a tendency to involve the biliary system, retroperitoneum, salivary and lacrimal glands, and retrobulbar space. The aim of this study was to determine whether Riedel's thyroiditis and MFS are part of the IgG4-related systemic disease spectrum.

MATERIALS AND METHODS

We searched the pathology department database for the terms "Riedel," "struma," "thyroid," and "fibrosis," and

identified 3 cases of Riedel's thyroiditis diagnosed between 1991 and 2009. Criteria for the diagnosis of Riedel's thyroiditis were modified from those of Papi and LiVolsi (10). Riedel's thyroiditis was diagnosed histopathologically if the following features were present: a fibroinflammatory process involving all or a portion of the thyroid gland and evidence of extension of the process into surrounding tissues. Occlusive phlebitis was not required for the diagnosis of Riedel's thyroiditis. In addition, giant cells, granulomas, extensive Hürthle cell change, and features of malignancy were absent. Patients with the diagnoses of Hashimoto thyroiditis or fibrosing Hashimoto thyroiditis were excluded from this study. The medical records of all 3 patients were reviewed to confirm that the clinical findings were compatible with Riedel's thyroiditis and to identify any extrathyroidal organ involvement consistent with IgG4-related systemic disease. The original hematoxylin and eosin–stained slides were reviewed and stained immunohistochemically using antibodies to IgG4 (Zymed; 1:200 dilution) and IgG (Dako; 1:3,000 dilution).

The degree of plasma cell infiltration and IgG4 staining within biopsy samples was quantified. For each case, the number of plasma cells staining for IgG4 was assessed in 3 non-overlapping high-power fields (hpf; magnification $\times 400$). The 3 fields with the highest degree of IgG4 reactivity were selected for quantitation. The number of IgG4+ plasma cells was then divided by the total number of IgG-bearing plasma cells in these fields.

The diagnosis of IgG4-related systemic disease was based on the following criteria: 1) histopathologic features consisting of a lymphoplasmacytic infiltrate and fibrosis with or without obliterative phlebitis within involved organs (20,29–31), and 2) either an IgG4/IgG plasma cell ratio of $>50\%$ within the thyroid or the parenchyma of other affected organs, or more than 10 IgG4-bearing plasma cells per hpf (32,33).

RESULTS

The demographic, pathologic, and immunohistochemical features of the 3 patients are shown in Table 1. The clinical history of patient 1 is detailed below, followed by brief clinical histories of patients 2 and 3.

Patient 1. A 39-year-old woman with hypothyroidism and anxiety presented with an enlarging goiter. A thyroid

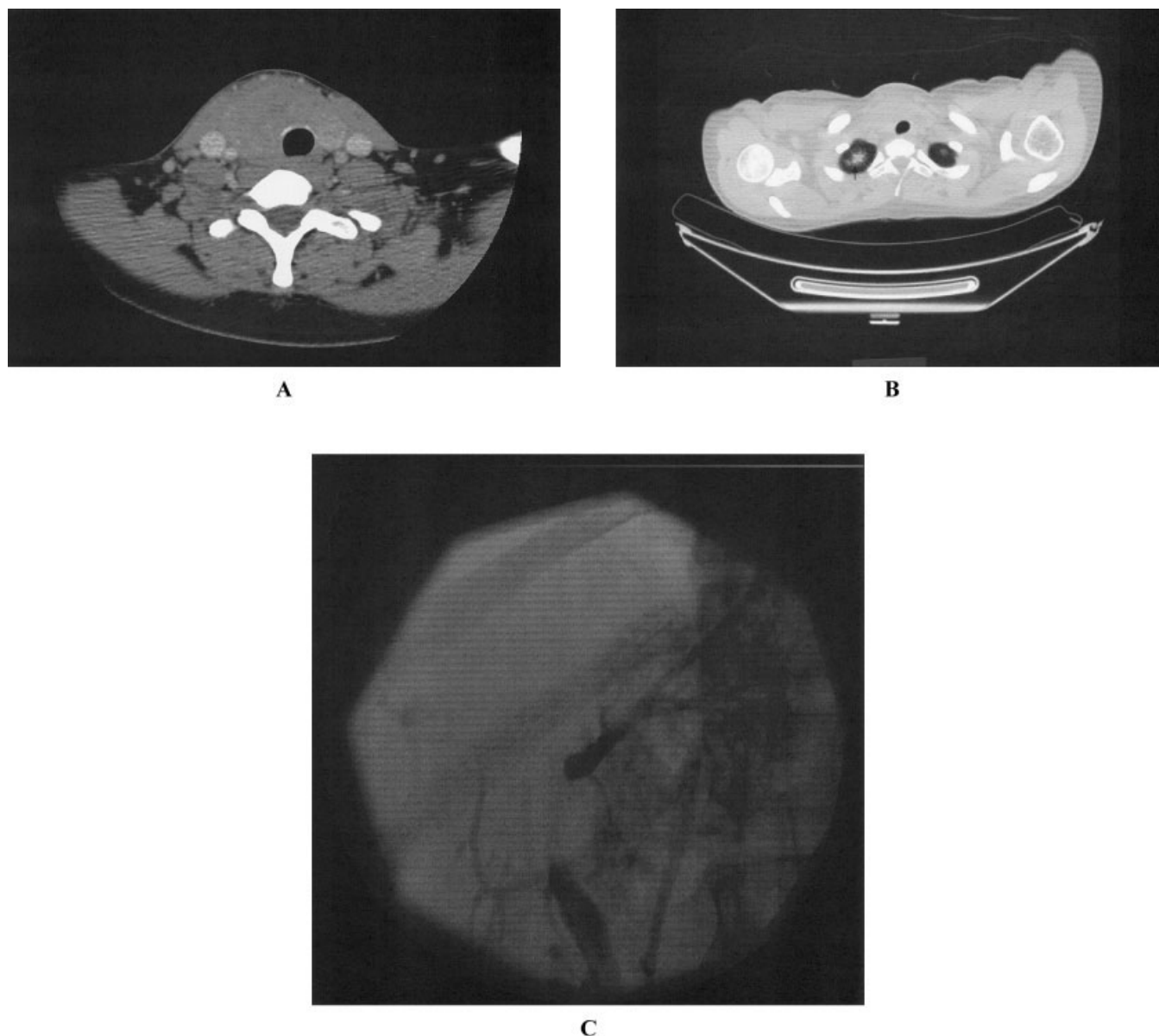


Figure 1. Imaging studies on patient 1. **A**, Computed tomography (CT) scan showing diffuse enlargement of the thyroid gland. Fibrous extension into adjacent tissues was found at the thyroidectomy. **B**, CT scan revealing a spiculated, 1.8-cm nodule (**arrow**) within the right apex of the lung. **C**, Endoscopic retrograde cholangiopancreatogram. This study reveals high-grade obstruction of the biliary tree at the confluence of the left and right hepatic ducts.

ultrasound showed a heterogeneous, vascular goiter consistent with thyroiditis. A fine needle aspirate was nondiagnostic, but a core biopsy sample of the right thyroid gland revealed dense sclerosis with scattered lymphocytes, plasma cells, and eosinophils. These histopathologic features were thought to be consistent with Riedel's thyroiditis. A computed tomography (CT) scan of the neck showed diffuse enlargement of the thyroid gland but no fibrous extension to adjacent tissues (Figure 1A). However, it also revealed a spiculated, 1.8-cm nodule within the right apex of the lung (Figure 1B).

A positron emission tomography (PET) scan was performed to evaluate the possibility of metastatic disease. The PET scan showed diffuse fluorodeoxyglucose (FDG) uptake within both the thyroid gland and the lung nodule.

In addition, focal FDG uptake was present within the liver and 2 iliac and mesenteric lymph nodes. The patient was referred for consideration of both thyroidectomy and lung biopsy. However, her preoperative evaluation demonstrated elevations of liver function tests. The serum aspartate and alanine aminotransferase concentrations were 220 units/liter (normal range 9–32) and 443 units/liter (normal range 7–30), respectively. The serum alkaline phosphatase and total bilirubin concentrations were 932 mg/dl (normal range 30–100) and 0.4 mg/dl (normal value <1.0), respectively. The lung biopsy was deferred.

Viral hepatitis serologies, a serum ceruloplasmin concentration, and a serum protein electrophoresis were all normal. The serum IgG4 concentration was 97.9 mg/dl (normal range 8.0–140.0). A magnetic resonance cholan-

giopancreatogram showed intrahepatic biliary duct dilatation involving both lobes of the liver and a 3.4×1.0 -cm mass, highly suspicious for cholangiocarcinoma, that arose from the confluence of the hepatic biliary duct. An endoscopic retrograde cholangiopancreatogram demonstrated high-grade obstruction at the confluence of the left and right hepatic ducts (Figure 1C). Two biliary stents were placed. Biliary tree brushings and biopsy samples of the bile ducts and the ampulla of Vater were negative for malignancy. After stent placement, the patient's serum aminotransferase concentrations normalized within 15 days and her alkaline phosphatase level declined to 529 mg/dl. Seven weeks after her original thoracic surgery referral, the patient underwent a video-assisted thorascopic lung biopsy and thyroidectomy. Histologic examination of the thyroid and lung tissue excluded malignancy and was consistent with a fibroinflammatory process (see below). The initial diagnosis was MFS.

The patient began treatment with prednisone (60 mg/day) that was tapered to discontinuation over a 2-month period. Her serum alkaline phosphatase concentration normalized and a followup PET scan showed no residual FDG uptake within the liver or other organs. Her biliary stents were removed. Four months later, however, she experienced a recurrence of neck pressure and an enlarging goiter. She began treatment of her MFS with tamoxifen. One month after beginning tamoxifen, a full year following her presentation with a goiter, the patient developed enlargement of the left lacrimal gland.

Patient 2. A 43-year-old woman had been diagnosed with Hashimoto thyroiditis 16 years before presentation. She had received variable doses of levothyroxine to maintain a euthyroid state. One year before presentation, she had developed an asymptomatic thyroid nodule. A fine needle aspirate of the lesion was inconclusive. Although the nodule grew larger in the months before presentation, the patient remained asymptomatic. She underwent a thyroidectomy to rule out malignancy.

An intraoperative examination of the thyroid revealed an indurated, diffusely fibrotic goiter. There were adhesions to adjacent structures. The histopathology of the thyroid lesion was consistent with Riedel's thyroiditis (see below).

Patient 3. A 37-year-old woman with a history of asthma noticed an enlarging thyroid gland 5 years before presentation and was diagnosed with "thyroiditis." She remained euthyroid. Over the next 3 years, she became increasingly hoarse and experienced dysphagia. An ultrasound examination of the neck revealed a multinodular goiter with a complex, solid nodule measuring 3.4 cm in the left thyroid lobe. She underwent left thyroidectomy and isthmusectomy. Intraoperative examination of the mass described a densely fibrotic lesion that encased the left recurrent laryngeal nerve. The pathology of her thyroid was reported as consistent with Riedel's thyroiditis.

The patient's hoarseness and dysphagia improved after surgery. Two years later, however, a large right-sided neck mass was detected. A CT scan showed an enlarged thyroid

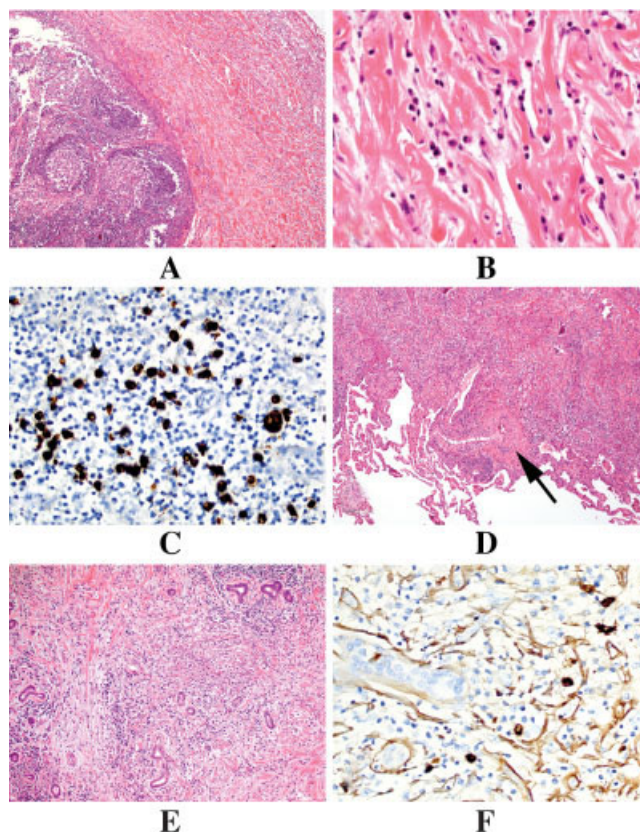


Figure 2. Pathology of multiple organs from patient 1. **A**, Low-power view of the neck mass showing inflammation and fibrosis and an entrapped lymph node (hematoxylin and eosin stained). **B**, High-power view of the neck mass. Note the plasma cells and eosinophils (hematoxylin and eosin stained). **C**, An entrapped lymph node adjacent to the thyroid gland demonstrates a marked infiltration of IgG4 cells (110/high-power field; immunoperoxidase stained). **D**, Inflammatory lung lesion with obliterative phlebitis (arrow; hematoxylin and eosin stained). **E**, Lacrimal gland partially replaced by fibrosis and inflammatory tissue. This histologic appearance is characteristic of IgG4-related systemic disease (hematoxylin and eosin stained). **F**, Lacrimal gland with few IgG4 positive plasma cells (immunoperoxidase stained).

gland that displaced the trachea to the left. The patient underwent a right completion thyroidectomy to alleviate obstructive compression of the trachea. A large thyroid mass was encountered. There were dense adhesions around the thyroid to the surrounding structures. Riedel's thyroiditis was confirmed upon histologic examination of the tissue. The pathologic features of these cases are described below.

Pathology. Patient 1. The thyroidectomy sample showed dense fibrosis and diffuse infiltration of lymphocytes, plasma cells, and occasional eosinophils. The fibrosis extended into the perithyroidal soft tissue and musculature (Figures 2A and B). Although phlebitis was not observed in this sample, the stromal tissue closely resembled that seen in autoimmune pancreatitis. An IgG4 stain revealed only 8 IgG4+ plasma cells per hpf within the fibroinflammatory mass (IgG4/IgG ratio = 80%) (Table 2), but an entrapped lymph node contiguous to the thyroid gland

Table 2. IgG4- and IgG-staining plasma cells in different involved organs*

Tissue	IgG4 per hpf	IgG per hpf	IgG4/IgG
Patient 1			
Thyroid gland	8	10	0.8
Cervical lymph node	110	113	0.97
Lung	13	15	0.87
Ampulla	12	ND	
Lacrimal gland	11	25	0.44
Patient 2			
Thyroid gland	53	95	0.56
Patient 3			
Left thyroid gland	10	51	0.20
Right thyroid gland	0	54	0

* hpf = high-power field; ND = not done.

demonstrated a marked infiltration by IgG4+ plasma cells (110/hpf) (Figure 2C).

The lung biopsy sample showed a subpleural fibroinflammatory mass lesion composed of lymphocytes, plasma cells, and eosinophils. A focus of obliterative phlebitis was present (Figure 2D). The ampullar biopsy showed 12 IgG4+ plasma cells per hpf. The biopsy from the lacrimal gland showed dense inflammation and fibrosis obliterating the glandular architecture, with 11 IgG4+ plasma cells per hpf (IgG4/IgG = 44%) (Figures 2E and F).

Patient 2. The thyroid gland was replaced by a fibroinflammatory infiltrate that extended into the extrathyroidal musculature. The inflammatory infiltrate was composed of lymphocytes, plasma cells, and eosinophils (Figure 3A). Rare foci of phlebitis were noted. There were 53 IgG4+ plasma cells per hpf (IgG4/IgG = 56%) (Figure 3B). Although the majority of the follicular epithelium was atrophic, extensive squamous metaplasia and rare foci of Hürthle cell changes were also noted.

Patient 3: left thyroidectomy. The thyroid was largely replaced by a hypercellular inflammatory process that was focally organized in a storiform pattern. The inflammatory infiltrate was composed of lymphocytes, plasma cells, and scattered eosinophils. The infiltrate extended into the extrathyroidal tissue. Immunohistochemistry studies re-

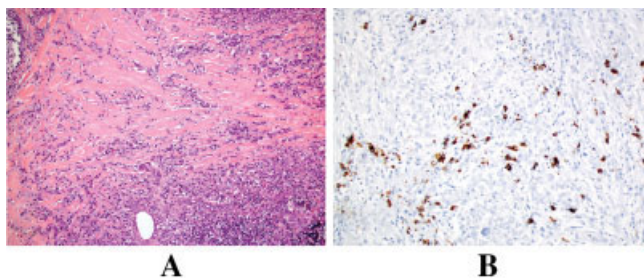


Figure 3. Thyroid gland pathology from patient 2. **A**, The thyroid parenchyma is replaced by fibrosis and a lymphoplasmacytic infiltrate. Small foci of residual thyroid tissue are present (hematoxylin and eosin stained). **B**, Numerous IgG4 positive plasma cells are noted between atrophic thyroid follicles (immunoperoxidase stained).

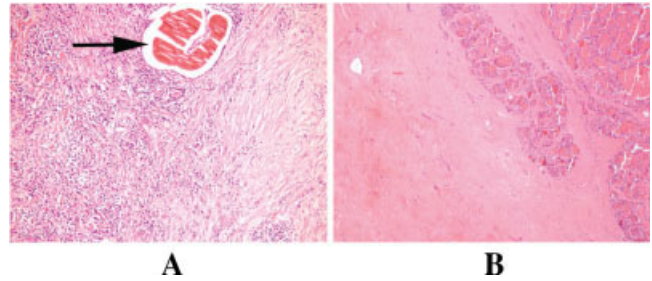


Figure 4. Thyroid gland pathology from patient 3. **A**, Left thyroid: hypercellular stroma composed of lymphocytes, plasma cells, eosinophils, and fibroblasts. Note the residual thyroid follicle (arrow). This histologic appearance is typical of IgG4-related systemic disease. **B**, Right thyroid: hyalinized and largely acellular fibrosis involving the thyroid (hematoxylin and eosin stained).

vealed 10 IgG4+ plasma cells per hpf and 51 IgG+ plasma cells per hpf.

Patient 3: right completion thyroidectomy. The right lobe (resected 2 years after the left) also showed extensive intra- and extrathyroidal fibrosis. However, in contrast to the left thyroid lobe, the fibrosis was largely acellular and hyalinizing in nature, lacking the dense inflammatory infiltrate seen in the left thyroidectomy sample (Figure 4B). Focal lymphoplasmacytic infiltrates were present, accompanied by reactive germinal centers. Neither Hürthle cell change nor phlebitis was observed in either the right or the left thyroid sample. IgG4+ plasma cells were not detected in this sample (Figure 4B).

DISCUSSION

Riedel's thyroiditis is a rare but fascinating condition that remains poorly understood more than 100 years after its initial description. All 3 Riedel's thyroiditis thyroidectomy samples in this series stained positively for IgG4-bearing plasma cells and had histopathologic features strongly consistent with IgG4-related systemic disease. In the patient who had a complete thyroidectomy accomplished in 2 different operations performed 2 years apart, the evolution of the histology from a picture of a lymphoplasmacytic inflammation at the first operation to diffuse fibrosis in the second demonstrates a link between these 2 histopathologies over time. Patient 1 also had extensive extrathyroidal involvement that was diagnostic of IgG4-related systemic disease, including IgG4-associated cholangitis and pseudotumors of both the lung and lacrimal gland. The histologic features of all of the organs involved in that patient were consistent with IgG4-related systemic disease. Therefore, Riedel's thyroiditis should be added to the growing list of lesions known to be associated with IgG4-related systemic disease. To our knowledge, this study is the first to establish Riedel's thyroiditis as part of the IgG4-related systemic disease spectrum and offers further evidence that MFS and IgG4-related systemic disease are one and the same entity in some cases.

Our data are intriguing in light of recent data from Japan that suggest a relationship between Hashimoto thyroiditis and IgG4-related systemic disease (34). This association is relevant to our cases because of the historic difficulties in distinguishing between Riedel's thyroiditis and the fibro-

sing variant of Hashimoto thyroiditis (35). Histopathologic features remain the gold standard for the diagnosis of both conditions. Riedel's thyroiditis is characterized by diffuse fibrosis that replaces much of the thyroidal tissue and typically extends into adjacent soft tissues. Extensive Hürthle cell metaplasia is not typical of Riedel's thyroiditis, but rather suggests Hashimoto thyroiditis or its fibrosing variant. None of our 3 patients had significant Hürthle cell changes. In contrast, obliterative phlebitis is considered essentially pathognomonic of Riedel's thyroiditis. The links of both Riedel's thyroiditis and Hashimoto thyroiditis to IgG4-infiltrating plasma cells may renew the debate about the relationships between these conditions, and clearly call for further investigation.

MFS, first described in the 1960s (15), has been considered to involve the simultaneous occurrence of the following conditions: Riedel's thyroiditis, sclerosing pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, mediastinal fibrosis, fibrosis of the lung and parotid gland, and pseudotumor of the orbit (15,16). However, the reason for the involvement of these different organs has remained obscure because no context existed for the fibrotic disease observed. The linkages of similar fibroinflammatory processes within several of these organs (now including the thyroid), the infiltration of IgG4+ plasma cells, and other histopathologic features characteristic of IgG4-related systemic disease frame a new disease context and pathophysiologic construct for MFS.

Recognition of the fact that patients with Riedel's thyroiditis can develop other features of IgG4-related systemic disease has implications for both diagnosis and prognosis. Because IgG4-related systemic disease can affect multiple organs at the same time or progress to involve them in a metachronous fashion, prompt recognition and treatment of this disorder at the stage of single-organ involvement might prevent other organs from becoming affected. Serum assays for IgG subclasses can complement the histologic features in diagnosis and help establish the existence of this condition at an early stage. An autoantibody associated with autoimmune pancreatitis has recently been reported (26), but the prevalence of this autoantibody in IgG4-related systemic disease patients who do not have autoimmune pancreatitis is not currently known.

Recognition of the link between Riedel's thyroiditis and IgG4-related systemic disease also has potential implications for therapy. Patients with IgG4-related systemic disease generally respond to glucocorticoid therapy, but clinical responses are often incomplete, requiring chronic glucocorticoid administration and the empiric use of azathioprine or other disease-modifying antirheumatic drugs (21,25,36). Rituximab, a B lymphocyte-depleting agent, has recently been reported to be an effective alternative approach to therapy in IgG4-related systemic disease (37). B lymphocyte depletion is theorized to work through elimination of the cell population that differentiates into short-lived IgG4-secreting plasma cells. The efficacy of such an approach might depend on the timing of the diagnosis with regard to the stage of disease. Patients with early Riedel's thyroiditis whose disease is more inflammatory than fibrotic are anticipated to respond more readily to B cell depletion. The advanced fibrotic state of the thyroid

shown in the second partial thyroidectomy from our patient 3 suggests a later stage of disease and a lower likelihood of response to antiinflammatory therapy. It might also explain the absence of IgG4-bearing plasma cells in that organ.

In conclusion, we have demonstrated that IgG4-related systemic disease is the underlying condition in some cases of Riedel's thyroiditis. We also provide evidence that MFS was actually IgG4-related systemic disease in one of our patients (patient 1) who had pulmonary, biliary tract, and lacrimal gland involvement, as well as thyroid disease. It is possible that a variety of etiologies could lead to the same histopathologic appearance of these conditions, particularly at the "burnt-out," fibrotic end of the disease spectrum. Therefore, IgG4-related systemic disease may not account for all of the cases recognized clinically as either Riedel's thyroiditis or MFS. Further investigations of patients with Riedel's thyroiditis in different phases of the disease are required to definitively address the frequency with which IgG4-related systemic disease is the underlying cause, and to understand the implications of this association for disease management.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Stone had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Dahlgren, Khosroshahi, Nielsen, Deshpande, Stone.

Acquisition of data. Dahlgren, Khosroshahi, Nielsen, Deshpande, Stone.

Analysis and interpretation of data. Dahlgren, Khosroshahi, Nielsen, Deshpande, Stone.

REFERENCES

1. Riedel BM. Die chronische, zur bildung elsenharter tumoren führende entzündung der schilddrüse. *Verh Dtsch Ges Chir* 1896;25:101–5.
2. Riedel BM. Vorstellung eines kranken mit chronischer strumitis. *Verh Dtsch Ges Chir* 1897;26:127–9.
3. Riedel BM. Über verlauf und ausgang der strumitis chronica. *MMW* 1910;57:1946–7.
4. Stuart AE. Riedel's thyroiditis. *Br Med J* 1959;12:2.
5. Woolner LB, McConahey WM, Beahrs OH. Invasive fibrous thyroiditis (Riedel's struma). *J Clin Endocrinol Metab* 1957;17:201–20.
6. Meijer S, Hausman R. Occlusive phlebitis, a diagnostic feature in Riedel's thyroiditis. *Virchows Arch* 1978;377:339–49.
7. Harach HR, Williams ED. Fibrous thyroiditis: an immunopathologic study. *Histopathology* 1983;7:739–51.
8. Schwaegerle SM, Bauer TW, Esselstyn CB. Riedel's thyroiditis. *Am J Clin Pathol* 1988;90:715–22.
9. Lee JG. Chronic nonspecific thyroiditis. *Arch Surg* 1935;31:982–1012.
10. Papi G, LiVolsi VA. Current concepts of Riedel's thyroiditis. *Am J Clin Pathol* 2004;121:S50–63.
11. Hay ID. Thyroiditis: a clinical update. *Mayo Clin Proc* 1985;60:836–43.
12. Brady OH, Hehir DJ, Hefferman SJ. Riedel's thyroiditis: case report and literature review. *Ir J Med Sci* 1994;163:176–7.
13. Few J, Thompson NW, Angelos P, Simeone D, Giordano T, Reeve T. Riedel's thyroiditis: treatment with tamoxifen. *Surgery* 1996;120:993–8.

14. De M, Jaap A, Dempster J. Tamoxifen therapy in steroid resistant Riedel's thyroiditis. *Scott Med J* 2001;46:56–7.
15. Comings DE, Skubi KB, Van Eyes J, Motulsky AG. Familial multifocal fibrosclerosis. *Ann Intern Med* 1967;66:884–92.
16. Bartholomew LG, Cain JC, Woolner LB, Utz DC, Ferris DO. Sclerosing cholangitis: its possible association with Riedel's struma and fibrous retroperitonitis. *N Engl J Med* 1963;269:8–12.
17. Barret NR. Idiopathic mediastinal fibrosis. *Br J Surg* 1958;46:207–18.
18. Owen K, Lane H, Jones MK. Multifocal fibrosclerosis: a case of thyroiditis and bilateral lacrimal gland involvement. *Thyroid* 2001;11:1187–90.
19. Drieskens O, Blockmans D, van den Bruel A, Mortelmans L. Riedel's thyroiditis and retroperitoneal fibrosis in multifocal fibrosclerosis: positron emission tomographic findings. *Clin Nucl Med* 2002;27:413–5.
20. Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, et al. A new clinicopathologic entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003;38:982–4.
21. Kamisawa T, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. *J Gastroenterol* 2006;41:613–25.
22. Neild GH, Rodriguez-Justo M, Wall C, Connolly JO. Hyper-IgG4 disease: report and characterization of a new disease. *BMC Med* 2006;4:23.
23. Stone JH, Caruso PA, Deshpande V. Case records of the Massachusetts General Hospital: case 24-2009. A 26-year-old woman with painful swelling of the neck. *N Engl J Med* 2009;361:511–8.
24. Morselli-Labate AM, Pezzilli RJ. Usefulness of serum IgG4 in the diagnosis and follow up of autoimmune pancreatitis: a systematic literature review and meta-analysis. *Gastroenterol Hepatol* 2009;24:15–36.
25. Khosroshahi A, Stone JR, Pratt DS, Deshpande V, Stone JH. Painless jaundice with serial multi-organ dysfunction. *Lancet* 2009;373:1494.
26. Frulloni L, Lunardi C, Simone R, Dolcino M, Scattolini C, Falconi M, et al. Identification of a novel antibody associated with autoimmune pancreatitis. *N Engl J Med* 2009;26:2135–42.
27. Chacko S, Taskapan H, Roscoe J, Stein J, Woods E, Denton T, et al. Treatment of hyper-IgG4 disease with sequential corticosteroids and tamoxifen: case report and review of the literature. *Clin Nephrol* 2009;72:414–7.
28. Beristain JL, Sabater L, Calatayud A, Calvete J, Rausell M, Lledo S, et al. Autoimmune pancreatitis: inflammatory pseudotumor, multifocal fibrosclerosis, portal hypertension, and long-term outcome. *Rev Esp Enferm Dig* 2008;100:652–8.
29. Hamano H, Kawa S, Ochi Y, Unno H, Shiba N, Wajiki M, et al. Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis [abstract]. *Lancet* 2002;359:1403–4.
30. Zen Y, Harada K, Sasaki M, Sato Y, Tsuneyama K, Haratake J, et al. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis: do they belong to a spectrum of sclerosing pancreatitis? *Am J Surg Pathol* 2004;28:1193–203.
31. Masaki Y, Dong L, Kurose N, Kitagawa K, Morikawa Y, Yamamoto M, et al. Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. *Ann Rheum Dis* 2009;68:1310–5.
32. Chari ST. Diagnosis of autoimmune pancreatitis using its five cardinal features: introducing the Mayo Clinic's HISORT criteria. *J Gastroenterol* 2007;42 Suppl:39–41.
33. Geyer JT, Ferry JA, Harris NL, Stone JH, Zukerberg LR, Lauwers GY, et al. Chronic sclerosing sialadenitis is an IgG4-associated disease. *Am J Surg Pathol* 2010;34:202–10.
34. Li Y, Bai Y, Liu Z, Ozaki T, Taniguchi E, Mori I, et al. Immunohistochemistry of IgG4 can help subclassify Hashimoto's autoimmune thyroiditis. *Pathol Int* 2009;59:636–41.
35. Ewing J. Neoplastic diseases. 2nd ed. Philadelphia: Saunders; 1922. p. 908.
36. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001;344:722–38.
37. Khosroshahi A, Bloch DB, Deshpande V, Stone JH. Rituximab therapy leads to swift decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease. *Arthritis Rheum* 2010. E-pub ahead of print.