

Fibrosing variant of Hashimoto thyroiditis is an IgG4 related disease

Vikram Deshpande,¹ Amelia Huck,¹ Esther Ooi,² John H Stone,³ William C Faquin,¹ G Petur Nielsen¹

¹Department of Pathology, Massachusetts General Hospital, Boston, Massachusetts, USA

²School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia

³Department of Medicine, Division of Rheumatology, Massachusetts General Hospital, Boston, Massachusetts, USA

Correspondence to

Dr Vikram Deshpande, Department of Pathology, Massachusetts General Hospital, 55 Fruit Street/Warren 2, Boston, MA 02114, USA; vdeshpande@partners.org

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ABSTRACT

Hashimoto thyroiditis (HT) and the fibrosing variant of Hashimoto thyroiditis (FVHT) are immune-mediated tumefactive lesions of the thyroid. Immunoglobulin G4-related disease (IgG4-RD) is now a widely recognised multi-organ system disease characterised by elevated serum and tissue concentrations of IgG4. In this study, the authors address several unresolved questions pertaining to the relationship between HT and FVHT, and the association of each of these diseases with IgG4-RD. The authors evaluated 28 consecutive cases of HT and nine cases of FVHT. The clinical, demographic and serological data were recorded. The slides were stained immunohistochemically using antibodies to IgG4 and IgG and the quantitative analysis was recorded. Data on thyroid function tests were available on seven cases of FVHT and 14 cases of HT. Based on the availability of data, hypothyroidism was noted in 62% (9/14) of HT and 86% of FVHT (6/7). FVHT demonstrated an exaggerated lobular pattern with lobules separated by cellular storiform-type fibrosis, resembling fibrosis seen in other forms of IgG4-RD. The median IgG4 counts per high power field ($\times 40$) in HT and FVHT were 2.3 and 22, respectively. The median IgG4:IgG ratios in HT and FVHT were 0.11 and 0.58, respectively. The authors propose that FVHT belongs to the spectrum of IgG4-RD. Although a proportion of cases of HT show elevated numbers of IgG4 positive plasma cells, these cases lack the histological features typically associated with IgG4-RD, and thus the relationship between HT and IgG4-RD remains unproven.

INTRODUCTION

Hashimoto thyroiditis (HT) is a form of chronic autoimmune thyroiditis.¹ It was first recognised in 1912 by Hashimoto, who described four women with enlarged thyroid glands that showed abundant lymphocytic infiltration (*struma lymphomatosa*).² The patients typically present with an enlarged thyroid gland but may also manifest with symptoms and signs of hypothyroidism, particularly in later stages. The histopathological hallmark of HT is a dense multifocal lymphoplasmacytic infiltrate, lymphoid follicles and accompanied follicular cell injury with associated Hürthle cell changes.

In 1974, Katz and Vickery redefined the fibrosing variant of HT (FVHT).³ Patients with the FVHT present with striking neck enlargement and pressure on local tissues often causing diagnostic confusion with malignant disease.³ FVHT demonstrates the same marked female predominance that

characterises HT, and thyroid function tests indicate hypothyroidism in virtually all patients. Histologically, FVHT is characterised by a marked fibrous replacement of the parenchyma and changes typical of HT in the remaining thyroid. In contrast to Riedel thyroiditis, the fibroinflammatory reaction in FVHT is confined to the thyroid and does not extend beyond the capsule to involve adjacent structures. FVHT does, however, show overlapping features with HT, namely, the presence of Hürthle cell change and a dense lymphoplasmacytic infiltrate.

Immunoglobulin G4-related systemic disease (IgG4-RD) is now increasingly recognised as a multi-organ system disease characterised by tumefactive enlargement of affected organs and, in the majority of cases, elevated serum concentrations of IgG4. The *sine qua non* of IgG4-RD is its histological appearance: lymphoplasmacytic inflammation, fibrosis (frequently in a storiform pattern), obliterative phlebitis, increased numbers of IgG4-positive plasma cells and elevated IgG4:IgG ratios. The tumefactive nature of HT and the anecdotal association of this disease with IgG4-RD had led investigators to evaluate IgG4-bearing plasma cells in HT and related tumefactive lesions.⁴

A study published from this institution documented the presence of elevated tissue levels of IgG4 in Riedel thyroiditis.⁵ One of the patients reported in that study also showed evidence of multifocal fibrosclerosis, with hepatobiliary, pulmonary and lacrimal gland involvement. Multifocal fibrosclerosis is believed to be a component of the IgG4-RD spectrum.^{6,7}

Recent data from Japan suggest that a subset of patients with HT also belong to the IgG-RD spectrum.⁴ Although an association between IgG-RD (ie, autoimmune pancreatitis) and HT has been demonstrated in the North American population,⁸ the larger significance of IgG4 in immune-mediated disease of the thyroid in this population is currently unknown. In this study, we address several unresolved questions pertaining to the relationships between HT and FVHT, and the association of each of these diseases with IgG4-RD.

MATERIALS AND METHODS

We identified 28 consecutive cases of HT from our files. The histological diagnosis of HT was based upon the presence of a dense lymphoplasmacytic infiltrate with destruction of follicular cells, extensive Hürthle cell change and germinal centre formation. We searched the pathology department database for potential cases of FVHT using the

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search terms 'Hashimoto and fibrosis'. Clinical files were reviewed for each case and the presence of serum antithyroid peroxidase antibodies was recorded where information was available.

Morphological definitions

Distinctions between HT and FVHT were based on previously published criteria,^{5 9–11} as shown below:

- 1) HT: HT cases showed a dense lymphoplasmacytic infiltrate, lymphoid follicles and extensive Hürthle cell change. Cases with areas of acellular fibrosis were accepted within the spectrum of HT.
- 2) FVHT: The hallmark of FVHT was considered to be the presence of fibrosis. However, unlike the acellular fibrosis that is sometimes detected in HT, we required cases of FVHT to show zones of cellular fibrosis with plump fibroblasts interspersed with lymphocytes and plasma cells (figure 1A,B). The fibrous bands usually (but not invariably) carved the thyroid parenchyma into lobules, but the fibrosis did not extend beyond the thyroid. In addition to fibrosis, FVHT cases also displayed the other histological features of HT.

Cases with incidental findings of focal, non-specific lymphocytic thyroiditis were excluded from this study.

The clinical, demographic and serological data were recorded and the H&E stained slides were reviewed. Only patients with resections of one or both lobes were evaluated: fine needle aspiration biopsy or core biopsies were not included in this study. The slides were stained immunohistochemically using antibodies to IgG4 (Zymed; 1:200 dilution) and IgG (Dako; 1:3000 dilution). The degrees of plasma cell infiltration and IgG4 staining within samples were quantified. For each case, the number of plasma cells staining for IgG4 was assessed in non-overlapping high-power fields ($\times 40$). The three fields with the highest degree of IgG4 reactivity were selected for quantitation. We obtained digital photographs of these fields (area of each field photographed = 0.0588 mm^2). To facilitate comparisons with previous work on HT,⁴ the numbers of IgG4- and IgG-staining

plasma cells per 0.034 mm^2 (this representing the size of a high power field in this study) were calculated. The number of IgG4-positive plasma cells was then divided by the total number of IgG-bearing plasma cells in these fields to obtain the IgG4:IgG ratio.

Statistical analyses

Statistical analyses were performed using STATA (V.11.1). Data are presented as medians and IQR to account for the skewed nature of the parameters. Mann–Whitney tests were performed to test for difference between groups. The p values are reported, with statistical significance set at the 5% level.

RESULTS

We identified 28 cases of HT and nine cases of FVHT.

Demographic data

The median (IQR) ages of the patients with HT and FVHT were 47 (42, 67) and 50 (44, 61) years, respectively ($p=0.82$). There were three male subjects in the HT cohort (11%) and one male subject (11%) in the FVHT cohort.

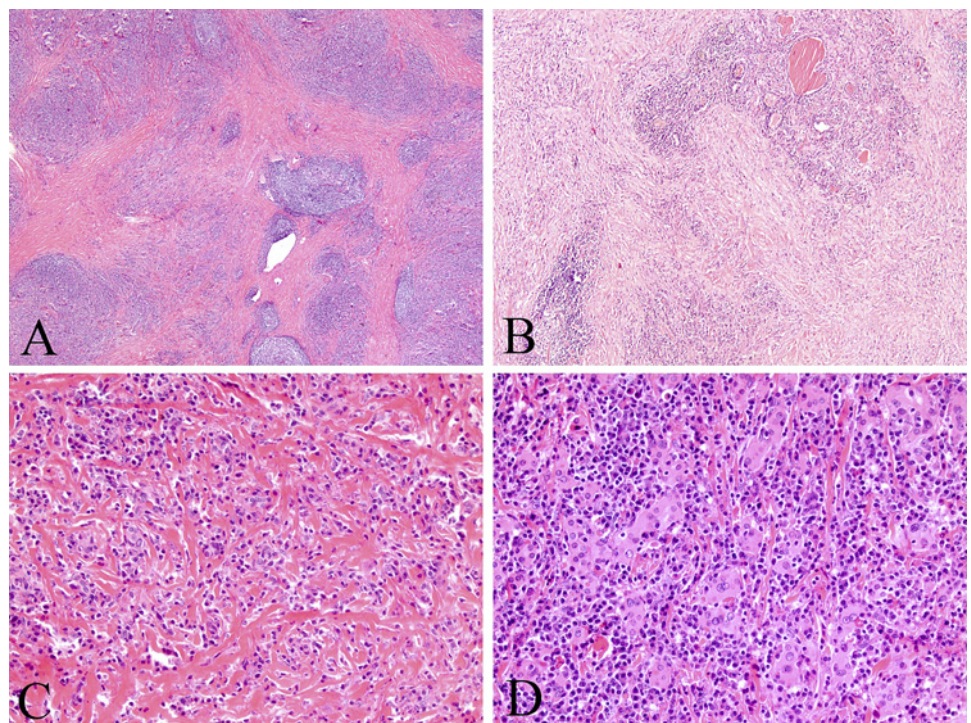
Evidence of hypothyroidism

Data on thyroid function tests were available on seven cases of FVHT and 14 cases of HT. The majority of patients with FVHT showed either clinical or subclinical evidence of hypothyroidism (6/7 or 86%). Numerically fewer patients with HT (9/14 or 62%) had evidence of hypothyroidism, but this comparison did not achieve statistical significance ($p=0.61$).

Serological findings

Data on serum antithyroid peroxidase antibody were available on 10 HT and four FVHT cases. These antibodies were positive in all 10 HT cases and all four cases of FVHT in which these data were available. Data on serum IgG4 were not available on these cases.

Figure 1 Fibrosing variant of Hashimoto thyroiditis. A nodular pattern is evident and the lobules are separated by cellular fibrous tissue (A). The fibrosis is arranged in a storiform pattern (B). Dense fibrosis with a brisk lymphoplasmacytic infiltrate (C). Microfollicular pattern with dense interfollicular lymphoplasmacytic infiltrate (D).



Morphological features

Hashimoto thyroiditis

These cases demonstrated the characteristic histological features of HT. This included a prominent intrathyroidal lymphoplasmacytic infiltrate with focal to diffuse Hürthle cell change and lymphoid follicles. Phlebitis and extrathyroidal extension were absent.

Fibrosing variant of Hashimoto thyroiditis

The thyroid gland demonstrated an accentuated lobular pattern, with lobules separated by cellular and inflamed fibrous tissue. This histological appearance was remarkably similar to the interlobular stroma of IgG4-associated sialadenitis and the type 1 variant of autoimmune pancreatitis.¹² The fibrous zones occupied >20% of the thyroid parenchyma and a storiform pattern of fibrosis was evident in all cases (figure 1A,B). In addition, the Hürthle cell change was both diffuse and quantitatively more prominent than that seen in HT. These follicular cells were predominantly arranged in a microfollicular pattern, and an intense inflammatory infiltrate composed of lymphocytes and plasma cells was identified between follicles (figure 2D). This pattern of lymphoplasmacytic infiltration was seen in eight of nine FVHT cases. One of the FVHT cases also showed a focus of obliterative phlebitis. However, none of the cases showed evidence of extracapsular extension.

Tissue IgG4 and IgG

The median (IQR) IgG4 counts per high power field in HT and FVHT were 2.3 (1.0–5.5) and 22.0 (11.9–42.1), respectively (table 1). The median (IQR) IgG4:IgG ratios in HT and FVHT were 0.11 (0.05–0.27) and 0.58 (0.34–0.96), respectively. In general, the markedly fibrotic foci showed lower numbers of IgG4 positive cells (figure 2). Four of the 28 (14%) HT cases showed IgG4:IgG ratios of more than 0.4 but only one of these cases showed an IgG4 count of >30/high power field. By contrast, 66.7% (6/9) of the FVHT cases had IgG4:IgG ratios greater than 0.4, and four of these cases showed IgG4 counts >30/high power field.

DISCUSSION

Features known to be associated with IgG4-RD include elevated serum concentrations of IgG4, increased numbers of IgG4-positive plasma cells within involved organs, elevated IgG4:IgG ratios, and the histopathological findings of lymphoplasmacytic infiltrates, storiform fibrosis, and obliterative phlebitis.^{12–13} Using an IgG4:IgG ratio of 0.4 and an IgG4 cell count of >30 per high power field, 4% of HT patients and 44% of those with FVHT would meet this guideline for the diagnosis of IgG4-RD.⁴ The cases we categorised as FVHT showed an exaggerated

Table 1 Quantitation of IgG4 and IgG in Hashimoto thyroiditis and fibrosing variant of Hashimoto thyroiditis

	IgG4 per HPF	IgG per HPF	IgG4:IgG ratio
Hashimoto thyroiditis	2.3 (1.0–5.5)	20.8 (13.5–29.9)	0.11 (0.05–0.27)
Fibrosing variant of Hashimoto thyroiditis	22.0 (11.9–42.1)	38.2 (30.8–54.2)	0.58 (0.34–0.96)
p Value	<0.001	0.003	<0.001

Data are presented as median (IQR).

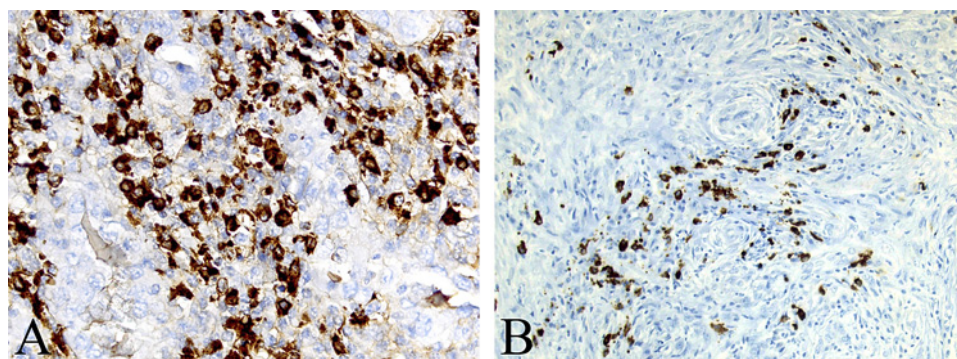
HPF, high power field; Ig, immunoglobulin.

lobular architecture, one created by cellular stromal fibroinflammatory proliferation. This stromal proliferation was remarkably similar to the interlobular stroma seen in the type 1 variant of autoimmune pancreatitis.¹² Obliterative phlebitis was identified in one case of FVHT. The concomitant presence of characteristic morphological and immunohistochemical features argues for the inclusion of FVHT in the spectrum of IgG4-RD. One potential drawback of this study is the lack of serum IgG4 levels. However, while serum IgG4 levels are elevated in a significant number of cases of IgG4-RD, the absence of elevated levels of serum IgG4 does not rule out the presence of this disease. In fact, in cases with localised disease serum IgG4 levels are frequently not elevated.¹⁴ Furthermore, neither elevations of either tissue or serum IgG4 are entirely specific for IgG4-RD.^{15–20} Instead, histopathological features often provide a more robust means of establishing the diagnosis of IgG4-RD.

In a previous study we have shown that cases with Riedel thyroiditis exhibit elevated numbers of IgG4 positive cells.⁵ Significantly, one of these cases also showed extrathyroidal manifestations, which included involvement of the lung, lymph node, lacrimal gland and the hepatobiliary tract.⁵ Furthermore, in this case IgG4-positive plasma cells were documented in the ampulla, cervical lymph node and lacrimal gland.⁵

The lack of histopathological features characteristic of IgG4-RD in the majority of HT cases makes its relationship with IgG4-RD far less certain. Nonetheless, there is anecdotal evidence that some cases of thyroiditis are related to IgG4-RD. Some of this evidence comes from the observation that a quarter of the patients with autoimmune pancreatitis have clinical evidence of hypothyroidism.⁸ In this study from the Mayo Clinic, clinical hypothyroidism requiring thyroxine supplementation was observed in 14 patients (14.4%) with autoimmune pancreatitis versus 4 (4%) in the control group.⁸ The prevalence of hypothyroidism in autoimmune pancreatitis in two Japanese studies was 22.2% and 26.8%.^{21–22} Notably, hypothyroidism was the fourth most common extrapancreatic manifestation of autoimmune pancreatitis.²² Furthermore, antithyroglobulin and antithyroid peroxidase antibodies were identified in 36.6%²¹ and 40.7%²² of patients with autoimmune pancreatitis. In addition,

Figure 2 Immunoglobulin (Ig)G4 immunohistochemical stain in a case of fibrosing variant of Hashimoto thyroiditis. Areas without fibrosis (A) show higher numbers of IgG4 positive cells than foci with fibrosis (B).



Take-home messages

- We propose that fibrosing variant of Hashimoto thyroiditis belongs to the spectrum of immunoglobulin G4-related disease (IgG4-RD). Based on our data, we cannot endorse an association among the more common variant of thyroiditis, Hashimoto thyroiditis and IgG4-RD.
- A prospective analysis of such cases will be required to further confirm our observations.

a favourable response of hypothyroidism to treatment with glucocorticoids was also observed.²² However, a histopathological evaluation of thyroids from individuals with autoimmune pancreatitis has not been performed.

In a prior study that investigated the relationship of IgG4 with HT, Li and co-workers classified 27% of cases of HT as IgG4 thyroiditis.⁴ IgG4 thyroiditis cases showed a higher grade of stromal fibrosis, lymphoplasmacytic infiltration and follicular cell degeneration than did patients whose thyroiditis was not associated with IgG4. Furthermore, these two groups showed different clinical features, with IgG4 thyroiditis cases associated with male gender, rapid progression, subclinical hypothyroidism, more diffuse low echogenicity and higher levels of circulating antithyroid antibodies. Furthermore, the IgG4 thyroiditis cases also showed elevated levels of serum IgG4. We note that the percentage of HT cases in this series (21%) with IgG4:IgG ratios greater than 0.3 was remarkably similar to that of series of Li and colleagues (27%).⁴ In fact, since Li and coworkers did not exclude cases of FVHT as we did, the percentage of cases of HT may be even closer than a cursory look at the numbers would suggest.⁴

Elevated numbers of IgG4 positive plasma cells are identified in a wide variety of conditions including primary sclerosing cholangitis, anti-neutrophil cytoplasmic antibody-associated vasculitis, rheumatoid arthritis, inflammatory bowel disease, rhinosinusitis, rheumatoid arthritis, Rosai–Dorfman disease, splenic sclerosing angiomatoid nodular transformation, cutaneous plasmacytosis, perforating collagenosis and autoimmune atrophic gastritis (pernicious anaemia).^{17–20} Thus, histopathological features are an integral component of IgG4-RD and that for a class of diseases to be accepted within the IgG4-RD fold, a significant component of that cohort should show these key histopathological features. In our series, the cases of HT lacked histological features of IgG4-RD: storiform fibrosis and obliterative phlebitis. Furthermore, on an IgG4 immunostain only a single case of IgG4-RD met the stringent criteria proposed for IgG4-RD. Thus, after exclusion of FVHT cases, the HT cohort failed to meet these minimal criteria for IgG4-RD.

The therapeutic implications of this diagnosis are uncertain at this point. IgG-RD is generally a steroid-responsive disease. A recent report from this institution showed that IgG4-RD shows a swift response to rituximab.²³ Potential clinical applications of identifying subsets of patients with IgG4 thyroiditis (FVHT and

Riedel thyroiditis) include a trial of immunosuppressive therapy if a resection is deemed inadvisable. Furthermore, particularly in cases of FVHT that mimic malignancy, tissue and serum IgG4 may provide supportive diagnostic information.

Contributors All the authors have made significant contributions to the manuscript and approve of the version submitted.

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