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Case Report

# IgG4-Related Hashimoto's Thyroiditis of the Thyroid Gland

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**Immunoglobulin (Ig) G4-related Hashimoto's thyroiditis is a newly discovered subtype of Hashimoto's thyroiditis and characterized by thyroid inflammation and marked fibrosis. IgG4-related Hashimoto's thyroiditis is very rare and there has been relatively little information available to date. A 46-year-old woman with a past history of thyroid dysfunction visited our outpatient clinic for severe anterior neck swelling. She complained of swallowing discomfort and pain due to severe goiter and was successfully treated with total thyroidectomy. Immunohistochemistry showed thyroid invasion by IgG4-positive cells and an IgG4/IgG ratio over 40%. The patient was diagnosed with IgG4-related Hashimoto's thyroiditis. We report a very rare case of IgG4-related Hashimoto's thyroiditis with severe goiter. A more comprehensive understanding of the IgG4-related Hashimoto's thyroiditis may help physicians to allow proper diagnosis and treatment of patients with severe goiter.**

*Key words:* Hashimoto's thyroiditis – Autoimmune disease – Immunoglobulin

Hashimoto's thyroiditis (HT), the most common cause of hypothyroidism in patients with sufficient dietary iodine, is characterized clinically by the presence of goiter and serum thyroid antibodies.[1] Although its diagnosis and treatment have remained unchanged, HT presents with various clinicopathologic characteristics, and its pathogenesis is poorly understood.

Immunoglobulin (Ig) G4-related HT is a new subtype of HT,[2] characterized by thyroid inflamma-

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tion, including invasion by large numbers of IgG4-positive cells, and marked fibrosis. This report describes the first patient diagnosed with IgG4-related HT in Korea.

## Case Report

A 46-year-old woman visited the outpatient clinic for progressive neck swelling over the previous 5 months. No symptoms of thyroid dysfunction were observed. Her medical history included primary hyperthyroidism, for which she had been treated with the antithyroid drug methimazole and radioactive iodine for the previous 24 years. Due to progressive goiter and hypothyroidism, however, methimazole was discontinued in July 2014 and she was started on L-thyroxine in October 2014. She had no family history of thyroid dysfunction. Her general condition was good, but she complained of swallowing discomfort and pain due to severe anterior neck enlargement.

Cervical palpitation identified an enlarged, hard and painless thyroid gland, but no palpable adenopathies. No other changes were observed on physical examination. Laboratory testing, including complete blood count and liver function tests, showed that all parameters were within their normal ranges. Thyroid function test revealed mild hyperthyroidism, with a reduced thyroid-stimulating hormone (TSH) concentration of 0.06 mIU/L (normal, 0.17–4.05 mIU/L) and an elevated free thyroxine (FT4) concentration of 23.7 pmol/L (normal, 11.5–23 pmol/L). Cervical computed tomography (CT) showed a diffuse enlarged thyroid gland, especially of the right thyroid lobe. The dimensions of the trachea were narrowed by the enlarged thyroid gland (Fig. 1A), with the upper pole of the right thyroid gland reaching the level of the submandibular gland (Fig. 1B).

Total thyroidectomy was performed. Due to the size of the gland and the presence of thyroiditis, the surgical procedure was complex and time-consuming, with difficulties mobilizing the thyroid gland, such that resection of a strap muscle was required. The recurrent laryngeal nerve and parathyroid glands were preserved, and there were no other complications. The right thyroid lobe measured 8.9 $\times$ 5.2 $\times$ 3.3 cm, whereas the left thyroid lobe measured 10.8 $\times$ 6.2 $\times$ 5.4 cm (Fig. 2A). Macroscopic examination of the thyroid gland revealed diffuse enlargement with firm consistency and a nodular appearance (Fig. 2B). Pathologic examination of the excised thyroid tissue showed a nodular pattern of growth with lymphoid follicles and marked fibrosis (Fig. 3A). Inflammatory infiltration by lymphoid follicles containing germinal centers and atrophic follicles was observed (Fig. 3B). The thyroid tissue was tested immunohistochemically for the expression of IgG and IgG4. Numerous IgG-positive plasma cells were detected, with many also being IgG4-positive. There were over 50 cells per high-

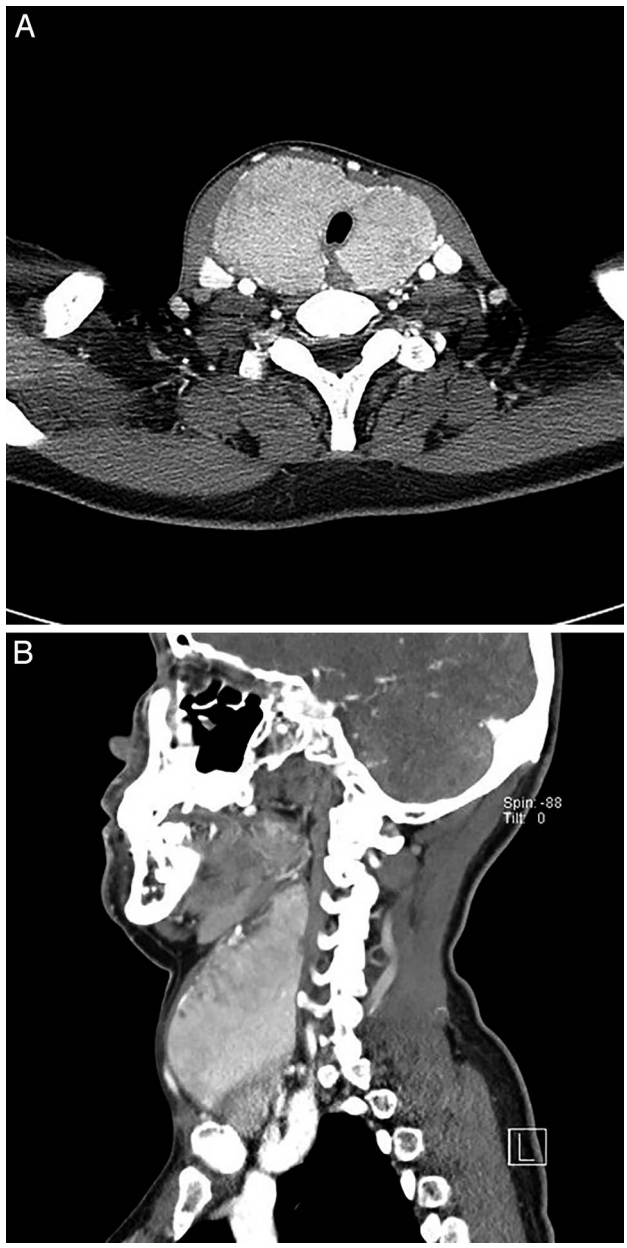


**Fig. 1** Cervical computed tomography of our patient, showing (A) enlargement of the thyroid gland with increased dimensions, resulting in a mass effect on the trachea, and (B) extension to the level of the submandibular gland.

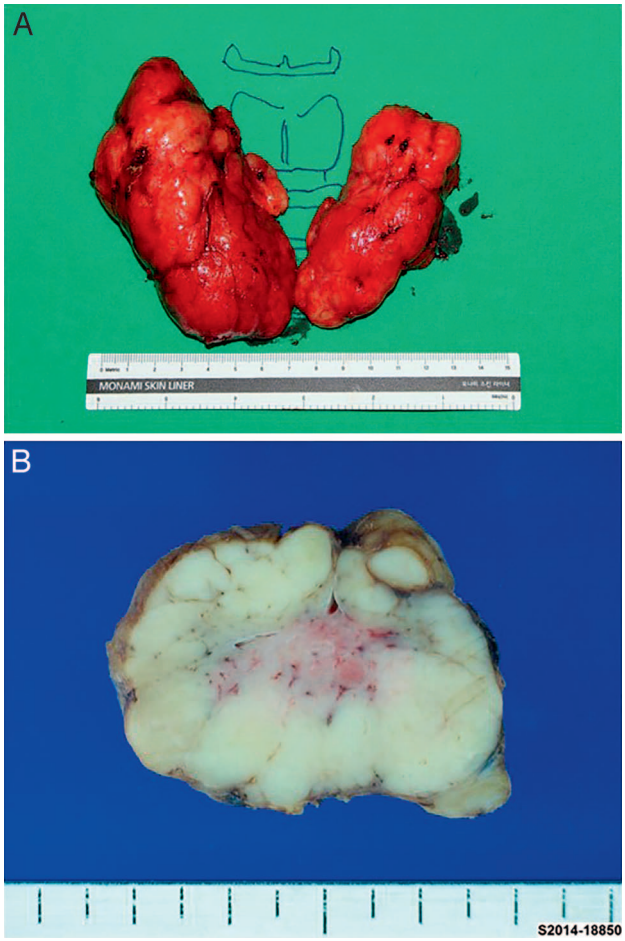


**Fig. 2** Macroscopic features of the resected thyroid gland, including (A) diffuse enlargement and (B) firm consistency and a nodular appearance.

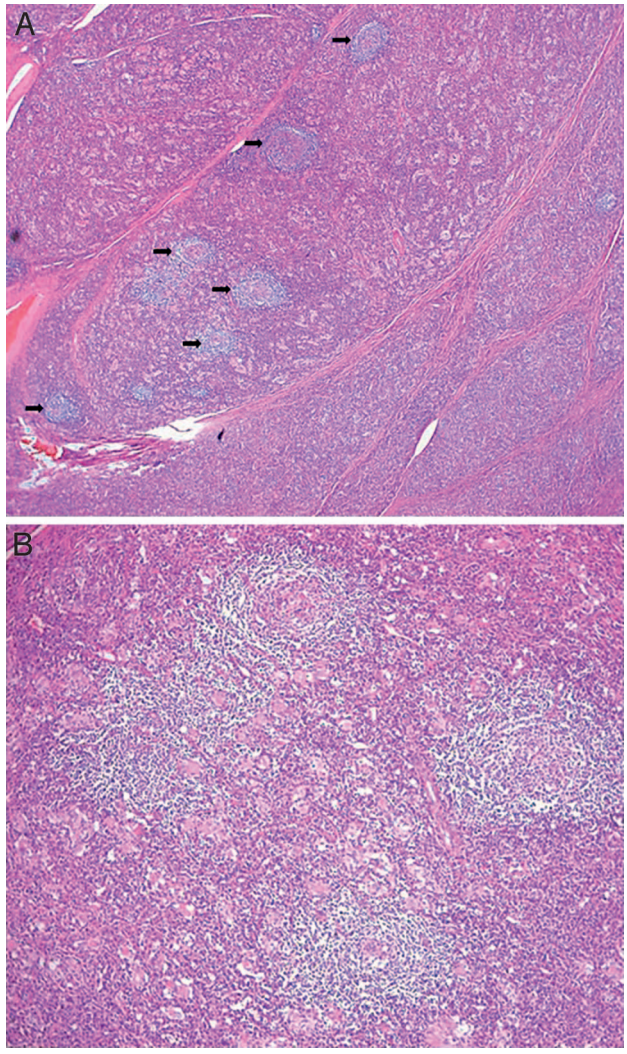


**Fig. 3** Histopathology of the resected thyroid. (A) Nodular pattern of growth with lymphoid follicles (arrow) and marked fibrosis (H&E; original magnification, ×20). (B) Medium power view, showing inflammatory infiltration with lymphoid follicles containing germinal centers and atrophic follicles (H&E; original magnification, ×100).

powered field (HPF), with these cells having an IgG4/IgG ratio over 40% (Fig. 4A and 4B). Based on these findings, the patient was diagnosed with IgG4-related HT. Two months after surgery, the patient has not experienced any symptoms or complications. Her thyroid function is controlled with levothyroxine 0.2 mg/d.

## Discussion

IgG4-related sclerosing disease is characterized pathologically by lymphoplasmacytic infiltration and sclerosis, as well as by infiltration by IgG4 plasma cells.[3] This condition was first observed in patients with autoimmune pancreatitis (AIP),[4] but was later observed in various other organs throughout the body.[5] IgG4-RD is now considered a systemic disease that may affect various organs and that is characterized by progressively growing fibroinflammatory lesions causing mass effects.[6] Since its first description,[2] IgG4-related thyroiditis has been considered a subtype of Hashimoto's thyroiditis.[7] Its clinicopathologic features are similar to those of the fibrous variant of HT and Riedel's thyroiditis (RT), suggesting that IgG4-related HT is a type of fibrous variant of HT and RT. However, fibrous variants of HT and RT do not exactly correspond to IgG4-related HT immunohistochemically.[5]

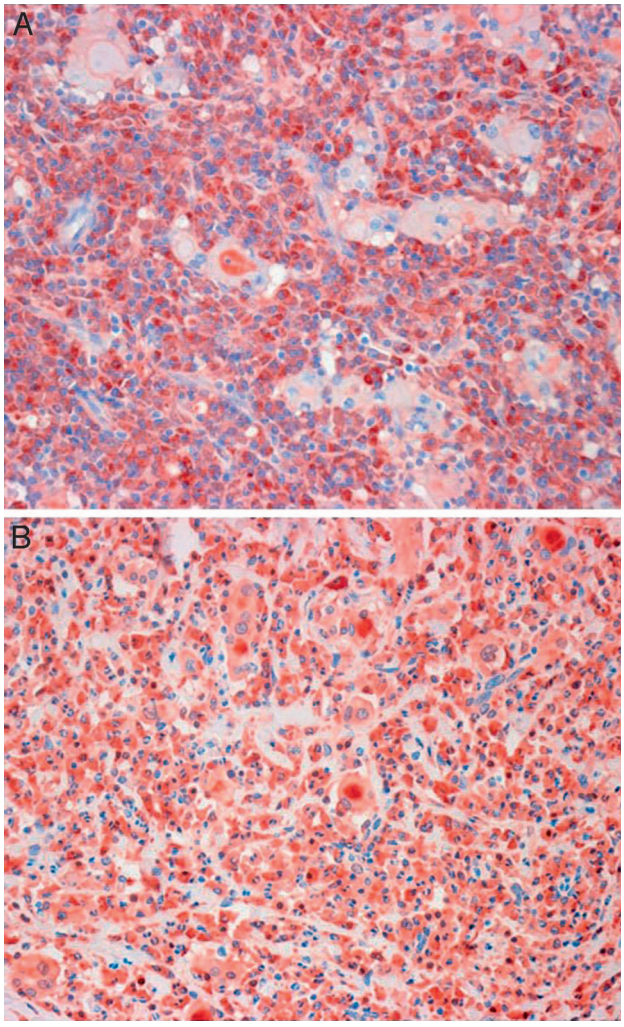


**Fig. 4** Immunohistochemistry of IgG and IgG4. (A) Numerous IgG-positive plasma cells were found (IgG immunostaining, ×400). (B) Increased ratio of IgG4-positive plasma cells, with >50 cells per high-power field and an IgG4/IgG ratio > 40% (IgG4 immunostaining, ×400).

Few studies have systematically assessed the clinical features of IgG4-related HT. Compared with conventional HT, however, IgG4-positive HT has been associated with younger age, a lower female-to-male ratio, rapid progression requiring surgery, more frequent subclinical hypothyroidism, and higher levels of thyroid autoantibodies.[8]

Although diagnostic criteria have been proposed for IgG related diseases, there is no universal consensus to date. Diagnostic criteria are based on the affected organ, histologic features such as dense lymphoplasmacytic infiltration, storiform-type fibrosis and obliterative phlebitis, and an increased number of IgG4-positive plasma cells. Patients with RT and the fibrous variant of HT show a greater degree of fibrotic changes immunohistochemically than patients with IgG4-associated HT, but no increase in the number of IgG4 positive plasma cells.[5] In a recent study, a diagnosis of IgG4-RD required >50 IgG4-positive cells/HPF and an IgG4-positive/IgG-positive ratio > 40%.[9] Organ-specific diagnostic criteria have been suggested for some IgG4-related diseases, but few criteria are known for IgG4-related thyroiditis since few such patients have been identified to date. Suggested diagnostic criteria for IgG4-related HT include >20 IgG4-positive plasma cells/HPF and an IgG4/IgG ratio > 30%.[2] On ultrasonography, patients with IgG4-related HT showed more diffuse low echogenicity than patients with conventional HT.[3] Patients who fit these diagnostic criteria should be suspected of having IgG4-related HT.[5]

Usually, HT is treated medically, but thyroidectomy is sometimes required, especially for patients who present with locally compressive symptoms, including pain, dyspnea, hoarseness, and dysphagia, and those with suspicious nodules suggesting carcinoma. As IgG4-related disease often shows good response to steroid therapy, IgG4-related HT may also show effective responses to steroid therapy.[10]

Awareness of those conditions may help physicians suspect IgG4-related HT, thus avoiding unnecessary operation. However, when initial symptoms recur after steroid therapy, surgical treatment is required to relieve the symptoms completely. The prognosis of patients with IgG4-related HT remains unknown, because of its recent identification and the few patients diagnosed with this condition.

This study had several limitations. For example, some important clinical and laboratory parameters, including serum IgG4 level, thyroid peroxidase concentrations, and the presence of antithyroglobulin antibodies, were not measured preoperatively. Because of the complexity of the surgery, IgG, IgG4 and antithyroid autoimmune antibody concentrations should be measured preoperatively in patients with severe HT. The histologic data, including lymphoplasmacytic infiltration and marked fibrosis, were similar to those in a previous study of IgG4-related HT, leading us to assay the removed thyroid immunohistochemically for expression of IgG and IgG4.

In conclusion, we report the first case of IgG4-related HT in a Korean woman with progressively growing enlargement of the anterior neck. The signs and symptoms of IgG4-related HT may be more severe than those of conventional HT. In addition,

IgG4-related HT had histologic features distinct from non-IgG4-related thyroiditis. A more comprehensive understanding of the IgG4-related HT may yield important information about HT and IgG4 related disease, and may help physicians to allow proper diagnosis and treatment.

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