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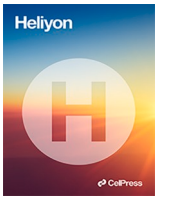

Case report

Immunoglobulin G4-related thyroiditis associated with Graves' disease: A case report

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ABSTRACT

We report a case of immunoglobulin (ig)-g4-related thyroiditis associated with graves' disease. a 45-year-old man was diagnosed with graves' disease due to asymptomatic enlarged thyroid gland and high serum levels of thyrotropin receptor antibodies and thyroid hormones. surgical resection of the thyroid gland was performed because of further thyroid gland enlargement and severe fluctuations in the thyroid hormonal levels, despite medical therapy with a combination of an antithyroid drug and a thyroid hormone preparation. macroscopic examination of the resected thyroid gland revealed a grayish-white diffuse swelling, and histopathological findings revealed follicular destruction, chronic inflammatory cell infiltration with diffuse igg4-positive plasma cells (IgG4/IgG >40%), storiform fibrosis, and phlebitis obliterans throughout the thyroid tissue. Additionally, there were small foci of high columnar follicular components with scalloping, resembling Graves' disease. We propose that all patients with Graves' disease should be evaluated for coexisting IgG4-related thyroiditis to detect ophthalmopathies as soon as possible.

1. Introduction

Immunoglobulin-G4-related thyroid disease (IgG4-RTD) is a condition that associates thyroid diseases with a spectrum of IgG4-related disease (IgG4-RD) that encompass Riedel's thyroiditis, Hashimoto's thyroiditis, and peculiar cases of Graves' disease [1]. Riedel's thyroiditis is commonly considered an IgG4-RTD, owing to its histopathological and immunohistochemistry for IgG4 findings [2,3]. Although >20 cases with histopathological findings of IgG4-RTD associated with Hashimoto's disease have been reported [4–7], little is known about the pathological findings of IgG4-RTD associated with Graves' disease. In this case report, we present a detailed macroscopic, histopathological, and immunohistochemical findings in a case of IgG4-thyroiditis associated with Graves' disease.

1.1. Case presentation

A 45-year-old man underwent a medical examination by his family doctor for an asymptomatic enlarged thyroid gland one year ago. He had no significant medical or family history; however, he smoked 20 cigarettes per day. Based on blood thyroid function test

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results, including thyroid-stimulating hormone (TSH) level of 0.004 μIU/mL, free triiodothyronine (fT3) of 10.04 pg/mL, and free thyroxine (fT4) of 2.17 ng/dL, the patient was diagnosed with Graves' disease. He was initially administered medical treatment with anti-thyroid drugs (thiamazole). Because the patient did not follow the doctor's instructions, his thyroid hormone levels repeatedly decreased and then increased with medical treatment. Therefore, we decided to start a thyroid hormone preparation (levothyroxine sodium hydrate) instead of reducing the dose of the thiamazole in a state of decreased thyroid function. However, further thyroid gland enlargement and severe fluctuations in thyroid hormonal levels were observed. He was referred to our hospital by his family for surgical evaluation.

On physical examination, his height was 168.8 cm, and weight was 59.7 kg (body mass index: 20.95 kg/m2). He had clear consciousness, diffusely enlarged thyroid gland, normal thoracoabdominal region, and no edema, finger tremors, or abnormal neurological findings. Additionally, there was no ophthalmopathy on examination and measurements.

Laboratory examination revealed no definite abnormalities in his blood count or biochemical parameters. Endocrine examination revealed thyrotropin receptor antibody level of >40 IU/L, fT3 level of 1.46 pg/mL, fT4 level of 0.19 ng/dL, and TSH level of 32.8 μIU/m L (table 1). The thyroid hormone levels were within normal range; however, TSH receptor antibody level was very high.

Neck ultrasonography revealed a diffusely enlarged thyroid gland with hypoechoic and heterogeneous internal echoes. Color Doppler ultrasonography revealed increased intraparenchymal blood flow and a flame-shaped appearance. Neck computed tomography showed a diffusely enlarged thyroid gland with internal uniformity and low absorption. The trachea was slightly stenosed due to compression by an enlarged thyroid gland. Preoperative imaging revealed that the size of the right lobe of the thyroid gland was 64.7 × 42.4 × 27.3 mm, and that of the left lobe was 67.6 × 39.4 × 32.1 mm. The shortest tracheal diameter at the point of compression by the thyroid gland was 13 mm. These findings indicated pressure from the goiter, but no dyspnea.

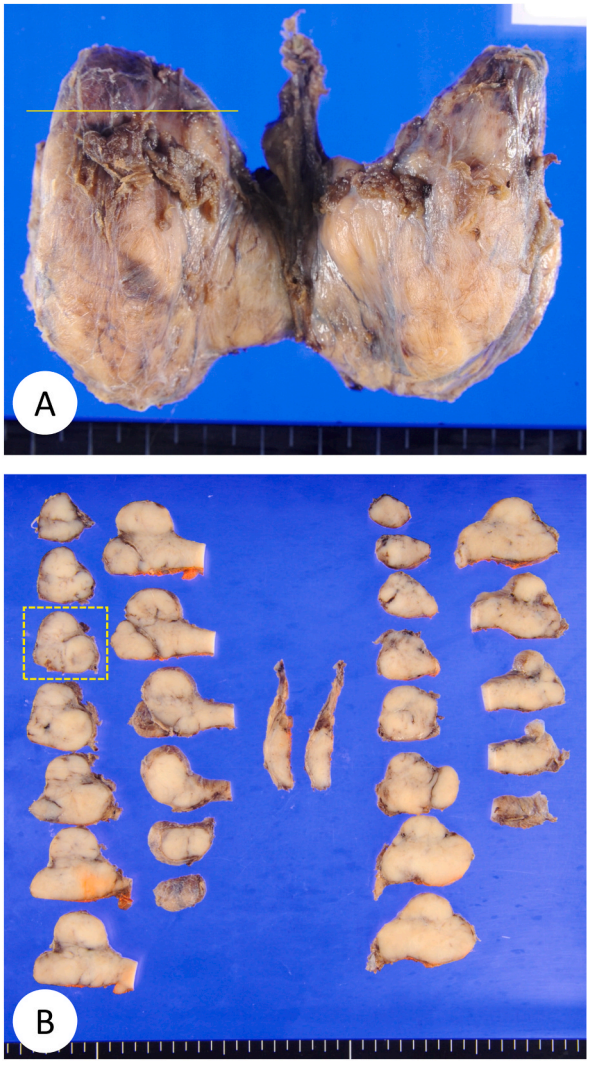

Fig. 1. A) Gross pathology showing a diffuse symmetric enlargement of the thyroid gland. B) The cut section showing a grayish-white elastic hard mass with lobulations.

Fifteen days after administration of potassium iodide (100 mg daily), the patient underwent total thyroidectomy. The resected thyroid tissue weighed 73 g. Gross examination revealed diffuse symmetric enlargement of the thyroid gland. A cut section showed a grayish-white, elastic, hard mass with lobulations (Fig. 1A and B). Histopathological examination of the thyroid gland specimen revealed severe stromal fibrosis and diffuse lymphoplasmacytic infiltration with proliferation of regenerative small follicles (Fig. 2A and B). Some thyroid follicles had tall columnar epithelia, and the colloids in the follicles showed a scalloped appearance (Fig. 2C). The fibroinflammatory process also extended slightly into the surrounding adipose tissue (Fig. 2D), and obstructive phlebitis was rare (Fig. 2E). Additionally, immunohistochemical staining showed positive thyroglobulin staining in the colloid and tall columnar epithelium of the thyroid follicles (Fig. 2C); however, there was negative staining in the regenerating small follicles (Fig. 2B). Immunohistochemical analysis revealed >400 IgG4-positive plasma cells per high-power field, with an IgG4/IgG ratio of >40% (Fig. 2B). Moreover, infiltrating lymphocytes were predominantly T cells, which were more commonly CD3-positive than CD20-positive B cells (Fig. 2B). In particular, CD4-positive T cells were slightly more predominant than CD8-positive T cells (Fig. 2B). No organs other than the thyroid gland were involved. This patient with Graves' disease was diagnosed with IgG4 thyroiditis. Serum IgG4 levels remained high on postoperative day 20. However, 52 days after the thyroidectomy, the serum IgG4 level decreased to normal reference range. Twelve months postoperatively, the patient remained well and had no neck wounds, phonation, or swallowing problems. Thyroid function tests showed a serum TSH level of 0.85 μIU/mL, fT3 of 3.22 pg/mL, and fT4 of 2.18 ng/dL, with oral levothyroxine sodium hydrate 135 μg/day.

2. Discussion

We report a case of IgG4-related thyroiditis associated with Graves' disease, which demonstrated unique pathological findings, including macroscopically diffused, swollen, hard nodules, with grayish-white lobes, histopathological fibrosis, and chronic inflammatory cell infiltration, mainly composed of plasma cells and phlebitis obliterans in almost the entire thyroid tissue. Majority of the residual thyroid follicular components showed destructive and regenerative changes due to chronic inflammation, whereas small foci of high columnar follicular epithelium and vacuoles were present at the margin of the colloid adjacent to the residual follicles, resembling Graves' disease. Immunohistochemical staining revealed diffuse IgG4-positive plasma cell infiltration and a high IgG4/IgG ratio (>40%). Thus, it seems likely that IgG4-related thyroiditis associated with Graves' disease leads to severe chronic inflammation

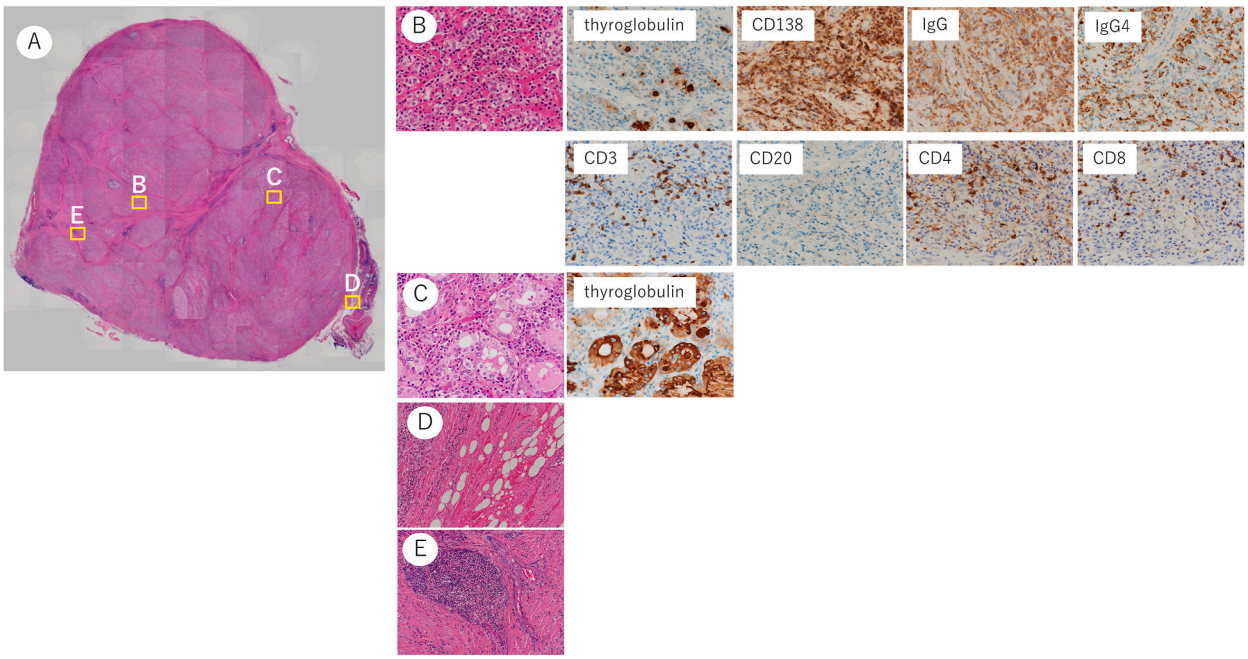

Fig. 2. Histological images. A) Loupe image (H & E) of the cut surface enclosed by the yellow dotted line in Fig. 1B. The boxes with solid outlines are shown microscopically in images B, C, D, and E, respectively. B) Severe stromal fibrosis and proliferation of regenerative small follicles (H & E; 400 ×); immunohistochemistry of thyroglobulin in severe stromal fibrosis area (400 ×); and immunohistochemistry of CD138 (400 ×). Plasma cells were CD138-positive; IgG-positive plasma cells were abundantly observed in the fibrous stroma (400 ×); immunostaining of IgG4 also showed marked infiltration of IgG4-positive plasma cells (400 ×); T lymphocytes were CD3-positive (400 ×); B lymphocytes were CD20-positive (400 ×); helper T lymphocytes, T regulatory cells, T follicular helper cells, and CD4-positive T cells with cytotoxic activity were CD4-positive (400 ×); cytotoxic T lymphocytes were CD8-positive (400 ×); C) tall columnar epithelia of the thyroid follicles and colloid with scalloped appearance (H & E; 400 ×); immunohistochemistry of thyroglobulin in tall columnar epithelia of the thyroid follicles (400 ×); D) severe stromal fibrosis slightly extending into surrounding adipose tissue (H & E; 200 ×); and E) obliterative phlebitis (Weigert + H & E; 200 ×). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

of the entire thyroid gland, along with small foci of Graves' disease-related lesions.

Riedel's thyroiditis is a thyroid disease characterized by a spectrum of IgG4-RD [1]. In general, IgG4-related thyroiditis associated with Reidel's thyroiditis clinically presents with compressive symptoms (dyspnea, hoarseness, and dysphagia) that cause suspicion of malignancy. This is in line with the histopathological findings of dense lymphoplasmacytic infiltration, a high content of IgG4-positive plasma cells, storiform fibrosis with extra-thyroid fibrosis, and obliterate phlebitis [8]. However, few studies have reported the histology of IgG4-RTD in Graves' disease [9]. In contrast, phlebitis obliterans, a characteristic feature of this disorder, was absent in a previous report [9]. In our case, although some macroscopic and histopathological findings were similar to those of IgG4-RTD associated with Riedel's thyroiditis, including obliterate phlebitis, the coexistence of regenerative follicular findings and hyperplastic follicles within the fibrosis area were specific features of IgG4-RTD associated with Graves' disease.

Concerning Graves' disease and serum IgG4 concentration, patients with high serum IgG4 levels are more likely to have ophthalmopathy than those with low levels [10]. In severe cases of ophthalmopathy, quality of life deteriorates, owing to visual dysfunction [11]; therefore, early treatment is required. Furthermore, there are few data to prove the relationship between IgG4-RTD in patients with Graves' disease and ophthalmopathy [9]. In this patient with Graves' disease, it was impossible to predict IgG4 -RTD preoperatively. The serum IgG4 level measured immediately after the surgery was high, which decreased during the postoperative course, suggesting that the serum IgG4 level may have been high before the surgery. If left untreated, ophthalmopathy can develop. It is difficult to predict IgG4-RD in Graves' disease. From the perspective of early detection of ophthalmopathy, it may be effective to measure IgG4 in all cases of Graves' disease.

2. 1. Limitations of the study

This case report has some limitations. First, no tests, such as serum IgG, IgG4, or immunohistochemical findings of the IgG4/IgG ratio, were performed before the surgery. Second, the exact effects of medical treatment are unknown because the patient rarely followed the doctors' instructions. Therefore, the Graves' disease became poorly controlled. Surgery was performed, and a histopathological image of the disease was observed. The histopathological finding that some thyroid follicles had tall columnar epithelia, and the colloids in the follicles showed a scalloped appearance may reflect the poorly controlled medical treatment status.

3. Conclusion

IgG4-RTD associated with Graves' disease is rare, and its diagnosis before surgery is difficult in patients with Graves' disease. Therefore, measuring IgG4 in all patients with Graves' disease might be useful in the early detection of ophthalmopathy.

Ethics approval and consent to participate

This study was approved by the Kitasato University Medical Ethics Committee (approval number: B20-338). Informed consent was obtained from the patient for publication of this case report, including the publication of all images, clinical data, and other data included in the manuscript.

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Data availability statement

Data used to support the findings of this study are available from the corresponding author upon request.

CRediT authorship contribution statement

Hiroyuki Takahashi: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Investigation, Data curation. **Sabine Kajita:** Project administration. **Hiroshi Katoh:** Validation, Supervision, Investigation, Data curation. **Toshihide Matsumoto:** Investigation. **Akemi Inoue:** Investigation. **Takafumi Sangai:** Supervision. **Makoto Saegusa:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no competing financial interests or personal relationships that may have influenced the work reported in this study.

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