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CASE REPORT

IgG4-Related Disease of the Thyroid Gland Requiring Emergent Total Thyroidectomy: A Case Report

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Abstract

IgG4-related disease of the thyroid gland is a recently recognized subtype of thyroiditis, often with rapid progression requiring surgical treatment. It is considered as a spectrum of disease varying from early IgG4-related Hashimoto's thyroiditis (HT) pattern to late fibrosing HT or Riedel's thyroiditis patterns. Here, we report a 47-year-old Malay woman presenting with progressively painless neck swelling over 3 years and subclinical hypothyroidism. Computed tomography (CT) scan revealed diffuse thyroid enlargement (up to 13 cm) with retrosternal extension and without regional lymphadenopathy. Fine needle aspiration of the thyroid showed a limited number of follicular epithelial cell groups with widespread Hurthle cell change and scanty background colloid, but no evidence of lymphocytosis. The cytologic features fell into the category of 'atypia of undetermined significance'. Subsequently, the patient developed hypercapnic respiratory failure secondary to extrinsic upper airway compression by the thyroid mass and underwent emergent total thyroidectomy. Histology of the thyroid showed diffuse dense lymphoplasmacytic infiltrate and fibrosis. Follicular cells exhibited reactive nuclear features and some Hurthle cell change. IgG4+ plasma cells were over 40/high power field while overall IgG4/IgG ratio was above 50%. The overall features suggest the diagnosis of IgG4-related disease of the thyroid gland in the form of IgG4-related HT. Post-surgery, the patient was found to have markedly elevated serum IgG4 concentration but PET/CT did not show significant increased fludeoxyglucose uptake in other areas. Her recovery was complicated by a ventilator-associated pneumonia with empyema, limiting early use of corticosteroids for treatment of IgG4-related disease.

Keywords Thyroid · IgG4-related disease · Hashimoto's thyroiditis · Emergent total thyroidectomy

Introduction

IgG4-related disease is a recently recognized fibroinflammatory condition characterized by tumefactive lesions at multiple sites, a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and, often but not always, elevated serum IgG4 concentrations [1]. It has now been described in virtually every organ system: the pancreatobiliary tree, salivary glands, periorbital tissues, kidneys, lungs, lymph nodes, meninges, aorta, breast, prostate, thyroid, pericardium, and skin [2].

IgG4-related disease of the thyroid gland is a similarly newly recognized entity with four postulated subcategories: IgG4-related Hashimoto's thyroiditis (HT), fibrosing variant of HT, Riedel's thyroiditis (RT) and Graves disease with elevated IgG4 levels [3]. Here, we report a rare case of IgG4-related disease of the thyroid gland requiring emergent total thyroidectomy.

Case Presentation

A 47-year-old Malay woman presented with progressive painless neck swelling over 3 years. Clinical examination revealed a diffusely enlarged thyroid that was non-tender and without any bruit. Pemberton's sign was negative. She was clinically euthyroid and noted to be overweight with a body mass index of 40.2. A thyroid function test revealed

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subclinical hypothyroidism, with a raised thyroid-stimulating hormone at 9.8 mU/L (reference range 0.65–3.7 mU/L), mildly decreased free thyroxine at 8.4 pmol/L (reference range 8.8–14.4 pmol/L) and normal triiodothyronine at 3.7 pmol/L (reference range 3.2–5.3 pmol/L). Computer tomography (CT) scan showed diffuse thyroid enlargement with retrosternal extension but there was no regional lymphadenopathy (Fig. 1). Fine needle aspiration (FNA) of the thyroid showed a limited number of well-visualized follicular cells, arranged in acini, solid groups and papillaroid clusters. There was widespread Hurthle cell change and scanty background colloid, but no clear evidence of lymphocytosis (Fig. 2). The cytologic features fell into the category of 'atypia of undetermined significance (AUS)'.

Subsequently, the patient developed hypercapnic respiratory failure secondary to extrinsic upper airway compression by the thyroid mass, contributed by obesity hypoventilation syndrome. She underwent emergent total thyroidectomy and bilateral tonsillectomy. The received thyroid specimen weighed 417 g, with a homogeneous tan-colored lobulated appearance without discrete nodules. Histology of the thyroid showed diffuse dense lymphoplasmacytic infiltrate and areas of fibrosis with fibrotic septae separating lobules of atrophied follicles with little residual colloid. Follicular cells exhibited reactive nuclear features and Hurthle cell change. Focally some vessels showed perivascular plasmacytic infiltrate. IgG4+ plasma cells were over 40/high power field while overall IgG4/IgG ratio was above 50% (Fig. 3).

Post-operatively, the patient was found to have markedly elevated serum IgG4 concentration (> 3.4 g/L, reference range 0.04–1.57 g/L), but positron emission tomography (PET)–CT did not show significant increased fludeoxyglucose uptake in other areas. Her recovery was complicated by a ventilator-associated pneumonia with empyema, limiting early use of corticosteroids for treatment of IgG4-related disease.

Discussion

In 2005, Komatsu et al. noted the association of hypothyroidism with positive thyroglobulin antibody in patients with autoimmune pancreatitis, shedding light on IgG4-related disease of the thyroid gland as a distinct entity [4]. So far, four subcategories have been proposed within this entity, including IgG4-related HT, fibrosing variant of HT, RT and Graves disease with elevated IgG4 levels. Both IgG4-related HT and fibrosing variant of HT are considered as organ-specific forms, while RT is considered as part of a systemic process.

In 2010, Li et al. found that a subset of HT (19/70, 27.1%) patients were IgG4-related, which was associated with a younger age group, lower female to male ratio, higher likelihood of subclinical hypothyroidism, higher levels of thyroid autoantibodies and diffuse low echogenicity on ultrasound, compared to non-IgG4-related HT [5]. Patients in this group had an elevated serum IgG4 level, which decreased significantly after thyroidectomy. In these cases, the thyroid is usually diffusely enlarged, without a dominant mass. Macroscopically, it is soft, with a non-adherent and easily-separated capsule. Histologically, there is classic organ-specific inflammation as in other IgG4-related disease, including fibrosis, lymphoplasmacytic infiltrate and increased IgG4+ plasma cells. Obliterative phlebitis, however, is not a common feature. Fibrosis is predominantly in an interfollicular pattern, accompanying small thyroid follicles, marked follicular cell degeneration and increased giant cell/histiocyte infiltrate [6].

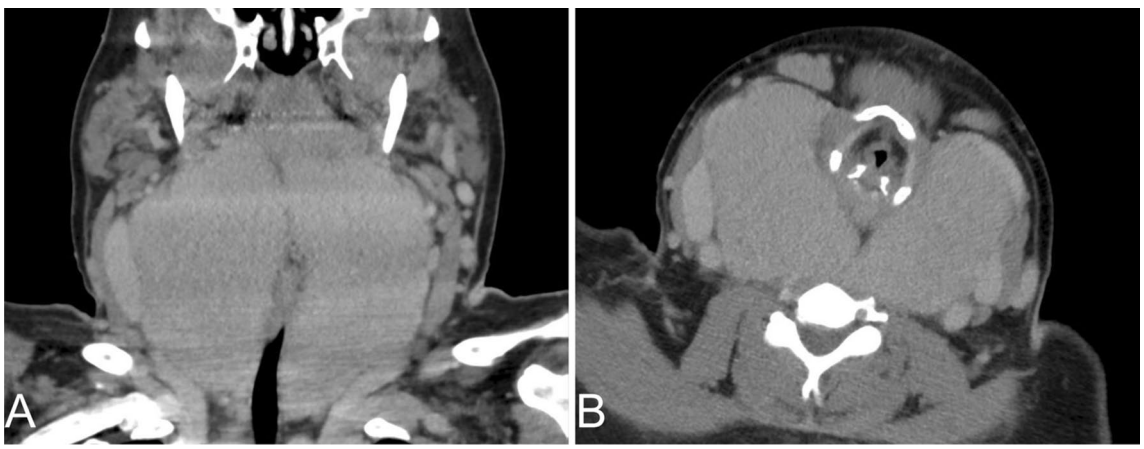

Fig. 1 Computed tomography scan showed homogenous and diffuse thyroid enlargement measuring 8.4 × 13.0 × 12.7 cm with retrosternal extension. It displaced the surrounding structures and compressed the trachea (**a** coronal plane, **b** transverse plane)

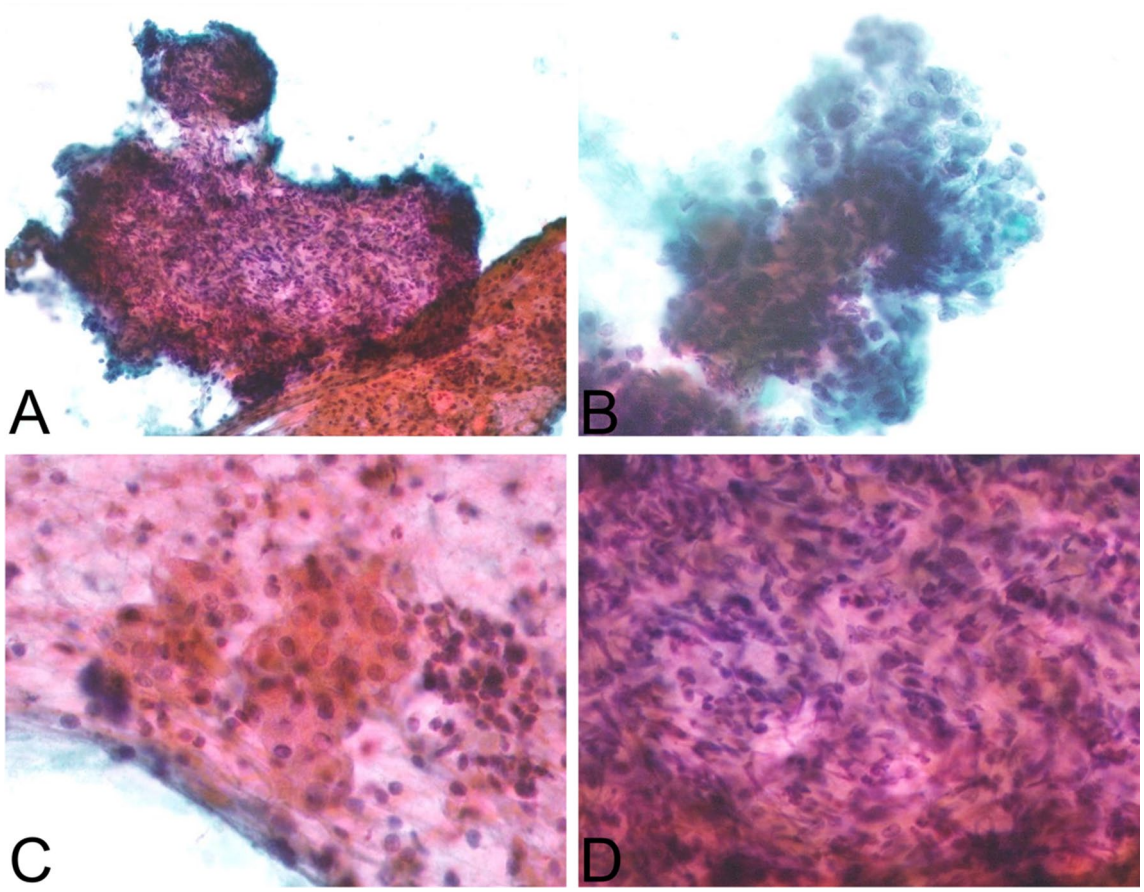

Fig. 2 FNA cytology of the thyroid showed an adequate but low yield of follicular epithelial cells, which were mostly obscured by blood clot (**a**, original magnification ×200). They were arranged in acini, solid groups and papillaroid clusters (**b**, ×400). There was widespread Hurthle cell change (**c**, ×400), without lymphocytosis. Admixed stromal spindle cells were noted (**d**, ×600)

Fibrosing variant of HT is seen in about 10% of patients with HT. A group of patients (9 cases) with fibrosing variant of HT were found to have a higher IgG4+ cell count and higher IgG4/IgG ratio [7]. Histologically, the thyroid has an exaggerated lobular pattern, with lobules separated by cellular storiform fibrosis. Similar to IgG4-related HT, the involvement of other organs does not seem to be a feature.

RT, which is extremely rare, is another candidate for IgG4-related disease of the thyroid gland, often as part of a systemic disease spectrum [8]. The patients are often clinically euthyroid at presentation [3]. Compared to IgG4-related HT, the thyroid in RT is often palpably very hard. In addition to the classic organ-specific inflammation, including obliterative phlebitis, there is also destructive inflammation extending beyond the thyroid to the surrounding tissue, creating an indistinctive dissecting plane intra-operatively. Hurthle cell change, often seen in both IgG4-related HT and fibrosing variant of HT, is not a usual feature of RT. Elevated serum IgG4 levels do not appear to be a feature of RT, although data is somewhat limited, given the limited number of studies focusing on the subject, as well as the number of patients investigated [8–10].

Recently, a small subset of patients (7/109, 6.4%) with Graves disease were found to have elevated serum IgG4 levels and elevated ratios of IgG4/IgG [11]. Further research into this particular area will be useful in clarifying the exact connection, if any, between IgG4 and Graves disease, as well as the histologic changes and other parameters that may or may not be distinct from other forms of IgG4-related thyroid disease.

Although the above four are described as separate diseases, overlap among them has been observed [3] and it has been suggested that they are all part of a spectrum of IgG4-related thyroid disease, with IgG4-related HT as the early phase at one end, with fibrosing variant of HT and RT as the later stage of the disease at the other end [12]. The diagnosis of IgG4-related disease of the thyroid gland requires typical histologic features with clinical correlation, although 30% of patients with IgG4-related disease have normal serum IgG4 concentrations [2]. There is no consensus yet on the IgG4 cut off value in the affected thyroid tissue. One study

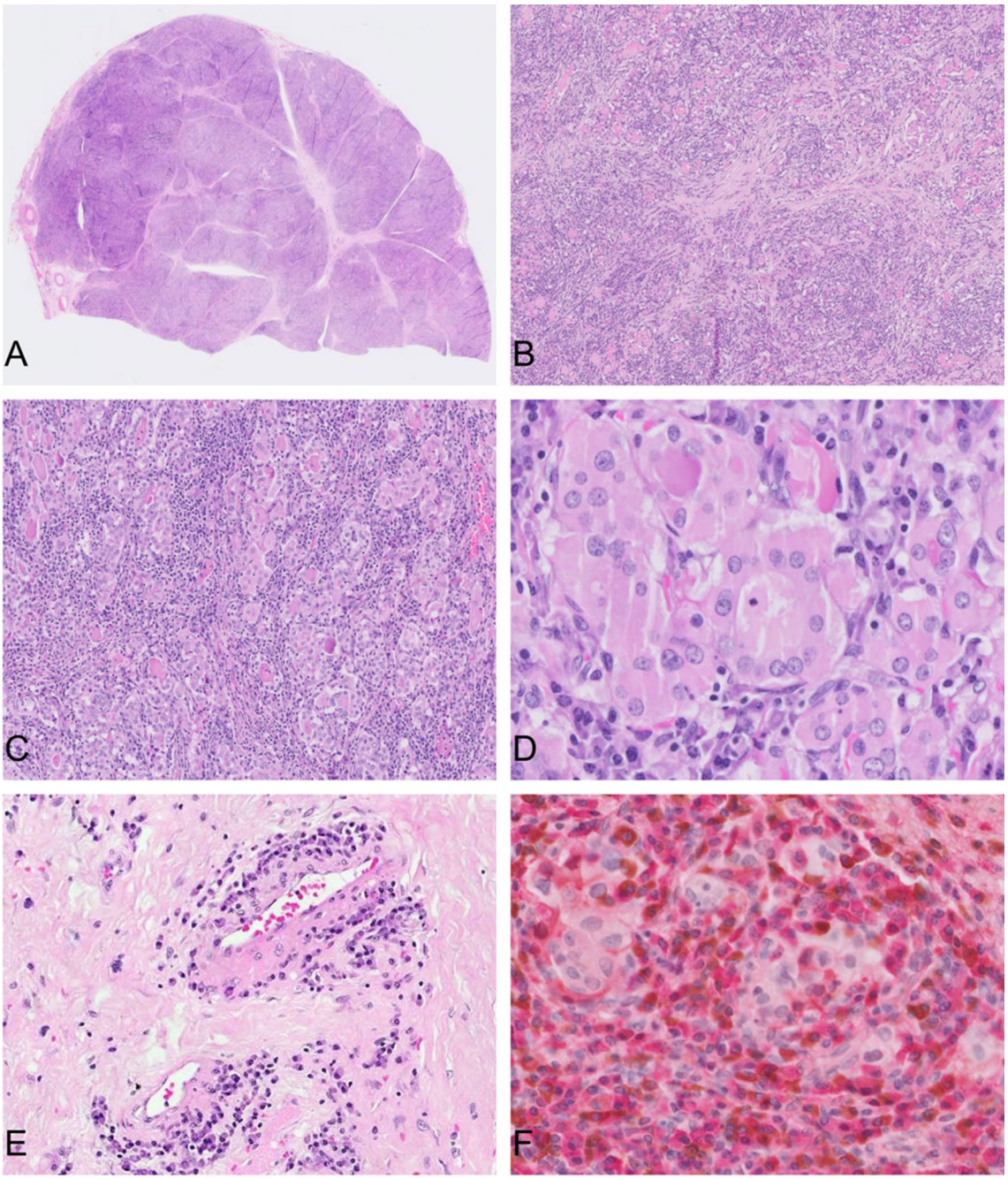

Fig. 3 Histology of the thyroid showed a multi-lobulated appearance with separating fibrous septae (**a**, original magnification ×2.5). Focal storiform fibrosis (**b**, ×50), diffuse dense lymphoplasmacytic infiltrate (**c**, ×100) with Hurthle cell change of follicular cells (**d**, ×400) were demonstrated. Focal vessels showed perivascular plasmacytic infiltrate (**e**, ×200). IgG4+ plasma cells were over 40/high power field and an overall IgG4/IgG ratio was above 50% (**f**, ×400: IgG in red, IgG4 in brown)

of 28 patients with IgG4-related HT reported over 20 IgG4+ plasma cells per high power field and over 30% IgG4/IgG ratio [12].

Interestingly, another rare but distinct pattern of IgG4-related disease of the thyroid gland has been reported, namely IgG4-related mass-forming thyroiditis [13], whereby the fibrotic changes are localized into an enlarged mass-forming focus that is histologically distinct from the background thyroid tissue. Thyroid carcinoma would be a potential diagnostic pitfall, especially with the concurrent regional lymphadenopathy that was noted in the reported case [13]; by contrast, our patient presented with a diffusely enlarged thyroid and no regional lymphadenopathy. That is not to say that neoplasia could not be a consideration in

other forms of IgG4-related thyroid disease, as in our own case where the extensive fibrosis and Hurthle cell change contributed to low-colloid, Hurthle cell-rich findings on the FNA, making Hurthle cell neoplasm a potential differential and resulting in AUS as the final diagnosis.

In terms of subtyping our patient's IgG4 disease, our patient presented with a diffusely enlarged thyroid and subclinical hypothyroidism, though unfortunately, a thyroid autoantibody test was not done. The thyroid gland had a grossly distinctive capsule, and microscopically limited changes confined within the thyroid gland, making RT less likely. The presence of extensive Hurthle cell change is also in favour of HT over RT. The storiform and relatively acellular fibrosis points toward IgG4-related HT, rather than the fibrosing variant. Therefore, the overall features suggest the diagnosis of IgG4-related disease of the thyroid gland in the form of IgG4-related HT. Normally, an FNA result of AUS would have prompted the recommended management of a repeat FNA within the appropriate clinical interval [14, 15], but in this case, the clinical status of the patient necessitated emergent surgical excision due to airway compromise. Post-operatively, the patient had persistent elevated serum IgG4 level, but PET–CT scan did not identify any systemic involvement of IgG4-related disease in other organs. In this situation, the distinction between organ-specific and systemic manifestation of IgG4-related disease is not clear.

In conclusion, IgG4-related disease of the thyroid gland is a spectrum of disease varying from early IgG4-related HT pattern to late fibrosing HT or RT patterns. The diagnosis is based on the combination of clinical findings, serology and histology, while histology currently remains the gold standard. As with other organ-specific IgG4-related diseases, steroids are a potential treatment option, and surgical debulking is carried out according to clinical necessity, such as with airway obstruction [3]. Better recognition of this entity facilitates prompt and appropriate treatment for the patient.

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