Proposal of diagnostic criteria for IgG4-related thyroid disease

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Abstract. Patients with IgG4-related disease (IgG4-RD) are diagnosed in Japan by comprehensive or organ-specific diagnostic criteria. To date, organ-specific criteria have been established for several organs, but not for the thyroid. We attempted to establish diagnostic criteria for IgG4-related thyroid disease (IgG4-RTD) based on IgG4-RD research by The Research Program on Intractable Diseases from the Ministry of Health, Labour and Welfare of Japan. These criteria have been publicly reported to members of both the Japan Endocrine Society and the Japan Thyroid Association. Thyroid diseases associated with IgG4 include Hashimoto’s thyroiditis, Graves’ disease and Riedel’s thyroiditis. As a comprehensive definition that includes both systematic and organ-specific forms, we use the broad term ‘IgG4-related thyroid disease’. Diagnostic criteria for IgG4-RTD comprise the following five items: I) enlargement of the thyroid, II) hypoechoic lesions in the thyroid by ultrasonography, III) elevated serum IgG4 levels, IV) histopathological findings in the thyroid lesion (IgG4+ plasma cells >20/HPF and IgG4+/IgG+ plasma cell ratio >30%) and V) involvement of other organs. “Definitive” diagnosis of IgG4-RTD is made when I, II, III, IV and V are all fulfilled, while “probable” diagnosis of IgG4-RTD is when I, II, and IV or V are fulfilled. Patients who fulfill I, II and III criteria are considered as “possible” IgG4-RTD. We believe that the proposed diagnostic criteria contribute to more accurate diagnosis of IgG4-RTD as well as exclusion of mimicry. Furthermore, they may lead to better understanding of the clinical implications and underlying pathogenesis of IgG4-RTD.

Key words: IgG4-related thyroid disease, IgG4 thyroiditis, Hashimoto’s thyroiditis, Riedel’s thyroiditis, Grave’s disease

Introduction

IgG4-related disease (IgG4-RD) was first reported as a subtype of autoimmune pancreatitis with elevated serum IgG4 levels [1, 2]. It is characterized by mass-forming lesions within multiple organs including the pancreas, salivary gland, lacrimal gland, pituitary, thyroid, lung, kidney, bile duct, aorta, and peritoneum [3]. Multiple organs are usually involved, but there may be significant numbers of cases with only single organ involvement [4]. This disease typically affects middle-aged to elderly men. In Japan, the estimated prevalence is reportedly 6 cases per 100,000 people [5]. Most reported cases have been from Asian countries, but race-dependent prevalence has not been described [6].

Diagnosis of IgG4-RD in Japan is made based on either comprehensive or organ-specific diagnostic criteria proposed by an IgG4-RD research group [3, 7-9]. Definitive diagnosis of IgG4-RD is made when any of the criteria are fulfilled. Items included in the criteria are masses within or swelling of organs, elevation of serum IgG4 levels and histopathological findings. Serum IgG4 levels can be elevated in various conditions and diseases, such as infection, allergy, malignancy, autoimmune disease and Castleman disease [3]; its elevation should therefore be carefully interpreted despite it being an important clue for diagnosis of IgG4-RD [10, 11]. Where possible, histological confirmation is recommended for
diagnosis, in combination with biochemistry and imaging studies. Highly sensitive and specific classification criteria for IgG4-RD were recently proposed by Wallace et al. [12].

Regarding the association between IgG4-RD and thyroid disease, Watanabe et al. reported that patients with IgG4-RD were highly positive for anti-thyroid antibodies and were predisposed to hypothyroidism [13]. One of their patients with hypothyroidism was shown to have improved thyroid function after steroid therapy. IgG4-rich inflammation has been reported in three inflammatory thyroid diseases (Hashimoto’s thyroiditis, Graves’ disease, and Riedel’s thyroiditis) with either systemic or organ-specific manifestations [14]. These thyroid diseases associated with IgG4+ plasma cell-rich inflammation could share common underlying conditions with IgG4-RD, although the spectrum of IgG4-related thyroid disease (IgG4-RTD) is still under discussion. To clarify the underlying pathogenesis and clinical implications, it is important to accumulate cases based on the unified diagnostic criteria for IgG4-RTD that broadly cover these thyroid diseases.

Three Thyroid Diseases with Conditions that Overlap with IgG4-related Disease

Thyroid diseases associated with increased number of IgG4+ plasma cells in the thyroid lesions are thought to include Hashimoto’s thyroiditis, Graves’ disease and Riedel’s thyroiditis (Fig. 1). We summarized the differences and common features between these diseases based on published reports.

**IgG4 and Hashimoto’s thyroiditis**

Li et al. first reported IgG4-rich inflammation in the thyroid gland as a novel subset of Hashimoto’s thyroiditis, exhibiting pathological features indistinguishable from IgG4-RD [15]. They proposed organ-specific diagnostic criteria of IgG4 thyroiditis that slightly differed from the comprehensive diagnostic criteria for IgG4-RD. The histopathological features of 120 patients with Hashimoto’s thyroiditis were recently reevaluated and the cut-off values of infiltrated IgG4+ plasma cells were validated to diagnose IgG4 thyroiditis. Thyroid-specific cut-off values (IgG4+ plasma cells >20/HPF and IgG4+/IgG+ plasma cell ratio >30%) were thought to better identify early phase of IgG4 thyroiditis than by adapting the cut-off values in comprehensive diagnostic criteria [16]. Patients with IgG4 thyroiditis are predominantly male, are susceptible to becoming hypothyroid with higher titers in anti-thyroid antibodies (TgAb), and are characterized by a hypoechoic area in the thyroid by ultrasonography [17]. Serum IgG4 levels are markedly decreased after thyroidectomy, implying that serum IgG4 originates from the enlarged thyroid [18].

Several candidate antigens have been suggested as corresponding antigens for IgG4 antibodies in IgG4-RD [19-21]. When focusing on the subtypes of antibodies associated with autoimmune thyroid disease, antithyroglobulin antibody is IgG4 dominant [22]. Sera from patients with IgG4 thyroiditis were analyzed by Inomata et al., who showed that thyroglobulin was one of the candidate antigens for IgG4 antibody [23].

Takeshima et al. prospectively evaluated serum IgG4 levels in 149 patients with Hashimoto’s thyroiditis and six of their patients (4.0%) had elevated serum IgG4 levels above 135 mg/dL, the cut-off value employed in the comprehensive diagnostic criteria [24]. The patients with elevated serum IgG4 levels were older and exhibited enlarged hypoechoic areas in the thyroid gland by ultrasonography. Two patients had swelling in the salivary and pituitary glands, typical of systemic lesions observed in patients with IgG4-RD. Hashimoto’s thyroiditis with elevated serum IgG4 levels is therefore suspected to include IgG4-RD and IgG4 thyroiditis [24, 25].

Patients with autoimmune pancreatitis were reported to be highly positive for anti-thyroglobulin antibodies and susceptible to hypothyroidism [26]. An investigation of 114 patients with IgG4-RD reported that 19% of patients had hypothyroidism and some had improved thyroid function by steroid therapy [13]. Neither Riedel’s thyroiditis nor Graves’ disease were found in the patient series reported by Watanabe [13] or in the series of patients with IgG4-RD reported by Ceresini [27].

**IgG4 and Riedel’s thyroiditis**

Riedel’s thyroiditis was first reported by Riedel in 1896 as a hard infiltrative lesion in the thyroid gland.
IgG4-related thyroid disease

[28]. It is a rare disease with a reported prevalence of between 0.06% and 0.3% in surgical series [29]. Most symptoms are due to local compression by thyroid lesions, but systemic organs can be involved [30, 31]. Steroids, tamoxifen, and rituximab are effective treatment options for Riedel’s thyroiditis [32, 33]. The pathological features are characterized by severe fibrosis with extension into surrounding tissues, inflammatory cell infiltrates, destruction of the thyroid follicles, and obliterator phlebitis. Infiltration of IgG4+ plasma cells has been reported, suggesting an association with IgG4-RTD [31, 34].

Takeshima et al. performed a literature search of electronic databases between 1988 and 2012 using the keywords “Riedel” and “Riedel’s thyroiditis,” and identified 10 Japanese patients with pathologically diagnosed Riedel’s thyroiditis [35]. Immunohistochemistry revealed infiltration of IgG4+ plasma cells in two patients, but they did not fulfill either the comprehensive or thyroid-specific diagnostic criteria. One patient had a retroperitoneal fibrosis that improved dramatically by steroid therapy. Takeshima’s study also showed that clinicopathological features of Riedel’s thyroiditis were similar to those of IgG4-RTD.

Serum IgG4 levels had been evaluated in only four patients with Riedel’s thyroiditis; none of the patients had elevated serum IgG4 levels [30, 31, 34, 35]. A greater number of patients are needed, however, to calculate the ratio of patients with elevated serum IgG4 levels in Riedel’s thyroiditis.

Anti-thyroid antibodies are reported to be frequently positive in Riedel’s thyroiditis [30, 31, 34]. In the literature, three patients with Riedel’s thyroiditis had infiltration of IgG4+ plasma cells in the thyroid and were analyzed for antibodies. One was positive for TgAb [34, 35]. TgAb is one of the candidates for IgG4 antibodies in Riedel’s thyroiditis, but there is currently insufficient evidence.

IgG4 and Graves’ disease

Takeshima et al. prospectively measured serum IgG4 levels in 109 patients with Graves’ disease and 6.4% of them were above 135 mg/dL [36]. A similar percentage was also found in another group [37]. Patients with elevated serum IgG4 levels were older and had a lower echoic area in the thyroid by ultrasonography [36]. Seven patients with elevated serum IgG4 levels were treated with low dose of anti-thyroid drugs (ATDs) for controlling their thyroid functions and two patients became hypothyroid, suggesting good responses to ATDs. The clinical course was similar to that in a previous case report by Nishihara et al. [38]. No patients underwent thyroidectomy or had extra-thyroid lesions associated with IgG4-RTD.

According to a pathological analysis of 1484 thyroidectomized patients with Graves’ disease, 0.3% of them showed infiltration of IgG4+ plasma cells in the thyroid [39]. Two patients had elevated serum IgG4 levels, although not all patients had their levels measured.

Candidates for IgG4 antibodies are TgAb, TSH receptor autoantibody (TRAb), and thyroid stimulating antibody (TSAb) in Graves’ disease. TgAb is IgG4 dominant, which is frequently positive in patients with Graves’ disease. The presence of IgG4 subclass in TRAb has also been reported [40]. TSAb has also been reported as one of the candidates for IgG4 fraction in patients with Graves’ disease with elevated serum IgG4 levels [36].

Diagnostic Criteria for IgG4-related Thyroid Disease (Table 1)

We attempted to create diagnostic criteria for IgG4-RTD based on the IgG4-RTD research by The Research Program on Intractable Diseases from the Ministry of Health, Labour and Welfare of Japan, which aims at the establishment of diagnostic criteria and guidelines for IgG4-RTD [41]. As mentioned previously, thyroid diseases associated with IgG4 include autoimmune thyroid diseases and Riedel’s thyroiditis. Whether these diseases share common pathogenesis remains unclear. To clarify the underlying pathogenesis, we considered it important to avoid missing the true IgG4-RTD of either systemic or organ-specific forms. We therefore broadly defined IgG4-RTD to cover all of the diseases, and created a set of specific diagnostic criteria. Criteria were then reported publicly to members of Japan Thyroid Association and Japan Endocrine Society, and then were revised as necessary.

Diagnostic criteria for IgG4-RTD (Table 1) are comprised of the following five items: I) enlargement of the thyroid, II) hypoechoic lesions in the thyroid by ultrasonography, III) elevated serum IgG4 levels, IV) histopathological findings in the thyroid lesion (IgG4+ plasma cells >20/HPF and IgG4+/IgG+ plasma cell ratio >30%) and V) involvement of other organs. IgG4-RTD is considered definitive when items I to IV are fulfilled based on the comprehensive diagnostic criteria for IgG4-RTD. Some patients with IgG4 thyroiditis and Riedel’s thyroiditis, such as those with IgG4-RTD involving other organs, had been reported to have no elevation in serum IgG4 levels [31, 33, 35]. Histopathological findings are the most important items to demonstrate the infiltration of IgG4+ plasma cells and to exclude malignancy and other mimics, so organ-specific or systemic forms of IgG4-RTD are probable when items I, II and IV or V are
fulfilled. Patients who have autoimmune thyroiditis with elevated serum IgG4 levels and characteristic features by ultrasonography without histopathological findings are considered to have possible IgG4-RTD because serum IgG4 levels can be elevated in various pathological conditions.

Organ-specific histopathological criteria reportedly improve accuracy because histopathological findings vary depending on the organ in IgG4-RD [42]. In the present criteria for IgG4-RTD, we adapted thyroid-specific diagnostic criteria for IgG4 thyroiditis (IgG4+ plasma cells >20/HPF and IgG4+/IgG+ plasma cell ratio >30%) to the histopathological findings in the thyroid [16]; however, future evaluation is needed to clarify whether or not the criteria is appropriate for the diagnosis of IgG4-RTD.

We outlined a concept of IgG4-RTD and the differential diagnosis of diseases or conditions that elevate serum IgG4 levels or cause infiltration of IgG4+ plasma cells (Table 1, notes) and detailed ultrasonographic features of the thyroid.

Conclusions

We proposed diagnostic criteria for IgG4-RTD. Accumulation of cases based on these unified diagnostic criteria will contribute to clarification of the common underlying pathogenesis and the clinical implications of IgG4-RTD.

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Disclosure

The authors declare that they have no conflicts of interest.

Table 1 Diagnostic criteria for IgG4-related thyroid disease

| Diagnostic criteria |
|---------------------|
| I. Enlargement of the thyroid |
| II. Hypoechoic lesions in the thyroid by ultrasonography |
| III. Elevated serum IgG4 levels (≥135 mg/dL) |
| IV. Histopathological findings in the thyroid lesion: prominent infiltration of lymphocytes and plasma cells with severe fibrosis in the thyroid (IgG4+ plasma cells >20/HPF and IgG4+/IgG+ plasma cell ratio >30%) |
| V. Involvement of other organs: prominent infiltration of lymphocytes and plasma cells with severe fibrosis in other organs (IgG4+ plasma cells >10/HPF and IgG4+/IgG+ plasma cell ratio >40%) |

Diagnosis

- **Definite**: I + II + III + IV
- **Probable**: (I + II + IV) or (I + II + V)
- **Possible**: I + II + III

Notes

- IgG4-related thyroid disease includes IgG4 thyroiditis, Riedel’s thyroiditis, and thyroid disease associated with IgG4-related disease. Overlapping of these diseases is speculated.
- Differential diagnosis of the following diseases or conditions that elevate serum IgG4 levels or cause infiltration of IgG4+ plasma cells are needed: an infection, allergic disease, malignant disease, and autoimmune disease.
- Ultrasonographic features of the thyroid are characterized by severe hypoechoic or anechoic area in IgG4-related thyroid disease.

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