DIAGNOSIS OF ENDOCRINE DISEASE

IgG4-related thyroid autoimmune disease

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Abstract

IgG4-related disease (IgG4-RD) is fibro-inflammatory, immune-mediated, systemic disease recognized as a defined clinical condition only in 2001. The prevalence of IgG4-RD is 6/100 000, but it is likely to be underestimated due to insufficient awareness of the disease. The diagnostic approach is complex because of the heterogeneity of clinical presentation and because of rather variable diagnostic criteria. Indeed, high concentrations of IgG4 in tissue and serum are not a reliable diagnostic marker. The spectrum of IgG4-RD also includes well-known thyroid diseases including Riedel's thyroiditis, Hashimoto's thyroiditis and its fibrotic variant, Graves' disease and Graves' orbitopathy. Results from clinical studies indicate that a small subset of patients with the above-mentioned thyroid conditions present some features suggestive for IgG4-RD. However, according to more recent views, the use of the term thyroid disease with an elevation of IgG4 rather than IgG4-related thyroid diseases would appear more appropriate. Nevertheless, the occurrence of high IgG4 levels in patients with thyroid disease is relevant due to peculiarities of their clinical course.

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Introduction

IgG4-related disease (IgG4-RD) is a fibro-inflammatory, immune-mediated, systemic disease, firstly recognized in 2001, when Hamano *et al.* reported high serum levels of IgG4 in patients with type 1 autoimmune pancreatitis (AIP1) (1). In 2003, Kamisawa *et al.* reported that, in patients with AIP, extra-pancreatic organs could also be involved (2). Since this first description, the condition has been reported to occur in nearly every organ. In particular, several diseases, previously regarded as confined to a single

organ, such as Mikulicz disease, retroperitoneal fibrosis, Küttner tumor and Riedel thyroiditis are now considered as the expression of the same disease in different organs. In 2012, a consensus guideline proposed the name 'IgG4-RD' to unify these apparently heterogeneous conditions into a definite clinical spectrum (3). The present review is aimed at providing an overview of the current knowledge about the role of IgG4 in a wide spectrum of thyroid diseases including, Hashimoto's thyroiditis (HT) and

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its fibrotic variant, Riedel's thyroiditis (RT) and Graves' disease (GD). In particular, diagnostic criteria and peculiar clinical characteristics of the above cited conditions in the presence of IgG4 will be discussed.

Epidemiology

IgG4 RD typically affects middle-aged to elderly men, with an estimated prevalence, according to Japanese studies of 6/100 000. However, recent views suggest that this prevalence is likely to be underestimated due to insufficient awareness and/or delayed diagnosis of this rather novel clinical entity (4). The disease shows a world-spread diffusion, even if nearly 75% of reported patients are from Japan. A surprising, although well-established finding, is the overall male predominance which would contrast with the typical female predominance of all other autoimmune diseases (4).

Pathophysiology of IgG4

In healthy subjects, IgG4 is the least represented subclass of IgGs accounting for less than 5% of total IgG (5). Despite the name, IgG4 seems to play a minor role in the pathogenesis of IgG4-RD. IgG4 antibodies are generally considered anti-inflammatory rather than pro-inflammatory antibodies owing to their unique structural and functional features. Indeed, the Fc portion displays low affinity for Fc receptors and for C1q. In addition, the disulfide bonds between the heavy chains of the IgG4 molecule are rather unstable, allowing re-association with similarly split IgG4 molecules with different antigen specificity (Fig. 1). This process is commonly referred to as 'Fab-arm exchange' – the final result being newly formed IgG4 molecules functionally bispecific, and thus, incapable of crosslinking antigen, which eventually prevents the formation of immune complexes (5).

Most recent views support the concept that an elevation of IgG4 levels should be regarded as an attempt to dampen inflammation mediated by a given antigen. CD4 cytotoxic T cells (CD4 CTLs), T follicular helper 2 (Tfh₂), B cells and other cells of their lineage, particularly plasmablasts, play an important role in IgG4-RD. As briefly reported in Fig. 2, Tfh₂ cells, through the secretion of IL-4, play a major role in class switching toward IgG4; B cells and plasmablasts present antigens to CD4+ T cells which, in turn, promote fibrosis through

Figure 1

Schematic representation of the formation of the Fab-arm exchange. The resulting asymmetric, bispecific antibody IgG4 acts as a monovalent antibody.

secretion of several cytokines including interleukin-1b, interferon- γ and tumor growth factor β (6).

Clinical aspects

IgG4-RD usually presents with tumefactive lesions and a subacute onset that may mimic malignant diseases. Clinical features are clearly dependent upon the specific organ involved, and subsequent organ failure stems from chronic autoimmune inflammation. Patients with IgG4-RD may have synchronous or meta-chronous lesions

Figure 2

The role of CD4⁺ CTLs, T cells and plasmablasts in the pathogenesis of the IgG4-RD. CD4 CTL, CD4 cytotoxic T cell; IL-4, interleukin 4; IL-1β, interleukin 1β; IFNγ, interferon γ; Tfh₂, T follicular helper 2; TGF-β1, tumor growth factor β1.

in several organs, even if single organ involvement has been reported (7).

Diagnosis

The diagnosis of IgG4-RD relies on the histopathological picture of the organ tissues involved. The four key histologic features of IgG-RD are 1) dense lymphoplasmacytic infiltrates; 2) fibrosis with a storiform pattern; 3) obliterative phlebitis and 4) eosinophilic infiltration (5). However, these peculiar features may be variably present according to the specific organ involved, duration of the disease and concomitant therapies with particular regard to glucocorticoids (7). To further complicate the issue, it should be emphasized that high levels of IgG4 in the serum could not be sufficient for diagnosing an IgG4-RD since an elevation of IgG4 may occur in patients harboring pathologic conditions other than IgG4-RD (8). Furthermore, significant infiltrates fulfilling the IgG4 typical criteria have been found in several inflammatory, infectious and malignant conditions (including thyroid cancer) other than IgG4-RD (8).

Therapy

Glucocorticoids currently represent the first-line therapy for IgG4-RD. Azathioprine, mycophenolate mofetil and methotrexate are commonly used as glucocorticoid-

sparing agents and/or to maintain remission after glucocorticoid administration (9). In case of recurrent or refractory disease, B-cell depletion with rituximab can also be considered. Generally, the presence of extensive fibrosis represents the major cause of current therapies' failure (9).

IgG4-thyroid diseases

The link between thyroid diseases and IgG4-RD was initially suggested, based on the epidemiologic consideration that the thyroid is the most commonly affected organ by autoimmune diseases (10) and by the observation that hypothyroidism is highly prevalent in patients with autoimmune pancreatitis (11). Indeed, as much as 25% of patients presenting with AIP1 are hypothyroid and have positive tests for circulating thyroid autoantibodies (Tg Ab and TPO Ab) (12).

Moving from these observations, a novel line of research started in Japan, aimed at relating thyroid diseases with the spectrum of IgG4RD. Nowadays, we know that IgG4-thyroid diseases can encompass some cases of chronic autoimmune thyroiditis (HT), the fibrotic variant of this disease, RT and peculiar cases of GD.

Hashimoto's thyroiditis

In 2009 Li *et al.* (13), based upon the immunostaining pattern for IgG4 on surgical thyroid specimens, demonstrated that HT could be sub-classified in IgG4 thyroiditis and non-IgG4 thyroiditis. While the typical changes of HT, which include formation of lymphoid follicles and oxyphilic changes of follicular epithelium were present in both groups of patients, the ones with IgG4 thyroiditis typically showed a histologic picture of severe lymphoplasmacytic infiltration, dense fibrosis and marked follicular cell degeneration (13). Based upon some histological similarities between IgG4 thyroiditis and IgG4-RD of the other organs (elevated serum IgG4, autoimmune mediated, mass-forming fibrosis with increased IgG4-positive plasma cells, subsequent organ failure), a relationship between IgG4 thyroiditis and IgG4-RD became clear (13). Two years later, Li *et al.* confirmed and extended these previous findings by describing a typical predominant interfollicular pattern of fibrosis in IgG4 thyroiditis, which contrasted with the predominant interlobular fibrosis of the non-IgG4 thyroiditis (14). In 2010, the same group of investigators

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performed a larger study in a series of 70 patients with HT. They found that 27% of them met the histologic criteria for a diagnosis of IgG4 thyroiditis (15). Younger patients and men had the highest prevalence of IgG4 thyroiditis, which appears overall in line with the previously reported male predominance of IgG4-RD. In addition, Li *et al.* also identified other specific clinical features associated with IgG4 thyroiditis, which included higher levels of thyroid autoantibodies, rapid progression to subclinical hypothyroidism, diffuse low sonographic echogenicity and larger thyroid size (15). Moreover, a trend for more severe compressive symptoms or suspicion of malignancy characterized these patients, which consequently drove a higher rate of thyroidectomies as compared with patients in the non-IgG4 thyroiditis group (15).

Since then, other studies were performed with the aim of establishing a correlation between serum IgG4 levels and histopathologic features, but contrasting findings emerged. Li *et al.* (15) found higher serum IgG4 concentrations in the IgG4 thyroiditis group, thus suggesting that serologic data could predict histologic evaluation. On the other hand, Zhang *et al.* reported similar levels of serum IgG4 between IgG4 thyroiditis and non-IgG4 thyroiditis (16). Similarly, Raess *et al.* found no correlation between serum IgG4 levels and tissue fibrosis (17). Based on the above results, it could be concluded that there is presently no definite proof that circulating IgG4 levels somehow reflect the intra-parenchymal presence of IgG4 as assessed by histology. This implies that, nowadays, the term 'IgG4 thyroiditis' is used when referring to both IgG4 thyroiditis with an established histologic diagnosis (gold standard), but also when elevated serum IgG4 levels are present in patients with thyroiditis without histologic confirmation. Due to the rather low rate of patients with thyroiditis requiring thyroidectomy, it is clear that for the vast majority of cases no histologic confirmation would be

available. Although the circulating titers of total IgG4 are not always elevated, the levels of TPOAb IgG4 and TgAb IgG4 were found to be significantly higher in patients with IgG4 thyroiditis (16). Based on this finding, Zhang *et al.* proposed that the level of thyroid antigen-specific IgG4 rather than total serum IgG4 could be more helpful for establishing a correct diagnosis (16).

As far as the prevalence of IgG4 thyroiditis is concerned, discrepant results were reported by different studies. While early studies, mainly conducted in Japanese patients, reported an up to 27% prevalence of IgG4 thyroiditis, a more recent study performed in Southern Germany and Austria found a much lower rate (12%) (18), being 5.3% the lowest so far reported prevalence (19). As a possible explanation, it should be highlighted that the presence of IgG4-positive plasma cells within germinal centers was not taken into account in the European study, at difference with the Japanese and American studies.

The heterogeneity of the histologic criteria for rendering a diagnosis of IgG4 thyroiditis adopted in different studies clearly represents a major factor accounting for epidemiologic discrepancies. Indeed, as shown in Table 1, variable thresholds to define increased IgG4-positive plasma cells and/or IgG4/IgG ratios were used. A second aspect to be considered is that the number of IgG4 positive plasma cell is also dependent upon the duration of the disease (which in the case of thyroiditis might not always reflect the time since diagnosis). Indeed, while an increase in IgG4-positive plasma cells characterize a recent-onset condition, in more advanced stages, due to the progressively dominant fibrosis, the number of IgG4-positive plasma cells decreases. Lastly, owing to the fact that histologic confirmation can be performed only in thyroidectomized patients, an enrichment of the IgG4 subtype is expected in the minority of patients with HT requiring thyroidectomy. This statement appears

Table 1 Summary of the currently available studies on IgG4 thyroiditis.

Author	Year	Prevalence	Sex, M/F	Age (years, mean $\pm$ s.d.)	Criteria for diagnosis	FVHT
Li (14)	2012	28/105 (26.6%)	7/21	52 $\pm$ 10	<ul style="list-style-type: none"> >20 IgG4-positive plasma cells/HPF >30% IgG4/IgG ratio 	24/28
Zhang <i>et al.</i> (16)	2014	12/53 (22.6%)	1/11	43.0 $\pm$ 18.7	<ul style="list-style-type: none"> >20 IgG4-positive plasma cells/HPF >30% IgG4/IgG ratio 	5/12
Kawashima (19)	2014	5/94 (5.3%)	0/5	58.2	<ul style="list-style-type: none"> IgG4 levels $\geq$ 135 mg/dL 	n.a.
Raess (17)	2015	8/23 (34.8%)	n.a.	n.a.	<ul style="list-style-type: none"> >30 IgG4-positive plasma cells/HPF >30% IgG4/IgG ratio 	5/8
Jokish (18)	2016	24/191 (12.6%)	1/11	42.1 $\pm$ 14.6	<ul style="list-style-type: none"> >20 IgG4-positive plasma cells/HPF >40% IgG4/IgG ratio IgG4 and IgG-positive plasma cells within germinal centers were not counted 	23/24

HPF, high power field; n.a., not assessed.

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particularly true if we consider the high rate of constrictive symptoms and/or of suspicion of malignancy which characterizes patients with IgG4-thyroiditis, thus favoring a surgical strategy. In this view, it was recently reported that the coexistence of IgG4 thyroiditis would be associated with a larger size of papillary thyroid carcinoma and with lymph-node metastasis at presentation. Although not fully elucidated, the putative mechanism would be related to the higher expression of the pro-tumorigenic molecule TGF β 1 found in patients with IgG4 thyroiditis as compared to those with non-IgG4 thyroiditis (20). In addition, although the presence of pain is not mandatory for the diagnosis of IgG4-related thyroiditis, it is worth noting that pathologic findings typical of IgG4-RD were observed in a Korean patient undergoing thyroidectomy for the rare painful variant of HT (21). Even if limited to a single case, a link between the painful variant of HT and IgG4 could be suggested (22).

Since IgG4 molecules are not able to activate complement, their pathogenic role yet remains to be completely unveiled. According to current views, the presence of IgG4-positive plasma cells would be secondary to the autoimmune process acting as a counter-regulatory mechanism against inflammation. The demonstration that a decrease in serum IgG4 concentration occurs following thyroidectomy (15), together with the detection of IgG4-positive plasma cells within the germinal centers of the thyroid (16, 17), clearly identify the thyroid gland as the major source of serum IgG4.

In spite of the above data, there is still controversy on whether HT should really be considered a member of the IgG4-RD spectrum. Despite significant similarities with IgG4-RD, Li *et al.* (14) firstly described crucial differences also, in particular, the lack of the following histologic features: (i) obliterative phlebitis; (ii) storiform-type fibrosis (iii) and, most importantly, the extra-thyroid involvement. On this basis, Li *et al.* (14) and Stone *et al.* (5) proposed that HT should not be viewed as an IgG4-RD, but rather a disease in which an elevation of both tissue and serum IgG4 may be present. Although Li *et al.* reported no systemic disease in their 105 cases of Hashimoto thyroiditis including 28 cases with IgG4 thyroiditis patients (14), owing to the fact that the lesions are meta-chronous, it could be at least theoretically possible that multiple organs' involvement might occur over a longer follow-up time. On the other hand, the recent demonstration that thyroglobulin is the antigen recognized by IgG4 in 8 out of 19 (42%) patients with IgG4-thyroiditis and elevated serum IgG4 levels would support the concept that IgG4 thyroiditis is indeed an

organ-specific condition at difference with IgG4-RD (23). In the last consensus statement on the pathology of IgG4-related disease, three levels of evidence (highly suggestive, probable and insufficient) were proposed (3). According to this statement, HT would not fulfill the highly suggestive (only partial histologic features) or probable (other organ involvement) criteria to enter the spectrum of IgG4-RD. Thus, the clinical significance of elevated levels of IgG4, both in tissue and serum of patients with HT, remains uncertain.

Fibrotic variant of HT

FVHT is a peculiar subtype of HT firstly described by Hashimoto in 1912 (24); its currently reported prevalence is lower than 10% of all cases of chronic autoimmune thyroiditis. Although FVHT has been initially considered as a late stage of HT, it is actually a distinct clinicopathological entity (25), which is characterized by severe constrictive symptoms and by a very firm thyroid mimicking a malignant disease.

The main histopathologic features of FVHT, as described by Katz and Vickery, are represented by marked fibrous replacement of more than one-third of the thyroid parenchyma, in the presence of the typical features of HT in the surrounding parenchyma (25). At difference with RT, the fibro-inflammatory process in FVHT is typically limited to the thyroid without extracapsular extension. The final diagnosis is rendered once malignancy is excluded.

In the only study specifically evaluating FVHT, Deshpande *et al.* (26) evaluated 28 consecutive cases of HT and 9 cases of FVHT reporting that both the number of IgG4-positive cells per high power field as well as the serum IgG4/IgG ratio were significantly higher in patients with FVHT as opposed to those with HT. Based on histologic criteria, an accentuated lobular pattern with lobules separated by cellular and inflamed fibrous tissue, resembling that observed in IgG4-RD, was found in eight out of nine patients with FVHT. A storiform pattern of fibrosis was evident in all cases and obliterative phlebitis was found in one case. None of the patients had evidence of extracapsular extension. However, neither storiform fibrosis nor obliterative phlebitis was observed in a large series of patients with IgG4 thyroiditis, while a peculiar interfollicular fibrosis was found in patients with IgG4 thyroiditis also including a fibrotic variant (14). It should be considered that in the previously reported series of 28 patients with IgG4-HT, severe and moderate stromal

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fibrosis were found in 17 and 7 patients, respectively (14). Similarly, Jokisch *et al.* reported that 96% of the cases of IgG4-related HT showed pronounced stromal fibrosis (fibrosis grade +3 or +2), which was present in only 18% of thyroid tissue specimens from non-IgG4-related HT (18). The results of this study would suggest that FVHT, rather than HT, could actually be an IgG4-RD. Taking together the above findings, it would seem reasonable to propose that, although FVHT and HT are not commonly considered as distinct entities, FVHT could actually account for the majority of cases of IgG4-HT.

Riedel's thyroiditis

RT, also referred to as invasive fibrous thyroiditis, was first described in 1896 by Bernhard Riedel (27). RT is a rare form of thyroiditis with an estimated incidence of 1.06 cases per 100 000 patients (28). The histologic diagnostic criteria of RT, as proposed by Dahlgren in 2010, are (1) fibro-inflammatory process involving all or a portion of the thyroid gland; (2) presence of fibrous extension beyond the thyroid capsule into adjacent anatomic structures; (3) infiltration of inflammatory cells without giant cells, lymphoid follicles, oncocytes or granulomas; (4) evidence of occlusive phlebitis and (5) absence of a neoplasm (29).

RT should be distinguished from FVHT. The main aspects driving the differential diagnosis are that Hürthle cell metaplasia is not typically found and, more importantly, extrathyroidal extension of fibrosis and obliterative phlebitis are absent in FVHT. The last feature is clinically relevant, because the presence of obliterative phlebitis plays a major role for developing extracapsular fibrosis (30).

Compressive symptoms (dyspnea, hoarseness and dysphagia) and suspicion of malignancy are the main features supporting the high rate of thyroidectomies performed in these patients, which in turn, make histologic diagnosis more often available. Since one-third of patients with RT develop extra-thyroid fibrosis, RT was typically regarded as being related to the so-called 'multifocal fibrosclerosis' (31). MFS encompass a wide spectrum of systemic fibroproliferative disorders which include sclerosing cholangitis, retroperitoneal fibrosis, pancreatic fibrosis and orbital pseudotumor. Owing to its peculiar histopathologic and clinical features, RT is commonly considered to be an IgG4-RD. The final proof was provided in 2010, by description of a case in which immunohistochemistry for IgG4 showed an intense

positive staining (29). The study by Stan *et al.*, although limited to six cases of RT, currently represents the largest published series (32). The relevance of this study stems from the finding that IgG4 staining was most intense in areas of marked inflammation and was virtually absent in fibrotic areas. Moreover, the intensity of IgG4 infiltration decreased over the time in long-standing R, which would be in line with what was reported in autoimmune pancreatitis, the prototypical IgG4-RD (33).

It is interesting to note that RT provides the first example of a thyroid IgG4 disease in which rituximab (an established therapeutic agent for IgG4-RD) was successfully used in a single patient with RT refractory to tamoxifen and glucocorticoid treatment (34). Overall, the above evidence strongly supports the concept that RT is an IgG4-RD in which the density of the IgG4+lymphocytic infiltrate is time dependent.

Graves' disease

The role of IgG4 was not systematically assessed in GD. There is, however, a number of published studies aimed at evaluating this relationship, as schematically presented in Table 2. First of all, it should be highlighted that our knowledge on this topic relies on data derived from less than 50 patients. Indeed, the prevalence of GD with elevated IgG4 in previously reported series ranges from 6.0 to 11.1%. The highest prevalence (23%) was reported by a single study on a GD series characterized by an extremely high (50%) prevalence of Graves' orbitopathy (GO) (35).

These epidemiologic data would indicate that the prevalence of IgG4-RD among GD patients is even lower than what was reported for HT.

Consistently reported features of IgG4-GD are an older age at diagnosis, a relative male sex predominance (36) and, from a more clinical point of view, a surprisingly good response to anti-thyroid drug (AITD) treatment (Table 3). Indeed, all previously published series consistently reported that a lower methimazole (MMI) dose was required to achieve euthyroidism in patients with IgG4-GD as opposed with control GD. Of note, the only patient with IgG4-GD who underwent thyroidectomy, as reported by Nishihara *et al.*, was not resistant to MMI (37). Indeed, this 47-year-old woman was diagnosed with Graves' hyperthyroidism and, started on MMI therapy, experienced a successful restoration of euthyroidism. More than 4 years after the initial diagnosis, and 6 months after the withdrawal of MMI, the patient developed overt hypothyroidism and, owing to the presence of a large

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Table 2 Summary of the main features of IgG4 Graves' disease.

Author	Year	Prevalence	Sex, M/F	Age (years, mean $\pm$ s.d.)	Criteria for defining elevated IgG4	IgG4 levels (mg/dL)	GO
Takeshima <i>et al.</i> (38)	2014	7/109 (6.4%)	1/6	54.7 $\pm$ 6.2	≥ 135 mg/dL	175.0 $\pm$ 44.5	5/7
Bozkily (35)	2015	15/65 (23.1%)	n.a.	n.a.	≥ 135 mg/dL	n.a.	12/15
Torimoto <i>et al.</i> (36)	2017	5/72 (6.9%)	4/1	43.0 $\pm$ 18.7	≥ 135 mg/dL	206.0 $\pm$ 115.8	n.a.
Martin <i>et al.</i> (39)	2017	8/80 (10%)	3/5	39.00 $\pm$ 15.09	>90th percentile of normal range	311.36 $\pm$ 21.37	3/8
Yu <i>et al.</i> (40)	2017	6/64 (9.6%)	2/4	32.3 $\pm$ 9.5	3.9–86.4 mg/dL	98.9 $\pm$ 9.8	6/6
Hiratsuka <i>et al.</i> (41)	2018	2/28 (7.1%)	0/2	66 and 70	≥ 135	163.5 and 214.4	1/2

GO, Graves' orbitopathy; n.a., not assessed.

goiter, underwent thyroidectomy. Histologic examination revealed a high-grade lymphoplasmacytic infiltration with stromal fibrosis and Hürthle cell changes. Further immunohistochemical studies showed a diffuse infiltration by IgG4-positive plasma cells. Similar to what was already described for IgG4-HT, also in this case, thyroidectomy was rapidly followed by a drop of circulating IgG4 levels (from 292 mg/dL just before thyroidectomy to 39.1 mg/dL 3 months later).

Discrepant results are reported regarding thyroid-specific autoantibodies. While Takeshima *et al.* reported a significant correlation between serum TSH-stimulating antibody (TSAb) levels and both serum IgG4 levels and IgG4/IgG ratios (38), no such a correlation was found by Martin *et al.* (39). On the other hand, the latter study reported that thyroid autoantibody-positive patients had significantly higher serum IgG4 levels compared to the negative ones. The association with GO is also a matter of interest. Bozkirly *et al.* first suggested that an elevation of IgG4 would preferably be observed in patients with GO (35). In their series the proportion of patients with an IgG4 serum level >135 mg/mL was significantly higher in patients with GO as opposed with that found in patients without GO (37.5 vs 9.1%, respectively). Moreover, IgG4 levels increased in parallel with the clinical activity

score (CAS) of GO. Similarly, Yu *et al.* reported that in a multivariate regression model, which included as covariates, gender, smoking history and serum levels of IgG, IgG4, T3, free T4, TRAb and TgAb, serum IgG4 levels were independently associated with the development of GO (40). Higher IgG4 levels as well as a higher IgG4/IgG ratio also characterized patients with moderate-to-severe and/or active GO as opposed with those having mild and/or inactive GO. In this study, serum IgG4 levels positively correlated with TRAb levels, similarly to the finding by Takeshima (38) and in contrast to those of Martin (39). Similarly to HT, also in GD, a decrease in IgG4 levels following thyroidectomy was described (41).

Based on the above data, some considerations are allowed: (1) the total number of patients with elevated IgG4 is rather small; (2) no histologic confirmation of IgG4-RD is available, with the exception of one patient (37); (3) similarly to what was reported for IgG4-HT, none of the IgG4-GD patients showed other organ involvement; (4) finally, the criteria for defining elevated IgG4 were highly variable from one study to the other. Thus, at present, there is no strong evidence for the existence of IgG4-GD. The above statement would be in agreement with what was proposed more generally on IgG4-thyroid diseases by Stone who suggested referring to thyroid disease with an elevation of IgG4 rather than IgG4-related thyroid diseases. It should, however, be remembered that as far as GD is concerned, it was previously demonstrated that long-term antigen stimulation might increase TRAb concentration with a subsequent switch from IgG1 to IgG4 subclass. This finding would ultimately point toward the fact that IgG4 infiltration might actually occur in long-standing disease (42).

A further issue regards the involvement of IgG4 in non-thyroid patients with Graves'-like orbitopathy. In 2011, Fonte *et al.* first described a patient with chronic autoimmune pancreatitis who had a Graves'-like orbitopathy in the absence of any clear feature of autoimmune thyroid disease. The patient was

Table 3 Summary of the main features of IgG4 thyroiditis and Graves's disease.

Pathology	Features
IgG4 thyroiditis	<ul style="list-style-type: none"> Male predominance Rapid progression Higher level of circulating thyroid autoantibodies Diffuse low echogenicity at ultrasound No extra-thyroid involvement
IgG4 Graves's disease	<ul style="list-style-type: none"> Male predominance Diffuse low echogenicity at ultrasound More favorable response to anti-thyroid drugs

successfully cured by intravenous glucocorticoids and orbital radiotherapy (43). Further to this study, an expert opinion recommended that endocrinologists and ophthalmologists, being involved in the management of GO, should be aware of IgG4-related Graves's-like orbitopathy, which should enter in the differential diagnosis with non-GO causes of extraocular muscle enlargement and exophthalmos (44, 45).

Conclusion

The present review article aimed at overviewing current knowledge about IgG4 related thyroid diseases. At variance with other pathologic conditions, involving several organs, for which IgG4-RD appears a well-established issue, evidence for an IgG4-RD involvement in the spectrum of thyroid diseases is limited to a few conditions. The strongest level of evidence regards RT and the fibrotic variant of HT, while for HT, GD and GO proofs are weaker, due to failure to fulfill all the main criteria for an IgG4-RD. Indeed, the number of studies and of investigated patients is limited, the diagnostic criteria for an IgG4-RD are heterogeneous, and, mainly, histologic confirmation is not systematically available. Based on the above considerations, the term 'thyroid disease with an elevation of IgG4' rather than 'IgG4-related disease' was proposed, and we would support the former terminology at least for those cases in which histopathologic confirmation is not available. Nevertheless, the fact that some thyroid conditions may arise concomitantly with an elevation of circulating IgG4 is, at least in our opinion, of clinical relevance. Indeed, there are several peculiarities which characterize the clinical course of a given thyroid disease occurring in patients with elevated IgG4: (1) in patients with HT a higher risk for developing hypothyroidism and larger thyroid volume, which likely carries an indication for thyroidectomy; (2) in patients with GD, an overall more favorable response to medical treatment, a higher rate of GO and a trend for a more severe and active GO at presentation. These clinically relevant aspects highlight the need for future longitudinal studies conducted on large series of patients together with the availability of a systematic histologic evaluation of thyroid specimen, aimed at providing more clues on this intriguing relationship.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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