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PATHOLOGY REVIEW

IgG4-related disease: a complex under-diagnosed clinical entity

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Abstract IgG4-related disease (IgG4-RD) encompasses a spectrum of complex fibro-inflammatory disorders which are often under diagnosed due to unfamiliarity by clinicians. A challenging multitude of clinical manifestations makes the diagnosis cumbersome. The primary clinical feature in IgG4-RD entails a tumor-like presentation coupled with tissue-destructive lesions. Histopathological findings include lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis. These findings, in combination with elevated serum immunoglobulin G4 levels, are diagnostic in the setting of single- or multi-organ involvement. A closer understanding of the role of T cells and B cells in the increased production of IgG4 has led to a notion that IgG4 can act as a pathogen, anti-inflammatory agent, or rheumatoid factor. Glucocorticoids are the primary treatment modality; however, relapse is common with prolonged therapy. Alternatively, immunomodulatory agents are being increasingly used as therapy. The aim of this article is to raise awareness of IgG4-RD and review the diagnostic algorithm, as IgG4-RD often mimics a wide array of clinical conditions. In addition, we summarize the pathogenesis and current treatment guidelines of IgG4-RD for clinicians. Awareness and accurate diagnosis are crucial in preventing progression to chronic diseases, thereby diminishing disease-related morbidity and mortality.

Keywords IgG4 · Fibro-inflammatory disease · AIP · IgG4-RD · Review

Introduction

Immunoglobulin-4-related disease (IgG4-RD) encompasses a spectrum of complex immune-mediated fibro-inflammatory diseases that share defined pathologic, serologic, and clinical features. Formerly known as "Hyper-IgG syndrome" or "IgG-related systemic disease," the term "IgG4-related disease" was recently coined in 2010 at a Japanese consensus conference [1, 2]. The disease entity is thought to be a result of plasma cell-mediated overproduction of the IgG4 subclass of immunoglobulin IgG [3], as outstanding serum IgG4 levels are seen in 60–70 percent of patients with IgG4-RD [4].

IgG4-RD can affect many organs, including but not limited to the pancreas, orbit, salivary tract, and lymph nodes [5], with clinical symptoms subsequently varying depending on the organ involved. The primary clinical feature of this disease entails tumefied lesions of the affected organ. Hallmark serological and histological features include lymphoplasmacytic proliferation, fibrosis, obliterative phlebitis, and elevated serum IgG4 [6].

IgG4-RD was first recognized as a systemic entity in the early 2000s, when autoimmune pancreatitis type I patients were noted to have conglomerations of extra-pancreatic manifestations [7]. Elevated IgG4-positive plasma cell infiltration has been described in patients with retroperitoneal and mediastinal fibrosis, inflammatory pseudotumor of lung and liver, Kuttner syndrome, as well as interstitial

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nephritis [8]. Together, these conditions are now collectively referred to as the new encompassing disease concept: IgG4-RD [5, 7].

Given the relatively recent discovery, minimal data exists on the epidemiology of IgG4-RD in the western world. In Japan, there is an estimated prevalence of 100 cases per 1 million, and an annual incidence of 1 per 100,000 [1, 9]. The population between 50 and 70 years of age are more susceptible in developing this disease, with men being affected more than women (2.8:1) [1, 9, 10]. However, gender distribution of IgG4-RD also varies depending on the tissue site involved. In a cross-sectional study conducted by Zen et al., 114 patients with IgG4-RD were compared in respect to demographic features and clinical presentations. The mean age of the affected population ranged from 59 to 68 years, and most patients were men (>75%) [11]; however, IgG4-RD of head and neck was found to be equally distributed among both men and women [11].

While IgG4-RD has a predilection for men, the severity of the disease is also comparable in both men and women. Wallace et al. compared the severity of tissue involvement and serologic differences in 125 men and women with biopsy-proven IgG4-RD. There were no significant gender-specific differences in severity of IgG4-RD as measured by IgG4-RD responder index (RI), organ involvement, or serum IgG4 concentration [12]. Another area yet to be fully understood is the genetic susceptibility to IgG4-RD among the general population. Genetic studies are limited, with only small subsets of the population having been studied. Genetic susceptibility has been mostly described in Japanese studies of autoimmune pancreatitis (AIP) and needs further validation in the western world [13].

In this review, we aim to highlight the prevalence, pathogenesis, clinical features, and laboratory diagnosis of IgG4-RD. Due to the rarity of the disease and variation in clinical presentation, the entity most often remains undiagnosed. This disease at its highest degree of severity can result in multi-organ dysfunction and ultimately fatality. Hence, we aim to review the relevant literature on this disease, particularly emphasizing on diagnostic and therapeutic strategies.

Methods

A systematic PubMed search was performed utilizing the following keywords: "fibro-inflammatory disease," "inflammation," "IgG4-RD," "Immunoglobulin-4-related disease," "IgG4," and "Autoimmune Pancreatitis," both separately and in combination. Inclusion criteria comprised full text articles, written in English, and published in the past 15 years. Articles were included on the basis of their relevance to the topic. Incorporated studies focused on epidemiology, etiopathogenesis, clinical presentation, diagnosis, and management of IgG4-RD.

Etio-pathogenesis

IgG4-RD is considered to be an immune-mediated syndrome, but the exact pathogenesis behind IgG4-RD has yet to be fully understood. Type I autoimmune pancreatitis (AIP) is considered the prototypical IgG4-RD. AIP is associated with a specific class II histocompatibility antigen type [14]. Several auto-antibodies against epithelial and cellular targets have also been seen in patients with IgG4-RD including antinuclear antibodies (ANA) as well as antibodies against lactoferrin, carbonic anhydrase II and IV, trypsinogens, and pancreatic secretary trypsin inhibitor [3, 15–17]. Other evidence suggesting the role of autoimmunity in IgG4-RD includes the deposition of immune complexes noted in organs such as kidney, pancreas, and other tissues affected by the disease process [18]. The presence of both T cells and B cells in the lymphoplasmacytic infiltrate of affected organs, in the presence of elevated IgG4-producing plasma cells, also suggests an immunologically mediated pathogenesis for IgG4-RD [19].

From a genetic standpoint, human leukocyte antigen (HLA) serotypes DRB1*0405 and DQB1*0401 have been shown to increase susceptibility of IgG4-RD in Japanese populations [20]. Interestingly, DQβ1-57 without aspartic acid is associated in Korean populations [21]. There exist additional non-HLA genes in which single-nucleotide polymorphisms (SNPs) are implicated in increased disease susceptibility and recurrence. These genes encode proteins such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), tumor necrosis factor-α (TNF-α), and Fc receptor-like 3 [22–24].

A potential role of molecular mimicry involving *Helicobacter pylori* has also been described by Frulloni and Guarneri et al. [25, 26]. Auto-antibodies against plasminogen-binding protein of *H. pylori* were seen in a large number of patients with AIP [25]. A significant similarity between human carbonic anhydrase II (CAII) and alpha-carbonic anhydrase of *H. pylori* was also reported by Guarneri et al. [26], which may explain how the antigen may cross react with human CAII, thereby contributing to the disease symptoms.

As a review, IgG antibody has four different isotypes: IgG1 through IgG4. Among these, IgG4 has special characteristics. For instance, IgG4 values tend to vary between 3 and 7% of total serum IgG. This translates to a normal range which varies from 0.01 to 1.4 mg/mL among different people [13]. IgG4 levels, however, ideally remain stable within one subject. Functionally, amino acid differences in the second constant domain of IgG4 leads to

negligible binding of IgG4 to both c1q receptors, as well as Fc receptors. As a consequence, IgG4 does not activate the classic complement cascade [27]. Additional differences in the IgG4 subclass include its ability to undergo "Fragment antibody (Fab)-arm exchange," in which the disulfide bonds of the heavy chains are weaker, leading to dissociation and random recombination. This ultimately results in "functionally monovalent" antibodies, which are in turn unable to cross-link antigens, losing their ability to form immune complexes [28].

IgG4 production, like that of IgE production, is controlled primarily by type 2 helper (Th2) T cells [4, 13]. Persistence of triggering factors coupled with immune deregulation eventually leads to a Th1-driven inflammatory process with massive cell infiltration (mediated by cytokines IFN-γ, IL1-β, IL-2, and TNF-α). Sustained inflammation leads to a Th2-predominant response and activation of peripheral *T* regulatory cells (T_{regs}), which produce IL-10 and TGF-β. This then leads to differentiation of IgG4-producing plasma cells (as well as of eosinophils, through Th2-mediated cytokines such as IL-4, IL-5, IL-10, and IL-13), which ultimately results in organ dysfunction and tissue fibrosis [3, 4, 29–31]. Through these mechanisms, IgG4 can, therefore, play several roles. IgG4 may be pathogenic or act as a rheumatoid factor [32]. As a rheumatoid factor, IgG4 may act as an autoantibody to IgG [33].

Clinical features

IgG4-RD should be suspected in patients presenting with unexplained enlargement of one or more organs. Symptoms are generally minimal, if any, at time of initial presentation, but vary substantially according to the organ of involvement (Table 1). In addition, the disease can be diagnosed incidentally on radiology studies or among biopsy specimens. Involvement of major organs is common, and IgG4-RD may contribute to organ failure. Diagnosis of IgG4-RD relies on co-existence of clinical, laboratory, and histopathological evidence, although none of these features is pathognomonic by itself [44].

IgG4-RD of pancreas (autoimmune pancreatitis type I)

Type I AIP presents with the hallmark histopathologic findings of IgG4-RD (Table 2). Up to a tenfold elevation in serum IgG levels are seen in the majority of the patients with AIP, particularly type I [45]. This distinction may be used to differentiate AIP from other pancreatic conditions such as pancreatic cancer, chronic pancreatitis, primary biliary cirrhosis, and/or primary sclerosing cholangitis. The sensitivity of utilizing IgG4 levels in diagnosis of AIP ranges from 50 to 92%, attributed to the variation in reference ranges among different test assays [32]. Interestingly, a positive correlation between the severity of symptoms and serum IgG4 levels has been described in patients with AIP, in as much as patients with elevated IgG4 levels had a higher incidence of jaundice and greater degree of pancreatic enlargement. Increased levels of 18F-2-fluoro-2-deoxy-D-glucose (FDG) uptake and greater requirements for maintenance therapy were also observed [46, 47]. Despite the sensitivity of IgG4 levels in the diagnosis of AIP, this assay is not an independently reliable indicator of pathology. Further corroboration with appropriate imaging and histopathology is still required. To this end, imaging techniques such as magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) may demonstrate structures along the pancreatic or common bile duct. CT and MRI show enlargement of the pancreas, a peri-pancreatic capsular rim, and features of peripheral fibrosis and inflammation [27, 48].

Few cases of AIP present with a tumorous appearance on imaging. In a study conducted by Hardacre et al., 2.2% of patients undergoing pancreaticoduodenectomy were diagnosed with AIP retrospectively [49]. Among these AIP patients, the majority were preoperatively diagnosed with pancreatic cancer and periampullary neoplasms. Hence, a thorough work-up is absolutely necessary prior in considering surgery or steroid therapy. Another notion complicating the management of AIP is the potential for development of pancreatic cancer in these patients [50].

IgG4-related sclerosing cholangitis (IgG4-SC)

Sclerosing cholangitis may occur in isolation or is present as an extra-pancreatic manifestation of IgG4-related AIP, serving as the most common extra-pancreatic manifestation of IgG4-RD. Based on the location of stricture, IgG4-SC is divided into four subtypes [29]:

Type 1 Isolated distal stenosis of the common hepatic duct.
Type 2 Diffuse stenosis.
Type 3 Hilar and distal common hepatic duct stenosis.
Type 4 Isolated hilar common hepatic duct stenosis.

The diagnosis of IgG4-SC requires a cholangiogram demonstrating pathologic stenosis (Type 1–4), serum IgG4 levels, co-existing AIP, sialadenitis or retroperitoneal fibrosis, and hallmark histologic findings. False-positive histologic results are noted in a few cases of sclerosing cholangitis or cholangiosarcoma [51]. Hence, response to steroid therapy is still a necessary determinant to confirm diagnosis.

Table 1 Clinical presentation of IgG4-RD per site of involvement

Organ system	Nomenclature	Clinical features	Literature reports
Orbit	IgG4-related ophthalmic disease IgG4-related orbital inflammatory pseudo-tumor IgG4-related pan-orbital inflammation IgG4-related orbital myositis	Swelling of orbital tissue and proptosis	Roughly 23% of 113 patients with IgG4-RD had orbital involvement [34]
Lacrimal gland	IgG4-related dacryoadenitis	Bilateral swelling of the glands and impaired production of secretions	Among 21 patients identified from the IgG4-RD registry in a single center study, 62% had lacrimal gland involvement [35]
Salivary gland	IgG4-related sialadenitis IgG4-related parotitis IgG4-related submandibular gland disease	Bilateral swelling of the glands and impaired production of secretions	Roughly 2% in a study of 129 patients with obstructive sialadenitis had IgG4-related pathology [36]
Thyroid	IgG4-related thyroid disease	Hypothyroidism, neck pain, dysphagia, dyspnea	A total 12 out of 53 patients with Hashimoto's disease were IgG4-positive in a retrospective study [37]
Liver	IgG4-related hepatopathy	Jaundice, right upper quadrant mass	Isolated cases [34, 38]
Biliary tract and gall bladder	IgG4-related sclerosing cholangitis IgG4-related cholecystitis	Jaundice, pruritus, cholestasis	Roughly 80% of AIP patients have concomitant involvement of biliary tract [39]
Blood vessels	IgG4-related aortitis/periaortitis IgG4-related periarteritis	Chest pain, dyspnea	Roughly 9% in 33 cases of non-infectious aortitis [40], and a total of 4 out of 10 patients with inflammatory aortic aneurysms in a 15-year study in Japan [41]
Retroperitoneal fibrosis	IgG4-related retroperitoneal fibrosis	Flank pain, obstructive symptoms, peripheral edema	A review of 14 published cases [40]
Kidneys	IgG4-related kidney disease Tubulo-interstitial nephritis secondary to IgG4-related disease	Hematuria, proteinuria, hypocomplementemia, chronic renal failure	A total of 23 patients(15%) in a study of 153 patients with IgG4 disease in multiple medical centers in Japan [42]
Skin	IgG4-related skin disease	Papulonodular lesions, plaques, purpura	A total 7 different subtypes of IgG4-related cutaneous involvement have been noted [43]

Table 2 Diagnostic criteria in IgG4-RD

Diagnosis	Criteria
Definitive	Diffuse or local swelling in single or multiple organs
	Serum IgG4 levels >134 mg/dL
	Histology (2 of 3) Lymphoplasmacytic infiltrate Fibrosis in storiform (whirled) pattern[a] Obliterative phlebitis[a]
	IgG4-positive plasma cells Ratio of IgG4 +/IgG + plasma cells < 40% and >10 IgG4 + plasma cells per HPF
Probable	Diffuse or local swelling in single or multiple organs
	Histology (2 of 3) Lymphoplasmacytic infiltrate Fibrosis in storiform (whirled) pattern[a] Obliterative phlebitis[a]
	IgG4-positive plasma cells Ratio of IgG4 +/IgG + plasma cells <40% and >10 IgG4 + plasma cells per HPF
Possible	Diffuse or local swelling in single or multiple organs
	Serum IgG4 levels >134 mg/dl or >Twofold upper limit of normal

[a]Lymph node, lung, minor salivary glands, and lacrimal glands may not have these features

IgG4-related lymphadenopathy

IgG4-related lymphadenopathy has to be distinguished from other causes of generalized or localized lymphadenopathy. IgG4-related lymphadenopathy usually presents with modestly enlarged non-tender nodes, absence of constitutional symptoms, and distinct histology findings on biopsy, along with response to steroid therapy. The typical histopathology features of IgG4-RD, such as storiform fibrosis and obliterative phlebitis, are typically missing in affected lymph nodes [52]. Although difficult to delineate IgG4-related lymphadenopathy from other causes of lymphadenopathy, biopsy is also useful to exclude malignancy. Five characteristic patterns are seen on histology, all of which feature an abundance of IgG4 positive cells with eosinophilic infiltration [53]:

Type 1 Multi-centric Castleman disease-like.
Type 2 Follicular hyperplasia.
Type 3 Interfollicular expansion.
Type 4 Progressive transformation of germinal center-like.
Type 5 Nodal inflammatory pseudotumor-like.

IgG4-related kidney disease

The common presentations of IgG4-related kidney disease (IgG4-KD) are tubulo-interstitial nephritis (TIN) and membranous glomerulonephritis (MGN). Other renal findings include, but are not limited to proteinuria, hematuria, hypocomplementemia, and renal space occupying masses. Renal biopsy in these cases will reveal typical findings suggestive of IgG4-RD, along with possible deposition of immune complexes in the tubular basement membrane. IgG4-related MGN is negative for phospholipase-A2 receptor on immunohistochemistry, unlike the classic form of MGN [54]. Based on the location of involvement within the kidney, IgG4-KD can be divided into parenchymal, pelvic, or perinephric diseases. In one study by Seo et al., 75% of patients had only parenchymal lesions, while the rest were other singular or co-existing lesions, suggestive of the systemic nature of the disease [55]. Delay in initiation of steroid therapy may result in severe fibrosis and atrophy of the kidneys, ultimately resulting in chronic renal insufficiency.

Head and neck manifestations of IgG4-RD

Salivary and lacrimal glands are commonly affected tissues in IgG4-RD. Patients present with bilateral swelling and impaired secretions. As a result, the differential in these cases commonly includes Sjogren's syndrome (SS), which must be ruled out before proceeding with further treatment. Further complicating diagnosis is the notion that patients with IgG4-RD also frequently test positive for anti-SSA and/or anti-SSB auto-antibodies, whereas conversely elevated IgG4 serum levels may be observed among patients with SS [56].

These diagnoses should thus be distinguished on the basis of clinical findings and pathology. Clinically, submandibular glands are usually spared in SS, thus their involvement may indicate more of an IgG4-RD process. Additionally, these diseases can be differentiated by means of histopathology, in as much as fibrosis, sclerosis, and lymphocytic follicle formation are more typical findings of IgG4-RD in lieu of SS.

IgG4-related retroperitoneal fibrosis

Although previously considered an idiopathic entity, several case series now suggest that IgG4-RD is responsible for most cases of retroperitoneal fibrosis. Fibrosis is usually in the infra-renal aortic area and iliac arteries and can involve local structures [40]. Clinical features range from back pain to obstructive uropathy and ureteral involvement [57]. IgG4-related retroperitoneal fibrosis rarely occurs in an isolated setting. It is commonly associated with

involvement of pancreas, lymph nodes, pituitary glands, salivary glands, and/or mediastinal involvement [58].

Other IgG4-RD

Other organs that may be affected by IgG4-RD include thyroid gland, liver, lung, pleural surfaces, synovitis, pericarditis, and hypophysitis (Table 1).

Diagnosis

As IgG4-RD can impact any organ or tissue, the clinical picture is highly heterogeneous, making diagnosis difficult. No specific diagnostic criteria has been approved nor accepted as definitive by international societies. The Japanese comprehensive diagnostic criteria are utilized but also heavily criticized (Table 2) [59]. If all four criteria are met, the diagnosis of IgG4-RD is considered definitive.

In addition to these criteria, appropriate imaging can be utilized to visualize the involved organs. On CT, AIP may present as a diffusely enlarged pancreas, the so-called "sausage-shaped pancreas," or with a focal mass, which tends to have a hypodense rim. The pancreatic duct is characterized by caliber irregularities, followed by a length of narrowing without distal dilation [29, 60]. On the other hand, IgG4-SC is characterized on ERCP, MRCP, CT, and/or endoscopic ultrasound (US) with concentric mural thickening and segmental or long ductal narrowing and possible prestenotic dilation with delayed contrast enhancing uptake [29]. Alternatively, IgG4-KD typically presents in one of three locations, with parenchymal lesions being the most common. Imaging will reveal a small, round, hypodense wedge-shaped lesion in renal parenchyma on contrast-enhanced CT [55].

Regarding tissue diagnosis, there are three main histopathological features of IgG4-RD: (1) dense lymphoplasmacytic infiltrate; (2) fibrosis, arranged at least focally in a storiform pattern; (3) obliterative phlebitis [59].

1. *Dense lymphoplasmacytic infiltrate* Small lymphocytes diffusely intermingled with plasma cells. Germinal centers may or may not be present. The lymphocytic infiltrate is composed predominantly of T cells with fewer aggregates of B cells. Plasma cells may be predominant. In addition, eosinophils and macrophages can be seen in setting of angiocentric fibrosis.
2. *Storiform-type fibrosis pattern* Spindle cells (either fibroblasts or myofibroblasts) radiating from a center and buried within lymphoplasmacytic infiltrate.
3. *Obliterative phlebitis* Venous channels damaged by a dense lymphoplasmacytic infiltrate.

Note that although a cut-off point has been proposed regarding the appropriate number of IgG4-positive plasma cells within a sample tissue, there exists a large variation from organ-to-organ. For this reason, a ratio of IgG4-positive plasma cells to IgG-positive plasma cells greater than 40% per HPF has been proposed to be significant for any organ [61]. This proposed universal ratio does present some drawbacks in terms of sensitivity depending on the organ in question, and therefore, continued research will be required to validate this test [61].

Finally, as suggested by the Japanese comprehensive diagnostic criteria, the addition of IgG4 serum levels to aforementioned findings may be helpful, in combination, to achieve a diagnosis. Indeed, there exists a positive correlation between disease severity and serum levels, as described in AIP [46, 47]. However, IgG4 serum level alone is not well established as a definitive test in isolation due to the variable utility of this assay. This unreliability may stem from the wide normal range of IgG4 within the population (0.01–1.4 mg/mL) [13], as well as variation in reference ranges among different assays. For example, the sensitivity of IgG4 levels has been reported to vary from 50 to 92% in AIP due to such heterogeneity [32].

Differential diagnosis

Regarding specificity, elevated serum IgG4 levels can also be seen in a variety of conditions [62] (Table 3). These conditions are not just limited to malignant processes, but also include several non-specific inflammatory conditions [63]. While elevation of IgG4 levels may be present, however, tissue biopsy will lack the histopathological diagnostic features of IgG4-RD. For example, malignancies may have infiltrates of IgG4-positive plasma cells, but the histology

Table 3 Differential diagnosis for elevated serum IgG4 levels

Differential diagnosis for elevated serum IgG4 levels
Allergic disorders
Pemphigus vulgaris
Parasitic infections
Primary sclerosing cholangitis (PSC)
ANCA vasculitis
Rheumatoid arthritis (RA)
Inflammatory bowel disease (IBD)
Pernicious anemia
Sjogren's syndrome (SS)
Castleman's syndrome
Thrombotic thrombocytopenia
Idiopathic membranous glomerulonephritis

will be patchy and fail to include the other two main histopathological features (Table 2) [61].

Treatment

Optimal treatment guidelines have yet to be established; however, broad management guidelines have been proposed by experts [64]. Highlights of these guidelines include (i) treatment of all symptomatic patients and a subset of asymptomatic patients; (ii) use of glucocorticoids as first line for remission induction, unless contraindicated; (iii) maintenance therapy indicated for most patients; and (iv) treatment of relapses with glucocorticoids or steroid-sparing agent.

The current approach to therapy is based on limited observational data including case reports and series. Several studies have reported a near complete response to therapy, but with higher relapse rates in patients with AIP [29]. Although most studies recommend steroid therapy to be effective in induction and maintenance, dosing recommendations vary. Suggested regimens include a 4-week course of 40–80 mg of prednisone every day, followed by steroid tapering leading up to discontinuation. Alternatively, 2–4 weeks of steady dose prednisone (0.6 mg/kg body weight) has been proposed, with gradual reduction to 5 mg for 2 weeks, followed by maintenance of 2.5–5 mg for the next 3 years [29]. Following the success of induction, a steady maintenance dose reduces the overall risk of relapse, particularly in those patients with severe IgG4-RD organ manifestations.

Clinical remissions are described differently from study-to-study because parameters of treatment response correlate imperfectly with one another. To generalize these findings, the IgG4-RD responder index (IgG4-RDI) was developed for more accurate characterization of disease activity and response [56]. Baseline levels of serum IgG4, IgE, and circulating eosinophils have been described as alternative markers for disease relapse in IgG4-RD [68]. Recently, circulating plasma blasts have also been reported as potent biomarkers for diagnosis, assessment of response, and maintenance therapy [69]. Initial relapses are also generally prognostic for ultimate relapse in the future.

In patients for who relapse occurs following a long period of remission, re-induction with steroid therapy may be effective. In those with recurrent relapses, alternative steroid-sparing therapies should be considered, including azathioprine, rituximab, and mycophenolate mofetil [65, 66]. Immunomodulatory agents may also be used in cases where steroids are contraindicated. As a final alternative, surgical intervention is typically reserved for those cases with organ-specific mechanical complications, such as bile duct or ureteral obstruction.

Treatment recommendations are generally specific to each patient, as little information exists on comparative efficacy of various treatment modalities [67]. Only one small clinical trial of rituximab in IgG4-RD disease currently exists, i.e., Carruthers et al. evaluated the efficacy of rituximab in IgG4-RD in their open-label clinical pilot trial, successfully enrolling 30 patients. Patients were treated with either rituximab alone or required to discontinue baseline glucocorticoids within 2 months. Disease response, defined by improvement of the IgG4-RDI and by the absence of flares, occurred in 97% of participants, supporting the efficacy of rituximab for these patients [56].

Discussion

At its highest degree of severity, IgG4-RD can result in multi-organ dysfunction and significant morbidity, which emphasizes the importance of increasing clinician awareness of this emerging entity. By reviewing the current literature, we have summarized the diagnosis and treatment of this disease to be incorporated into the clinician's armamentarium, with the goal of improving patient care.

Diagnosis is a challenge, as IgG4-RD can involve multiple different tissues, and thus present with a heterogeneous range of symptoms related to the specific organ(s) involved. To further complicate matters, no simple test exists for diagnosis. Instead, the practitioner must incorporate clinical, histopathologic, and laboratory findings together to generate an accurate picture, while successfully excluding the multitude of autoimmune and rheumatologic conditions in the differential [70].

Following diagnosis, treatment typically entails glucocorticoid therapy, with characteristic symptomatic and serologic improvement and consideration of maintenance therapy for remission thereafter. Relapses are common in these patients, however, reported to be as high as 50% [71]. For patients with refractory disease, alternative immunomodulatory agents are subsequently trialed, with rituximab demonstrating the strongest evidence thus far.

To highlight the potential severity of this disease and our relative lack of knowledge, it should be mentioned that an increased risk of malignancy has also been described for these patients. In a prospective study conducted by Hugget et al., 115 patients with either AIP or IgG4-SC were evaluated, with 50% of patients experiencing relapse, and 11% of patients developing malignancy. Indeed, the risk is significantly elevated for compared to the general population (odds ratio = 2.25, $P = 0.02$) [71]. Similar findings were also suggested by other reports [72, 73]. In a multicenter, retrospective study, Shiokawa et al. reported 18 cancers among 15 out of 108 patients with IgG4-related AIP (14%), with a relative risk of 4.9 [72]. Similarly, Takahasi

et al. found an increased risk of non-Hodgkin's lymphoma (NHL) for patients with IgG4-RD, with a standardized incidence rate as high as 16 [73].

Whether this increased risk is secondary to IgG4-RD, or whether IgG4-RD itself is a paraneoplastic manifestation of cancer has yet to be fully determined. In general, the natural progression, prognosis, and late morbidity of IgG4-RD require further study. These findings, among others, simply emphasize the importance of accurate diagnosis, as well as timely management of this disease process.

In conclusion, this review summarizes the current literature regarding IgG4-RD, highlighting relevant points for both clinicians and/or researchers. Additional studies are necessary to further improve diagnosis and identify alternative therapy options in the setting of relapse, so that long-term morbidity and potential mortality associated with this disease may be prevented.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest.

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