Published in final edited form as:

Expert Rev Clin Immunol. 2017 September ; 13(9): 867–875. doi:10.1080/1744666X.2017.1354698.

Diagnostic and treatment workup for IgG4-related disease

Mary Abraham and

Emory University School of Medicine, 1365 Clifton Rd, 3rd floor, Atlanta, GA 30322

Arezou Khosroshahi

Assistant Professor of Medicine, Emory University School of Medicine, 1365 Clifton Rd, 3rd floor, Atlanta, GA 30322

Abstract

Introduction—IgG4-Related Disease is a newly recognized condition which is increasingly diagnosed by practitioners due to improvement in clinical awareness. Men and women have been found to be affected by this disease in various organs, more commonly with involvement of the salivary and lacrimal glands as well as pancreas and liver.

Areas Covered—The diagnosis and management of this condition remain challenging as biomarkers and therapies are being investigated. Hallmark features on histology are still the gold standard for confirmation of diagnosis, whereas serum IgG4 level has been shown to be neither necessary nor sufficient for the diagnosis. Glucocorticoids remain the most effective initial management for this condition while there are limited clinical trials on the effectiveness of maintenance therapy.

Expert Commentary—This review serves as an update on approaches for diagnosis and management of IgG4-RD. Most of the known data in this field comes from retrospective cohort studies and expert consensus guidelines but new ongoing prospective studies, clinical trials and better understanding of the pathogenesis of this condition are promising.

Keywords

IgG4-RD; IgG4; Diagnosis and Management; plasmablasts; rituximab; glucocorticoids; autoimmune

1- INTRODUCTION

IgG4 related disease (IgG4-RD) is a systemic immune-mediated fibro-inflammatory condition often involving several organ systems at the time of diagnosis or over time. The concept of IgG4-RD emerged from an entity called autoimmune pancreatitis (AIP) only a decade ago when Dr Kamisawa, a Japanese gastroenterologist, observed identical pathological findings in other affected organs in patients with AIP(1). This disease is now

Correspondence to: Arezou Khosroshahi.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

well known to affect almost any organ, with the most common reported in the pancreatic and biliary systems as well as salivary/lacrimal glands (2). The diagnosis is not often straightforward, as clinical involvement of organs may occur in a chronological or metachronous fashion. The disease is defined by mass forming lesions containing abundance of IgG4 producing plasma cells, lymphocytes and fibrosis, mimicking malignancy. IgG4-RD is responsive to glucocorticoid treatment, and timely identification of the disease can prevent significant complications and organ damage. A series of previously idiopathic fibrosing disorders such as idiopathic retroperitoneal fibrosis named as Ormond's disease, Riedel's thyroiditis, sclerosing mesenteritis and Mikulicz disease among others have now been recognized as part of IgG4-RD spectrum. IgG4 related diseases are commonly misdiagnosed partly because of lack of familiarity of the clinicians and partly due to lack of a reliable biomarker for this condition. Often elevated serum IgG4 concentration (3) is considered as a biomarker to make the diagnosis and differentiate this condition from its mimickers (4) listed in Table 1 which can be misleading. The clinicohistopathological confirmation of IgG4-RD, yet remains the main approach for the diagnosis of this protean condition.

The epidemiology of IgG4-RD has not been fully determined due to the rarity of the diagnosis as well as misdiagnosis. A study from Japan in 2009 (5) revealed a prevalence of 8000 in their population, with males predominantly affected more than females, and an average age of onset of 58.8 years with peak age of onset between 61 and 70 years. Cohorts from Western countries have confirmed similar age and sex distributions but the true estimates of incidence and prevalence of this condition remain unclear in the United States and other countries, contributing to the difficulty in identifying those at risk of the disorder (6). Although this condition most commonly affects elderly men, its head and neck involvement seems to be equal between the two genders(7). IgG4-RD is typically reported to occur in elder adults mostly, however there have been case reports showing children, predominantly females, are also affected (8).

2- CLINICAL PRESENTATION

Patients usually present with subacute formation of a mass lesion in an organ. The disease itself does not cause constitutional symptoms or pain. Most often, patients' complaints that bring them to their physicians are due to cosmetic concerns because of salivary or lacrimal gland involvement, obstructive symptoms due to mechanical compression of the mass like obstructive jaundice in cases of pancreatitis and cholangitis, or obstructive uropathy due to retroperitoneal fibrosis.

The frequency of reported organ involvement and presenting manifestation of IgG4-RD varies significantly according to the subspecialty evaluating the patients. Most gastroenterologist see autoimmune pancreatitis followed by cholangitis as the most common presentation of the disease, while rheumatologists may see more involvement of the salivary and lacrimal glands.

60% of patients with IgG4-RD have more than one single organ involvement at the time of diagnosis. A thorough history and physical exam can reveal other asymptomatic organ involvement. As a common example, many patients with obstructive jaundice due to

autoimmune pancreatitis are found to have bilateral submandibular gland involvement which could guide the clinician to have high suspicion for IgG4-RD and spare the patient from invasive pancreatectomy due to concern for cancer. Many other organ involvements are asymptomatic and can only be found by comprehensive imaging of the chest and abdomen.

Lymphadenopathy has been reported between 25–60% in different cohorts of patients with IgG4-RD (6, 7) making lymphoproliferative disorders one of the big mimickers of IgG4-RD. Tissue biopsy of the lymph node is not diagnostic for IgG4-RD as the characteristic fibrosis of IgG4-RD does not happen in this tissue and other histologic features including IgG4 lymphoplasmacytic infiltrates are non-specific findings in lymph nodes. Based on the histological diversity, 5 different subtypes of IgG4-related lymphadenopathy have been proposed (9, 10) but none of the variants have the specific characteristics for the diagnosis of IgG4-RD. However, lymph node biopsy to exclude malignancy, specifically lymphoma, is necessary.

Approximately 30–40% of patients with IgG4-RD have history of allergies including asthma, eczema, seasonal or food allergy(11). More investigation is needed to clarify if this history plays any significant role in the pathogenesis of this condition.

3- PATHOGENESIS

Pathogenesis of IgG4-RD is not fully understood. Over the past few years, a few models of disease mechanism have been suggested. The abundance of plasma cells in the tissue and increased level of IgG4 produced by antibody producing cells suggested a major role for B cell and plasma cells. This role has been demonstrated by significant improvement of patients with IgG4-RD after B cell depletion. Recent studies are suggesting that dysregulated follicular helper T cells and CD4+ cytotoxic T cells may orchestrate IgG4-RD pathogenesis both by secreting profibrotic cytokines and by inducing IgG4 class switch, plasma blast expansion and production of autoantibodies (12) (13) (14) (15). The role of innate immunity also has been studied showing promotion of IgG4 production by innate immune cells, such as plasmacytoid dendritic cells and monocytes isolated from patients with IgG4-RD (16). The role of IgG4 molecule in pathogenesis of IgG4-RD has not been proven. In general, IgG4 antibody is considered a non-inflammatory antibody and traditionally dampens the activation of immune system. There are only a few specific conditions in which IgG4 antibody plays a pathogenic role such as in pemphigus vulgaris and thrombotic thrombocytopenic purpura. In IgG4-RD, the correlation between serum IgG4 and disease severity and observation of IgG4 immune complexes in IgG4-related tubulointerstitial nephritis may suggest a pathogenic role for this antibody but needs to be confirmed with further investigation

4- DIAGNOSIS

Clinical history and thorough physical examination, coupled with lab testing, imaging and most importantly histopathological examination remain the most accurate method to diagnose IgG4-RD. It is imperative to obtain histopathologic confirmation of IgG4-RD especially in tumefactive lesions where malignancy must be excluded. IgG4-RD should be

considered when mass lesions present in typical organs including pancreas, salivary and lacrimal glands, lungs, liver, kidney and retroperitoneum. Rigorous exclusion of IgG4-RD mimickers is the first and foremost important responsibility of clinicians. Although this disease has been under recognized, it is necessary to consider the diagnosis while evaluating patients with clinical findings suspicious of this condition. We can not emphasize enough the importance of a vigorous work up to ensure malignancy or infection is not the underlying cause of fibro inflammatory organ involvement.

Several conditions previously described as idiopathic fibrosing diseases are now considered part of IgG4-RD. Table 2 summarizes a list of such conditions previously known as separate entities which can now be categorized as different manifestations of IgG4-RD (17–21).

Although several diagnostic criteria for IgG4-RD, AIP, and IgG4-related kidney disease have been proposed (22–24), clinicopathological correlation for the diagnosis can not be substituted by any diagnostic criteria for clinical purposes.

1. Laboratory

Elevated serum IgG4 levels were initially pivotal to the diagnosis of IgG4-RD but it has been found that it is neither necessary nor sufficient for the diagnosis. Studies have shown elevated IgG4 levels do not confirm and low IgG4 serum levels do not rule out IgG4-RD. Great mimickers of IgG4-RD including pancreatic adenocarcinoma, lymphoma, and ANCA associated vasculitis can present with elevated serum IgG4 levels while biopsy confirmed IgG4-RD patients can have normal IgG4 concentrations. A meta-analysis of predominantly Caucasian and Asian patients did not reveal a specific cut off value for serum IgG4 level to diagnose IgG4-RD, but did find significantly high pooled sensitivity and specificity for serum IgG4 level testing (25). However, another study has shown specificity and positive predictive value of elevated serum IgG4 concentrations to be 60% and 34% respectively (26). Typically, an elevated serum IgG4 concentration in the right clinical setting with typical organ involvement of IgG4-RD can favor or heighten clinical suspicion of IgG4-RD. It is important to emphasize elevated IgG4 levels can be found in other diseases, especially other autoimmune conditions, asthma, allergies, plasma cell dyscrasia, multicentric castleman disease and other malignancies. Patients with more than 2 organ involvement of IgG4-RD, usually have higher serum IgG4 concentrations and it is unlikely to have normal serum IgG4 with multiple organ involvement. On another note, the higher serum IgG4 has higher likelihood of representing IgG4-RD. There are only a few conditions that can cause serum IgG4 concentrations > 5 times upper limit of normal. Increased ratios of IgG4 to total IgG (>10%) is also a helpful finding and can increase diagnostic specificity, especially when IgG4 concentrations are only slightly raised (27).

Monitoring of serum IgG4 concentrations in assessment of disease activity seems useful in some patients, but cannot be considered as the only determinant of disease activity and prompt treatment. The serum IgG4 concentration decreases rapidly after treatment with glucocorticoid or B cell depletion in most patients, but many patients do not achieve normal levels while in clinical remission. Disease relapses also can occur in 10% of patients with low serum IgG4 (28). In a prospective trial of rituximab in IgG4-RD, higher baseline elevations in serum IgG4, IgE and blood eosinophil concentrations predicted greater risk of

IgG4-RD relapse as well as shorter time to relapse (29), arguing for the measurement of these values prior to treatment.

When interpreting low serum IgG4 levels, one must rule out the effects of prozone phenomenon in the immunoassay, a condition in which excess antigen competes for binding sites on the antibody, and thereby causes immune complexes to resolubilize and reduce the signal detected. It is important to recognize this phenomenon as many clinicians rely on an elevated serum IgG4 level for diagnosis and often miss patients who actually have IgG4-RD due to inaccurately low serum IgG4 level. (30). Egner et al found that 4 years after the initial report of prozone phenomenon in IgG4 assay, this error still occurs in 41% of the high serum IgG4 measurements causing spurious reading in their cohort at UK (31). It is highly encouraged to dilute the test sample to allow the antibody concentration to remain in excess of the antigen concentration and check for prozoning in the initial sample. This simple check will enable the identification of elevated serum concentrations of IgG4 that may otherwise be missed.

The identification of high numbers of plasmablasts within blood by flow cytometry has been suggested to be a more sensitive biomarker than serum IgG4 concentrations for disease activity in IgG4-RD. Plasmablasts are usually found elevated in active IgG4-RD, even in those with normal serum IgG4 concentrations, and has been shown to decrease when compared to controls after treatment with rituximab (32). Measurement of plasmablasts is done by flow cytometry on fresh blood samples and is not easy to perform regularly other than in research settings.

Doorenspleet et al (33) have recently shown a significant role for measurement of dominant IgG4 B cell receptor clones as a biomarker for IgG4 related cholangitis. Their initial study showed abundance of these specific clones measured by next generation sequencing in both peripheral blood and tissue of the patients with IgG4 related cholangitis (34). They developed a more affordable and practical technique of quantitative polymerase chain reaction (qPCR) to measure the ratio of IgG4/IgG RNA of the same B cell receptors and found sensitivity of 94% and specificity of 99% for diagnosis of IgG4-related cholangitis. Serum IgG4 concentration's sensitivity and specificity were calculated in the same study and were 86% and 73% respectively (33). Measurement of IgG4/IgG RNA ratio by qPCR can be a promising biomarker for the disease but will need further validation in other cohorts.

Hypocomplementemia has been found among active IgG4-RD patients with systemic disease specifically with renal involvement (35). However, traditionally IgG4 molecule is not thought to bind complement well and the low complements associated with renal disease in these patients may be due to the associated higher concentrations of other IgG subclasses, such as IgG1(36) (37). Research on anti-hinge antibodies found in patients with RA, may help elucidate the role of complement activation in IgG4-RD ((38).

IgE levels and peripheral eosinophilia have been other common features in IgG4-RD as are positive anti-nuclear antibody and rheumatoid factor at low titers (35, 39). C-reactive protein and erythrocyte sedimentation rate are nonspecific markers of inflammation and are not typically elevated due to IgG4-RD unless associated with another type of inflammation at

the time of diagnosis like in cases of aortitis or cholangitis. (35) There has been significant debate between investigators if elevated CRP is more suggestive of multi-centric castleman disease rather than IgG4-RD. At this point, we conclude that if there is significant elevation of CRP, the clinician should consider other diagnoses including multicentric castlman disease and use their insightful interpretation of this laboratory finding in correlation with other clinicopathological features to make the diagnosis. A list of most common laboratory findings associated with IgG4-RD is summarized in Table 3.

2. Imaging

Often patients with IgG4-RD present with tumor like lesions and have already undergone either a computed tomography (CT) or magnetic resonance imaging (MRI) of the area affected by the disease to further characterize the disease.

Most cohorts report 56–60% of patients with IgG4-RD have multiple organ involvement at the time of diagnosis (40). However, many patients have clinical findings of one organ involvement at the time of diagnosis by history and physical exam, making the discovery of other organ involvement only possible by imaging studies.

As most symptoms of IgG4-RD are due to mass effect or damage to the organ due to fibroinflammatory infiltration, it is fair to say many patients may have evidence of other organ involvement on the cross -sectional imaging while being asymptomatic. Thus, performing a thorough imaging of chest and abdomen is necessary for assessment of disease activity at the time of the diagnosis. There have been much discussions among IgG4-RD investigators regarding the specific type of imaging and which modality is the best to evaluate the disease activity. 18-Fluorodeoxyglucose positron emission tomography (FDG PET/CT) has shown effective diagnostic utility in IgG4-RD due to its ability to identify active inflammatory lesions, enabling a delineation of disease extent (41). Most investigators find FDG PET/CT imaging a difficult and expensive test to perform at the diagnosis of each patient and for monitoring of disease activity. It may be best to conclude that IgG4-RD patients will require a whole body imaging assessment but leave it to the discretion of the clinician to choose between computed tomography with contrast, magnetic resonance imaging or PET/CT. There are certain imaging findings which in the right context would make the clinician more confident to make the diagnosis of IgG4-RD. The characteristic imaging patterns that are strong indicators of IgG4-RD (41, 42) are listed in Table 4.

Additionally, there have been suggestions for a role for gallium SPECT/CT in the diagnosis of IgG4-RD and its treatment response (43). As this test is cheaper and more readily available than FDG PET CT scan, if studies confirm that it offers similar diagnostic efficacy, it would be a better option (44). There are also thoughts that gallium SPECT/CT may be superior to PET/CT for IgG4-RD in the kidneys because it allows differentiation of renal involvement and perirenal pseudotumor (45).

3. Histopathology

Histopathologic assessment of the affected organs remains the gold standard for the diagnosis of IgG4-RD. In most cases the biopsy is the best way to exclude the mimickers of IgG4-RD including malignancy or infection. Needle biopsies may provide sufficient tissue

to exclude the mimickers but not enough evidence to evaluate for the characteristic histology for IgG4-RD. Pathological findings of dense lymphoplasmacytic infiltration, storiform fibrosis (an irregularly cartwheel like fibrotic pattern), and obliterative phlebitis are three hallmarks of IgG4-RD in the tissue [Figure 1A] (46). According to the consensus statement on the pathology of IgG4-RD, two out of the three histological findings are needed for IgG4-RD diagnosis (47). Findings of tissue eosinophilia and presence of germinal centers in the affected organs are common on biopsy specimens and can strengthen suspicion for this disease. On the other hand, presence of granuloma, prominent neutrophilic infiltration and necrosis are findings that would exclude the diagnosis of IgG4-RD and increase the suspicion for infections, sarcoidosis or other autoimmune process like granulomatosis with polyangiitis (GPA). For pathological diagnosis of IgG4-RD, in addition to the above histology, presence of IgG4 + plasma cells infiltrating the tissue is necessary [Figure 1B]. There has been controversy in the agreement for the required number of IgG4 plasma cells and it can vary in different organs. The consensus pathology statement considers at least > 10 in some organs including pancreas and >50 in most organs and a ratio of IgG4+ to IgG+ plasma cells of > 40% (47). This rate is associated with sensitivity of 94.4% and a specificity of 85.7% (48).

However, IgG4 + plasma cell infiltration has been frequently seen in mimickers of IgG4-RD and therefore, without the above mentioned histological findings, should not be diagnostic for the disease. Relying solely on the number of IgG4 + plasma cells may misdiagnose cases of pancreatic cancer, castleman disease, GPA, sarcoidosis, infections and lymphomas. Although pathology is the key in the diagnosis, similar pathologic findings in certain tissue in the absence of typical organ involvement may be considered nonspecific. Skin, lymph node, thyroid and nasosinus cavities are among the sites that can show IgG4+ plasma cells in the setting of fibro inflammation without specificity.

Also, it is important to highlight that a negative or inconclusive biopsy result should not rule out IgG4-RD due to inherent sampling variability present in needle biopsies and sometimes fibrotic phase of the disease which lacks inflammation and IgG4+ cells.

4- TREATMENT & MANAGEMENT

As there has been no randomized controlled study on the treatment of IgG4-RD, the best evidence-based optimal treatment of this disorder is still unknown. Several observational studies have reported the effectiveness of certain medications in inducing remission and maintaining lower relapse rates which are discussed here further. The choice of using certain medication for treatment of IgG4-RD varies in different countries, among specialties and different organ involvements (49).

1. Glucocorticoid treatment

Glucocorticoids are cornerstone therapy for this condition. There has been report of 97–100% response to glucocorticoid therapy in this disease (37). Response to glucocorticoids has become part of the diagnostic criteria for diagnosis of AIP (23). In most studies, glucocorticoids are used as the initial therapy for induction of IgG4-RD and many clinicians use low dose 5–7.5 mg of prednisone equivalent for maintenance therapy. Despite short

follow ups, between 40–76% of patient who had successful treatment with glucocorticoids will relapse in the same organ or another, requiring several induction treatments and long tapers (50). Patients with IgG4-RD are usually older and have a high tendency to develop diabetes due to pancreas injury and are subject to significant complications of steroid therapy including challenges with sugar control, cataract, osteoporosis and increased cardiovascular disease. The international consensus guidelines on the management of IgG4-RD recommends 2–4 weeks of induction therapy with prednisone equivalent of 0.6 mg/kg or 30 mg/day. The glucocorticoid dose can be tapered over 8–12 weeks (4). During tapering, IgG4-RD has been known to relapse frequently (51). The relapse episodes are treated with the same induction regimen and many clinicians decide to start patients on steroid sparing regimen after the first relapse. Some clinicians may keep the patients on long courses of low dose steroid as maintenance therapy.

2. Steroid Sparing Strategies

Due to the paucity of evidence on steroid-sparing agents in IgG4-RD and lack of any prospective controlled trials, it has been difficult for clinicians to choose one treatment strategy over others. According to a recent meta-analysis(49), azathioprine was used in 85% of cases, with the next common being mycophenolate mofetil, methotrexate, tacrolimus, leuflenomide and cyclophosphamide. Many patients have been reported to relapse on low doses of azathioprine (50 mg po daily) or mycophenolate (1 g po daily). It has been reported that the disease has been controlled by increasing the dose but upon evaluation of the series' most of the responses were achieved in combination with glucocorticoids making it difficult to assess their efficacy (49). There have been no studies comparing the efficacy of these conventional steroid sparing agents. The choice of immunosuppressive agent is heavily influenced by specific organ involvement and the specialty of the clinician taking care of the patient. Most studies on AIP have used azathioprine as steroid sparing agent of choice as it is most common immunosuppressive agent used by gastroenterologists.

3. Biologics

Rituximab has shown promise in treating patients with IgG4-RD in multiple case series (52) and a prospective open label study of 30 patients which showed 97% response rate with significant reduction in patient's baseline IgG4-RD responder index (IgG4-RD RI). The primary outcome of this trial was defined as decline in IgG4-RD RI >2 , no disease flare before month 6th and off any glucocorticoid between months 2 and 6 was achieved in 77% of the patients. Similar results were observed by other investigators conforming a significant role of B cell depletion in this condition (53). In clinical practice rituximab is usually considered the first steroid sparing agent after a relapse in countries that the medication is available (54).

Bortezomib, a proteasome inhibitor previously used to treat multiple myeloma, was reported in a patient with IgG4-RD refractory to steroids and surgical treatment, with clinical improvement in orbital pseudotumor and pulmonary infiltration (55). However, it is important to note bortezomib was used in combination with cyclophosphamide and therefore is unclear if bortezomib is truly clinically effective. Yamamota et al described the effectiveness of abatacept in a rituximab refractory IgG4-RD patient, suggesting a more

important role for T cells in the pathogenesis of IgG4-RD. The patient in this study had complete depletion of CD 19+ cells and still had a relapse (56). Although the mechanism in which abatacept helped maintain relapse-free period in this IgG4-RD patient is unknown, the author surmises a role for follicular helper T cells as well as a role in which abatacept makes dendritic cells and macrophages secrete indoleamine 2,3-deoxygenase, which can inhibit the proliferation of T cells (57, 58).

Infliximab, a monoclonal antibody against tumor necrosis factor alpha, was recently proposed for use in the treatment of IgG4-related orbital disease refractory to corticosteroid treatment. This biologic is known to be beneficial in severe orbital inflammation refractory to conventional immunosuppressive treatment and is suggested to have beneficial effects in IgG4-related orbital diseases through interference of IgG4 production in activated plasma cells and mediation by Th2 lymphocytes (59).

4. Radiation

Radiation has traditionally been a useful treatment for orbital pseudotumors. Since the understanding of IgG4-RD and its significant response to glucocorticoids and B cell depletion, clinicians try to spare patients from radiation therapy but there still exist cases who are intolerant to steroids and radiation therapy may be beneficial. One recent case series of IgG4-related ocular adnexal disease reported clinical improvement and ability to taper steroids with minimal complications (60).

5. Stents

IgG4-RD is a fibroinflammatory condition. Delay in prompt treatment, may lead to significant fibrosis and damage which will be refractory to glucocorticoid and other immunosuppressive treatment. The fibrotic tissue or mass can cause mechanical obstruction and dysfunction of the organ which can be relieved mechanically. In the setting of obstructive jaundice secondary to IgG4 related cholangitis, there is a role for relieving obstruction or biliary strictures through endoscopic placement of metal or plastic stents. (61). Similarly, in IgG4-RD retroperitoneal fibrosis, several case reports have shown the benefit of ureteral stenting when significant ureteral obstruction is present (62, 63). Sometimes these measures are used for temporary relief in the acute presentation until the medical treatment start working. In some cases, it may be the patient's only option because of end stage disease.

5- PROGNOSIS

As there have been limited studies on IgG4-RD, the natural course of IgG4-RD remains incompletely defined. Case reports and case series indicate some patients improve temporarily without treatment, but many experience a recurrence of their disease in the same or another organ and may have chronic progressive disease (64). It is important to evaluate for multiorgan involvement in patients who present with single organ disease because lack of prompt treatment of certain organs can cause irreversible damage. In those without any treatment, cirrhosis and portal hypertension, retroperitoneal fibrosis, complications from

aortic aneurysms, biliary obstruction and diabetes mellitus are all causes of significant morbidity and mortality. Further studies are needed to delineate long term prognosis.

There have been few recent studies, suggesting an increased risk of cancer in patients with IgG4-RD compared to general population. Yamamoto et al and Hugget et al reported an 10.4% and 11% rate of malignancy in their IgG4-RD cohort over a 3-year period with estimated risk of approximately 3 times higher than general population (65). Study by Asano et al (66) even showed more striking results with rate of 22% over a mean follow up of 6 years. The older age of these patients in the IgG4-RD cohorts and the frequent cross sectional imaging for monitoring their disease activity could be important bias in these studies. More detailed investigations are required to evaluate the true relationship between IgG4-RD and malignancy.

6- CONCLUSION

Tissue biopsy remains the gold standard for the diagnosis but vigorous clinicopathological correlation is the mainstay for confirming IgG4-RD [Figure 2]. Awareness of clinicians about this condition will increase their consideration and rate of prompt diagnosis which is essential to prevent damage in critical organs. The lack of reliable biomarker for this condition has been an important hurdle for diagnosis. Advances in understanding its pathogenesis, especially in the role of plasmablasts as well as the interaction between T cells and B cells has led to exciting and promising ideas which may lead to new biomarker and novel therapeutic options. It is still unknown which steroid-sparing medications would be beneficial in IgG4-RD due to lack of randomized controlled trials. However, with increased awareness and international collaborations, the field will move forward to conduct new clinical trials to show efficacy of medications for maintenance therapy in IgG4-RD.

Expert Commentary

IgG4-RD tend to present as tumorous lesions mimicking malignancy, infectious disorders or inflammatory conditions like GPA (Wegener's). Most patients undergo invasive procedures for resection or biopsy of the affected organ to exclude other conditions. Unfortunately, most of those patients get dismissed by the clinicians given the good news that their disease was not malignancy. Many of them have recurrence of the condition in other organs after a few months or years and return to the medical system for further burdensome and expensive work ups or present with dysfunction of the organ due to progression of fibrosis which can cause irreversible damage like cirrhosis, renal failure and loss of vision.

IgG4-RD is an under recognized condition but not a rare disease.

The most basic determination of the population burden of IgG4-RD is the estimate of its incidence and prevalence. These estimates do not exist for IgG4-RD because the diagnosis is so new. There have been only a few studies pertaining to the epidemiology of the disease from Japan, mostly focused on autoimmune pancreatitis. Understanding the true epidemiology of IgG4-RD has been hampered by insufficient awareness of this newly recognized condition. Definitive diagnosis generally requires a biopsy, insightful interpretation of the pathology by an expert pathologist who considers the disease, and

rigorous clinicopathological correlation with patient's history, radiology imaging and laboratory findings. Initiation of these protocols takes time and building of awareness to facilitate proper diagnosis is essential. On the other hand, identification of a reliable biomarker would facilitate such an effort to identify more patients based on the suggestive laboratory test. Since the initial recognition of this condition and even up to now in Japan, the elevation of serum IgG4 concentration and increased numbers of IgG4-positive plasma cells in tissue have been regarded as diagnostic hallmarks. However, there exists significant variability in the reported frequency of elevated serum IgG4 in the published series from 44%–100%. Recently, investigators in the West have been disregarding serum IgG4 as a diagnostic factor for the condition because of lack of accuracy in the assay and values.

Nonetheless, elevation of serum IgG4 is highly suggestive of IgG4-RD particularly in a patient with characteristic organ involvement such as an orbital tumefactive lesion. An elevation greater than 2 fold of upper limit of normal (normal: 140 mg/dl) has a specificity of 99% for IgG4-RD and is rarely observed in other conditions. Moreover, in the majority of patients' serum IgG4 concentrations correlate approximately with disease activity. Elevation of the serum IgG4 in many patients with multiple organ involvement is dramatic, occasionally reaching 30 to 40 times the upper limit of normal.

There is no one test or clinical feature that serves as a definitive marker for the disease. Lack of a reliable biomarker has caused difficulty in making diagnosis even when a clinician is aware of this condition. Diagnostic delays in the setting of IgG4-RD can lead to cirrhosis, pancreatic failure, aneurysms of the thoracic or abdominal aorta, advanced renal dysfunction, and many other complications. The failure of serum IgG4 assays to identify potential IgG4-RD patients accurately may also lead to additional morbidity and costs from unnecessary diagnostic procedures. For this reason, better understanding of the current diagnostic tests and correlation of clinicopathological findings summarized in this review can help the diagnosis and disease activity monitoring of this condition.

One of the most characteristic features of this condition is its responsiveness to steroid treatment. The response is usually striking and has been part of some of the classification criteria for diagnosis of IgG4-RD. Although patients with IgG4-RD have complete remission after a short period of treatment with glucocorticoid, there is a crucial need for an effective steroid sparing agent for their maintenance therapy. Glucocorticoid side effects are well known and more pronounced in this patient population as they are usually older and some have already developed diabetes due to pancreatic insufficiency. In this review, we have summarized the available treatment strategies which are vastly used by IgG4-RD experts for treatment of patients with this condition.

5-year view

This condition has received an official recognition by medical society in the past decade. Lots have been achieved in its clinical description and responsiveness to treatment. Many ongoing investigations in understanding the mechanism of the disease will be guiding the path in the next five years to identify reliable biomarkers for diagnosing the disease and to approach its management.

Acknowledgments

Funding

This manuscript was funded by the National Institutes of Health, National Center for Advancing Translational Sciences (KL2TR000455 and UL1TR000454)

References

*= of interest; **= of considerable interest

1. Kamisawa T, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. *J Gastroenterol*. 2006; 41(7):613–25. [PubMed: 16932997]
- 2***. Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med*. 2012; 366(6):539–51. A thoughtful review of clinical and pathological aspects of IgG4-RD. [PubMed: 22316447]
3. Culver EL, Sadler R, Simpson D, Cargill T, Makuch M, Bateman AC, et al. Elevated Serum IgG4 Levels in Diagnosis, Treatment Response, Organ Involvement, and Relapse in a Prospective IgG4-Related Disease UK Cohort. *Am J Gastroenterol*. 2016; 111(5):733–43. [PubMed: 27091321]
- 4***. Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN, et al. International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease. *Arthritis Rheumatol*. 2015; 67(7):1688–99. An important international consensus statement of the IgG4-RD experts on management of patients with systemic IgG4-RD. [PubMed: 25809420]
5. Uchida K, Masamune A, Shimosegawa T, Okazaki K. Prevalence of IgG4-Related Disease in Japan Based on Nationwide Survey in 2009. *Int J Rheumatol*. 2012; 2012:358371. [PubMed: 22899936]
6. Wallace ZS, Deshpande V, Mattoo H, Mahajan VS, Kulikova M, Pillai S, et al. IgG4-Related Disease: Clinical and Laboratory Features in One Hundred Twenty-Five Patients. *Arthritis Rheumatol*. 2015; 67(9):2466–75. [PubMed: 25988916]
7. Zen Y, Nakanuma Y. IgG4-Related Disease: A Cross-sectional Study of 114 Cases. *The American Journal of Surgical Pathology*. 2010; 34(12):1812–9. [PubMed: 21107087]
8. Karim F, Loeffen J, Bramer W, Westenberg L, Verdijk R, van Hagen M, et al. IgG4-related disease: a systematic review of this unrecognized disease in pediatrics. *Pediatr Rheumatol Online J*. 2016; 14(1):18. [PubMed: 27012661]
9. Sato Y, Yoshino T. IgG4-Related Lymphadenopathy. *Int J Rheumatol*. 2012; 2012:572539. [PubMed: 22719769]
10. Cheuk W, Yuen HK, Chu SY, Chiu EK, Lam LK, Chan JK. Lymphadenopathy of IgG4-related sclerosing disease. *Am J Surg Pathol*. 2008; 32(5):671–81. [PubMed: 18344866]
11. Della Torre E, Mattoo H, Mahajan VS, Carruthers M, Pillai S, Stone JH. Prevalence of atopy, eosinophilia, and IgE elevation in IgG4-related disease. *Allergy*. 2014; 69(2):269–72. [PubMed: 24266692]
12. Akiyama M, Yasuoka H, Yamaoka K, Suzuki K, Kaneko Y, Kondo H, et al. Enhanced IgG4 production by follicular helper 2 T cells and the involvement of follicular helper 1 T cells in the pathogenesis of IgG4-related disease. *Arthritis Res Ther*. 2016; 18:167. [PubMed: 27411315]
13. Ohno K, Sato Y, Ohshima K-i, Takata K, Miyata-Takata T, Takeuchi M, et al. A subset of ocular adnexal marginal zone lymphomas may arise in association with IgG4-related disease. *Scientific Reports*. 2015; 5:13539. [PubMed: 26311608]
14. Stone JH. IgG4-related disease: pathophysiologic insights drive emerging treatment approaches. *Clin Exp Rheumatol*. 2016; 34(4 Suppl 98):66–8. [PubMed: 27586808]
- 15**. Della-Torre E, Lanzillotta M, Doglioni C. Immunology of IgG4-related disease. *Clin Exp Immunol*. 2015; 181(2):191–206. A thorough and detailed review of immunologic aspects of the IgG4-RD with well illustrated model for mechanism of the disease. [PubMed: 25865251]
16. Watanabe T, Yamashita K, Kudo M. IgG4-Related Disease and Innate Immunity. *Curr Top Microbiol Immunol*. 2017; 401:115–28. [PubMed: 27744509]

17. Beltrame RC, Friderichs M, Fior BR, Schaefer PG, Thome GG, Silva DR, et al. Acute tubulointerstitial nephritis with severe renal impairment associated with multisystem IgG4-related disease. *J Bras Nefrol.* 2016; 38(3):374–8. [PubMed: 27737399]
18. Bennett AE, Fenske NA, Rodriguez-Waitkus P, Messina JL. IgG4-related skin disease may have distinct systemic manifestations: a systematic review. *Int J Dermatol.* 2016; 55(11):1184–95. [PubMed: 27419384]
19. Babur Guler G, Canturk E, Guler E, Oran G, Demir GG, Akcevin A, et al. IgG4-related aortitis mimicking intramural hematoma. *Anatol J Cardiol.* 2016; 16(9):728–9. [PubMed: 27609436]
20. Abe A, Manabe T, Takizawa N, Ueki T, Yamada D, Nagayoshi K, et al. IgG4-related sclerosing mesenteritis causing bowel obstruction: a case report. *Surg Case Rep.* 2016; 2(1):120. [PubMed: 27797069]
21. Acevedo Ribo M, Ahijado Hormigos FJ, Diaz F, Romero Molina M, Fernandez Rojo MA, Garcia Rubiales MA, et al. IgG4-related disease and idiopathic membranous nephropathy: “The clothes do not make the man”. *Clin Nephrol.* 2016; 86(12):345–8. [PubMed: 27737530]
22. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol.* 2012; 22(1):21–30. [PubMed: 22218969]
23. Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas.* 2011; 40(3):352–8. [PubMed: 21412117]
24. Kawano M, Saeki T, Nakashima H, Nishi S, Yamaguchi Y, Hisano S, et al. Proposal for diagnostic criteria for IgG4-related kidney disease. *Clin Exp Nephrol.* 2011; 15(5):615–26. [PubMed: 21898030]
25. Xu WL, Ling YC, Wang ZK, Deng F. Diagnostic performance of serum IgG4 level for IgG4-related disease: a meta-analysis. *Sci Rep.* 2016; 6:32035. [PubMed: 27558881]
26. Carruthers MN, Khosroshahi A, Augustin T, Deshpande V, Stone JH. The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. *Ann Rheum Dis.* 2015; 74(1):14–8. [PubMed: 24651618]
27. Boonstra K, Culver EL, de Buy Wenniger LM, van Heerde MJ, van Erpecum KJ, Poen AC, et al. Serum immunoglobulin G4 and immunoglobulin G1 for distinguishing immunoglobulin G4-associated cholangitis from primary sclerosing cholangitis. *Hepatology.* 2014; 59(5):1954–63. [PubMed: 24375491]
28. Kamisawa T, Shimosegawa T, Okazaki K, Nishino T, Watanabe H, Kanno A, et al. Standard steroid treatment for autoimmune pancreatitis. *Gut.* 2009; 58(11):1504–7. [PubMed: 19398440]
29. Wallace ZS, Mattoo H, Mahajan VS, Kulikova M, Lu L, Deshpande V, et al. Predictors of disease relapse in IgG4-related disease following rituximab. *Rheumatology (Oxford).* 2016; 55(6):1000–8. [PubMed: 26888853]
30. Khosroshahi A, Cheryk LA, Carruthers MN, Edwards JA, Bloch DB, Stone JH. Brief Report: spuriously low serum IgG4 concentrations caused by the prozone phenomenon in patients with IgG4-related disease. *Arthritis Rheumatol.* 2014; 66(1):213–7. [PubMed: 24431286]
31. Egner W, Swallow K, Lock RJ, Patel D. Falsely low immunoglobulin (Ig)G4 in routine analysis: how not to miss IgG4 disease. *Clin Exp Immunol.* 2016; 186(1):57–63. [PubMed: 27125474]
32. Wallace ZS, Mattoo H, Carruthers M, Mahajan VS, Della Torre E, Lee H, et al. Plasmablasts as a biomarker for IgG4-related disease, independent of serum IgG4 concentrations. *Ann Rheum Dis.* 2015; 74(1):190–5. [PubMed: 24817416]
33. Doorenspleet ME, Hubers LM, Culver EL, Maillette de Buy Wenniger LJ, Klarenbeek PL, Chapman RW, et al. Immunoglobulin G4(+) B-cell receptor clones distinguish immunoglobulin G4-related disease from primary sclerosing cholangitis and biliary/pancreatic malignancies. *Hepatology.* 2016; 64(2):501–7. [PubMed: 27015613]
34. Maillette de Buy Wenniger LJ, Doorenspleet ME, Klarenbeek PL, Verheij J, Baas F, Elferink RP, et al. Immunoglobulin G4+ clones identified by next-generation sequencing dominate the B cell receptor repertoire in immunoglobulin G4 associated cholangitis. *Hepatology.* 2013; 57(6):2390–8. [PubMed: 23300096]

35. Wallace ZS, Deshpande V, Mattoo H, Mahajan VS, Kulikova M, Pillai S, et al. IgG4-Related Disease: Baseline clinical and laboratory features in 125 patients with biopsy-proven disease. *Arthritis & rheumatology* (Hoboken, NJ). 2015; 67(9):2466–75.
36. Kawa, S. The Immunobiology of Immunoglobulin G4 and Complement Activation Pathways in IgG4-Related Disease. Berlin, Heidelberg: Springer Berlin Heidelberg; p. 1-13.
37. Muraki T, Hamano H, Ochi Y, Komatsu K, Komiyama Y, Arakura N, et al. Autoimmune pancreatitis and complement activation system. *Pancreas*. 2006; 32(1):16–21. [PubMed: 16340739]
38. van de Stadt LA, de Vrieze H, Derksen NIL, Brouwer M, Wouters D, van Schaardenburg D, et al. Antibodies to IgG4 Hinge Can Be Found in Rheumatoid Arthritis Patients During All Stages of Disease and May Exacerbate Chronic Antibody-Mediated Inflammation. *Arthritis & Rheumatology*. 2014; 66(5):1133–40. [PubMed: 24782178]
39. Kiyama K, Yoshifuji H, Kandou T, Hosono Y, Kitagori K, Nakashima R, et al. Screening for IgG4-type anti-nuclear antibodies in IgG4-related disease. *BMC Musculoskelet Disord*. 2015; 16:129. [PubMed: 26018403]
40. Inoue D, Yoshida K, Yoneda N, Ozaki K, Matsubara T, Nagai K, et al. IgG4-related disease: dataset of 235 consecutive patients. *Medicine (Baltimore)*. 2015; 94(15):e680. [PubMed: 25881845]
41. Zhang J, Chen H, Ma Y, Xiao Y, Niu N, Lin W, et al. Characterizing IgG4-related disease with (18)F-FDG PET/CT: a prospective cohort study. *European Journal of Nuclear Medicine and Molecular Imaging*. 2014; 41(8):1624–34. [PubMed: 24764034]
42. Inoue D, Zen Y, Abo H, Gabata T, Demachi H, Yoshikawa J, et al. Immunoglobulin G4-related periaortitis and periarteritis: CT findings in 17 patients. *Radiology*. 2011; 261(2):625–33. [PubMed: 21803920]
43. Chuang TL, Hsu BB, Chi CL, Wang YF. Gallium SPECT/CT in evaluation of IgG4-related disease: A case report and literature review. *Medicine (Baltimore)*. 2016; 95(37):e4865. [PubMed: 27631251]
44. Ishii S, Shishido F, Miyajima M, Sakuma K, Shigihara T, Kikuchi K. Whole-Body Gallium-67 Scintigraphic Findings in IgG4-Related Disease. *Clinical Nuclear Medicine*. 2011; 36(7)
45. Aoki A, Sato K, Itabashi M, Takei T, Yoshida T, Arai J, et al. A case of Mikulicz's disease complicated with severe interstitial nephritis associated with IgG4. *Clinical and Experimental Nephrology*. 2009; 13(4):367. [PubMed: 19142575]
46. Ghably JG, Borthwick T, O'Neil TJ, Youngberg GA, Datta AA, Krishnaswamy G. IgG4-related disease: a primer on diagnosis and management. *Ann Allergy Asthma Immunol*. 2015; 114(6): 447–54. [PubMed: 26021892]
47. Bateman AC, Culver EL. IgG4-related disease – experience of 100 consecutive cases from a specialist centre. *Histopathology*. 2016 n/a-n/a.
48. Masaki Y, Kurose N, Yamamoto M, Takahashi H, Saeki T, Azumi A, et al. Cutoff Values of Serum IgG4 and Histopathological IgG4+ Plasma Cells for Diagnosis of Patients with IgG4-Related Disease. *International Journal of Rheumatology*. 2012; 2012:580814. [PubMed: 22654917]
49. Brito-Zeron P, Kostov B, Bosch X, Acar-Denizli N, Ramos-Casals M, Stone JH. Therapeutic approach to IgG4-related disease: A systematic review. *Medicine (Baltimore)*. 2016; 95(26):e4002. [PubMed: 27368010]
50. Sah RP, Chari ST. Recent developments in steroid-responsive pancreatitides (autoimmune pancreatitis). *Curr Opin Gastroenterol*. 2015; 31(5):387–94. [PubMed: 26154429]
- 51***. Hart PA, Topazian MD, Witzig TE, Clain JE, Gleeson FC, Klebig RR, et al. Treatment of relapsing autoimmune pancreatitis with immunomodulators and rituximab: the Mayo Clinic experience. *Gut*. 2013; 62(11):1607–15. A thoughtful description of experience with treatment of relapses and maintenance of remission in IgG4-RD using different steroid-sparing agents. [PubMed: 22936672]
52. Khosroshahi A, Bloch DB, Deshpande V, Stone JH. Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease. *Arthritis Rheum*. 2010; 62(6):1755–62. [PubMed: 20191576]

53. Yamamoto M, Awakawa T, Takahashi H. Is rituximab effective for IgG4-related disease in the long term? Experience of cases treated with rituximab for 4 years. *Ann Rheum Dis*. 2015; 74(8):e46. [PubMed: 25862615]
- 54**. Carruthers MN, Topazian MD, Khosroshahi A, Witzig TE, Wallace ZS, Hart PA, et al. Rituximab for IgG4-related disease: a prospective, open-label trial. *Ann Rheum Dis*. 2015; 74(6): 1171–7. A two center prospective open label study of B cell depletion for treatment of IgG4-RD. [PubMed: 25667206]
55. Khan ML, Colby TV, Viggiano RW, Fonseca R. Treatment With Bortezomib of a Patient Having Hyper IgG4 Disease. *Clinical Lymphoma, Myeloma and Leukemia*. 10(3):217–9.
56. Yamamoto M, Takahashi H, Takano K, Shimizu Y, Sakurai N, Suzuki C, et al. Efficacy of abatacept for IgG4-related disease over 8 months. *Ann Rheum Dis*. 2016; 75(8):1576–8. [PubMed: 27147710]
57. Yamamoto M, Takahashi H, Takano K, Himi T, Nakase H. Response to: ‘Could abatacept directly target expanded plasmablasts in IgG4-related disease?’ by Alegria et al. *Ann Rheum Dis*. 2016; 75(11):e74. [PubMed: 27651399]
58. Davis PM, Nadler SG, Stetsko DK, Suchard SJ. Abatacept modulates human dendritic cell-stimulated T-cell proliferation and effector function independent of IDO induction. *Clin Immunol*. 2008; 126(1):38–47. [PubMed: 17945538]
59. Balaskas K, de Leval L, La Corte R, Zografos L, Guex-Crosier Y. Infliximab Therapy for a Severe Case of IgG4-related Ocular Adnexal Disorder Recalcitrant to Corticosteroid Treatment. *Ocular Immunology and Inflammation*. 2012; 20(6):478–80. [PubMed: 22946470]
60. Lin YH, Yen SH, Tsai CC, Kao SC, Lee FL. Adjunctive Orbital Radiotherapy for Ocular Adnexal IgG4-related Disease: Preliminary Experience in Patients Refractory or Intolerant to Corticosteroid Therapy. *Ocul Immunol Inflamm*. 2015; 23(2):162–7. [PubMed: 25010381]
61. Mahajan A, Ho H, Sauer B, Phillips MS, Shami VM, Ellen K, et al. Temporary placement of fully covered self-expandable metal stents in benign biliary strictures: midterm evaluation (with video). *Gastrointest Endosc*. 2009; 70(2):303–9. [PubMed: 19523620]
62. Maeta S, Munemura C, Ishida C, Fukui T, Murawaki Y. Case report; Acute renal failure due to IgG4-related retroperitoneal fibrosis. *Nihon Naika Gakkai Zasshi*. 2012; 101(4):1079–81. [PubMed: 22730738]
63. Hart PA, Moyer AM, Yi ES, Hogan MC, Pearson RK, Chari ST. IgG4-related paratesticular pseudotumor in a patient with autoimmune pancreatitis and retroperitoneal fibrosis: an extrapancreatic manifestation of IgG4-related disease. *Human Pathology*. 43(11):2084–7.
64. Khosroshahi A, Stone JH. Treatment approaches to IgG4-related systemic disease. *Curr Opin Rheumatol*. 2011; 23(1):67–71. [PubMed: 21124087]
65. Huggett MT, Culver EL, Kumar M, Hurst JM, Rodriguez-Justo M, Chapman MH, et al. Type 1 autoimmune pancreatitis and IgG4-related sclerosing cholangitis is associated with extrapancreatic organ failure, malignancy, and mortality in a prospective UK cohort. *Am J Gastroenterol*. 2014; 109(10):1675–83. [PubMed: 25155229]
66. Asano J, Watanabe T, Oguchi T, Kanai K, Maruyama M, Ito T, et al. Association Between Immunoglobulin G4-related Disease and Malignancy within 12 Years after Diagnosis: An Analysis after Longterm Followup. *J Rheumatol*. 2015; 42(11):2135–42. [PubMed: 26472416]

KEY ISSUES

- The true US prevalence of IgG4-RD is unknown, but is thought to affect males more than females and have an age of onset between 50–70 years old
- Organs can be metachronously affected often leading to clinical and diagnostic confusion
- Elevated IgG4 serum level is neither necessary nor sufficient to diagnose IgG4-RD and in cases of low IgG4 serum level with high clinical suspicion for the disorder, one must check for the presence of prozone effect
- Measuring circulating plasmablasts or IgG4/IgG RNA ratio may be superior biomarkers in active IgG4-RD than measuring serum IgG4 level
- Clinicohistopathological findings remain the diagnostic gold standard for this disorder
- Glucocorticoids remain the best initial therapy although disease relapse is common
- Rituximab has shown benefit as steroid sparing treatment of this disease
- Other steroid sparing agents such as methotrexate, azathioprine, mycophenolate mofetil have been used for maintenance therapy with unknown efficacy
- Surgical resection and placement of stents can be used if medical treatment not useful

Figure 1. Pathology of a lacrimal gland in a patient with multi systemic IgG4-RD

A: High power field view shows significant lymphoplasmacytic infiltration of the gland with fibrosis (Hematoxylin and Eosin staining)

B: IgG4 immunohistochemical staining of the gland shows marked infiltration of the gland by IgG4 + plasma cells

Figure 2. Summary of key elements in diagnosis of IgG4-RD

*Gold Standard and still necessary for diagnosis

Table 1**Mimickers of IgG4-RD**

Autoimmune	Malignancy	Other
Antineutrophil cytoplasmic antibody-associated vasculitis	Adenocarcinoma and Squamous Cell Carcinoma	Castleman's Disease
Granulomatosis with Polyangitis	Extranodal Marginal Zone lymphoma	Cutaneous Plasmacytosis
Eosinophilic Granulomatosis with Polyangitis	Inflammatory myofibroblastic tumor	Erdheim-Chester Disease
Microscopic Polyangitis	Lymphoplasmocytic Lymphoma	Inflammatory Bowel Disease
Sarcoidosis	Lymphoproliferative Disease	Perforating Collagenosis
Sjogren's Disease	Follicular Lymphoma	Primary Sclerosing Cholangitis
		Rhinosinusitis
		Rosai-Dorfman Disease
		Splenic Sclerosing Angiomatoid Nodular transformation
		Xanthogranuloma

Table 2

Conditions previously known as separate entities now mostly recognized as part of IgG4-RD

Mikulicz's disease
Kuttner's tumor
Eosinophilic angiocentric fibrosis
Riedel's thyroiditis
Idiopathic cervical fibrosis
Pulmonary inflammatory pseudotumor
Chronic sclerosing aortitis
Preaortitis and periarteritis
Autoimmune pancreatitis
Sclerosing cholangitis
Idiopathic tubulointerstitial nephritis
Retroperitoneal fibrosis
Sclerosing mesenteritis
Inflammatory aortic aneurysm
Multifocal fibrosclerosis

Table 3

Most common laboratory findings associated with IgG4-RD

Labs associated with IgG4-RD
IgG4 level > 135
Elevated IgG4: IgG ratio >10%
Peripheral eosinophils
CRP normal
ESR normal
ANA low titer positive
Elevated IgE levels
Hypocomplementemia
Increased number of circulating plasmablasts by flow cytometry
qPCR of IgG4/IgG RNA

Table 4

Imaging findings strongly suggestive of IgG4-RD

Imaging patterns strongly suggestive of IgG4-RD
Symmetric bilateral enlargement of salivary glands with even distribution of 18F-FDG uptake without signs of infection
Enlargement of lacrimal glands Involvement of trigeminal nerve branches Orbital myositis Orbital adnexal soft tissue
Bronchovascular and septal thickening in the lungs Pleural or parenchymal nodules
Diffusely enlarged pancreas with loss of lobulation with or without pancreaticobiliary duct narrowing Enhancement around the pancreatic rim Pancreatic atrophy due to damage
Patchy or diffuse thickness of aorta wall and soft tissue around the abdominal aorta
Patchy retroperitoneal lesion with moderate to intense 18F-FDG uptake
Bilateral renal cortex low density areas