Diagnosis and Treatment of IgG4-Related Disease

Terumi Kamisawa and Kazuichi Okazaki

Abstract It is critical to differentiate IgG4-related disease (IgG4-RD) from malignant tumor and similar disease of the affected organ to apply appropriate therapy and avoid unnecessary surgery. IgG4-RD is diagnosed on combination of typical radiological findings; elevation of serum IgG4 levels; histopathological findings of abundant infiltration of IgG4-positive plasma cells and lymphocytes, storiform fibrosis, and obliterative phlebitis; association with other IgG4-related diseases; and response to steroids. Histopathological approach is particularly recommended. Systemic glucocorticoids are currently the first-line approach for IgG4-RD, and the indications are symptoms. The initial recommended dose of oral prednisolone for induction of remission is 0.6 mg/kg/day, administered for 2–4 weeks. This dose is gradually tapered to a maintenance dose of 2.5–5 mg/day over a period of 2–3 months. As IgG4-RD sometimes relapses after steroids, maintenance therapy is usually performed in Japan. However, as IgG4-RD patients are typically elderly and are at high risk of developing steroid-related complications, cessation of the medication should be attempted at least within 3 years. For relapsed IgG4-RD, re-administration or dose up of steroid is effective, but the addition of immunomodulatory drugs such as azathioprine has been considered to be appropriate. B cell depletion with rituximab (an anti-CD20 antibody) is effective, even in many patients in whom treatment with immunomodulatory drugs was unsuccessful. The short-term clinical, morphological, and functional outcomes of most IgG4-RD patients treated with steroid therapy are good, but the long-term outcomes are less clear due to several unknown factors such as relapse, developed fibrosis, and associated malignancy.

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Current Topics in Microbiology and Immunology (2017) 401: 19–33
DOI 10.1007/82_2016_36
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Published Online: 13 February 2017
1 Introduction

IgG4-related disease (IgG4-RD) is a recently recognized inflammatory and fibrosing disease of unknown etiology, which can affect almost any organ and is characterized by abundant infiltration of IgG4-positive plasma cells and elevated serum IgG4 levels (Kamisawa et al. 2015). Prior to our proposal of the concept of IgG4-RD in 2003 (Kamisawa et al. 2003a), manifestations of IgG4-RD were regarded as isolated, organ-specific conditions that included Mikulicz’s disease (IgG4-related dacryoadenitis and sialoadenitis), mass-forming pancreatitis [autoimmune pancreatitis (AIP)], Ormond’s disease (IgG4-related retroperitoneal fibrosis), and idiopathic pseudotumor (IgG4-related pseudotumor). Some cases of IgG4-RD were surgically resected under the diagnosis of malignancy. While IgG4-RD responds well to steroid treatment, some cases of IgG4-RD relapse after such treatment. In this chapter, we focus on a description of the current status of diagnosis and treatment of IgG4-RD.

2 Diagnosis

Diagnosis of IgG4-RD remains a significant clinical challenge, and there is no simple diagnostic test for IgG4-RD. One problem in diagnosis is that IgG4-RD frequently presents both clinically and radiologically with findings that mimic malignancy. It is therefore critical to differentiate IgG4-RD from malignant tumor of the affected organ (cancer or lymphoma) in an accurate and timely manner to
avoid misdiagnosis of malignancy and apply appropriate therapy. It is also recommended to use a histopathological approach to differentiate IgG4-RD from similar diseases of the affected organ [e.g., Sjögren’s disease or primary sclerosing cholangitis (PSC)] that can be diagnosed using specific criteria.

2.1 Epidemiology

The epidemiology of IgG4-RD is difficult to ascertain. This is because awareness of this disease is low, its diagnosis is sometimes difficult, and its symptoms vary. However, it appears that IgG4-RD is a relatively rare disease. The annual incidence rate of AIP patients was estimated as 1.4 per 100,000 people in Japan in 2011 (Kanno et al. 2015). The incidence of IgG4-RD throughout Japan was estimated as 0.28–1.08/100,000 people, with 336–1300 patients newly diagnosed per year (Umehara et al. 2012a).

In terms of gender distribution, IgG4-RD occurs predominantly in elderly males, and the male-to-female ratio was 3.2 (Kanno et al. 2015). Exceptions are patients with IgG4-related dacryoadenitis and sialadenitis, in whom the gender distribution is almost equal. The mean age of AIP patients was reported as 66.3 years (Kanno et al. 2015).

2.2 Clinical Symptoms

The course of IgG4-RD is varied. Some cases improve spontaneously, and the natural course of IgG4-RD is unknown (Kamisawa et al. 2014a). Other cases of IgG4-RD may have a subacute or a chronic course. The clinical symptoms of IgG4-RD also vary and depend on the pattern of organ involvement and the severity of the disease activity. Thus, although severe constitutional symptoms are rare, organomegaly or hypertrophy can cause serious complications of obstruction or compression in some patients including obstructive jaundice in AIP or IgG4-related sclerosing cholangitis; visual disturbance in IgG4-related dacryoadenitis; and hydronephrosis in IgG4-related retroperitoneal fibrosis. Furthermore, persistent inflammation in affected organs has been shown to lead to fibrosis and permanent organ dysfunction or failure. Examples of such complications include exocrine and endocrine pancreatic dysfunction in AIP, liver fibrosis in IgG4-related sclerosing cholangitis, and renal dysfunction in IgG4-related kidney disease (Khosroshahi et al. 2015).

In addition, many patients with IgG4-RD have a history of allergic disease or atopic features (Kamisawa et al. 2009b).
2.3 Laboratory Tests

Although most patients with IgG4-RD have elevated serum IgG4-levels, IgG4-RD cannot be diagnosed solely on the basis of serum IgG4 levels for the following reasons. First, even though elevated serum IgG4 levels (to greater than 135 mg/dl) were reported in 84 % (1586/1883) of patients with IgG4-RD, and the mean serum IgG4 level was 769 mg/dl (Stone et al. 2015), some patients with early or limited stage of IgG4-RD do not present with high IgG4 levels. Second, elevation of serum IgG4 levels is not restricted to IgG4-RD and is also seen in other conditions such as autoimmune disease, allergic conditions, carcinoma, and Castleman’s disease. Indeed, a recent study reported that elevated serum IgG4 levels by themselves have a low specificity (60 %) and a low positive predictive value (34 %) for the diagnosis of IgG4-RD (Carruthers et al. 2015a). Therefore, if serum IgG4 levels are to be taken into account in the diagnosis of IgG4-RD, then rigorous clinicopathological correlation is required.

Routine laboratory tests often provide nonspecific indications of organ involvement in IgG4-RD that require further examination. For example, 34 % of patients with IgG4-RD were reported to have peripheral eosinophilia (Stone et al. 2015). Polyclonal hypergammaglobulinemia, elevation of IgE, the presence of antinuclear antigen, and the presence of rheumatoid factor were found in 61, 58, 30, and 20 % of IgG4-RD patients, respectively, in serological tests. Hypocomplementemia, which is particularly common in patients with IgG4-related kidney disease, was observed in 41 % of IgG4-RD patients (Stone et al. 2015).

2.4 Imaging

CT scanning, MRI imaging, and 18 F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) are popular methods of imaging IgG4-RD. On enhanced CT images of IgG4-RD, a diffuse or focal swelling of organs or soft tissue masses appears with soft tissue attenuation, well-defined margins, and homogeneous enhancement at late stage. These findings present as iso- to hypointense on T2-weighted MRI and reflect increased cellularity and fibrosis (Fujita et al. 2012). FDG-PET/CT is useful for mapping the sites of IgG4-RD by highlighting hypermetabolic activity (Nakatani et al. 2012).

It is sometimes possible to differentiate IgG4-RD from other diseases on the basis of characteristic imaging features of some organs. For example, AIP may be differentiated from pancreatic cancer based on imaging features. Thus, on CT images, typical AIP shows diffuse enlargement of the pancreas with delayed enhancement in association with a capsule-like low-density rim (Fig. 1). On endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP), AIP shows diffuse irregular narrowing of the main pancreatic duct (Fig. 2). On pancreatography, AIP rather than pancreatic
Cancer is suggested by long narrowing of the main pancreatic duct, skipped narrowed lesions, side branch derivation from the narrowed portion, and less upstream dilatation (Kamisawa et al. 2008). In AIP patients, the lower bile duct is frequently stenotic (Fig. 2). Imaging may also help to differentiate IgG4-related sclerosing cholangitis from PSC and hilar cholangiocarcinoma. Thus, dominant cholangiographic findings for PSC that are rarely observed in patients with IgG4-related sclerosing cholangitis include band-like stricture, a beaded or pruned-tree appearance, and diverticulum-like outpouching, while IgG4-related sclerosing cholangitis
commonly displays dilatation after a long stricture of the bile duct. While cholangiography cannot distinguish IgG4-related sclerosing cholangitis from hilar cholangiocarcinoma, IgG4-related sclerosing cholangitis rather than cholangiocarcinoma is highly suggested by wall thickness in the bile duct that appears normal in the cholangiogram on endoscopic ultrasonography or intraductal ultrasonography (Ohara et al. 2012; Kamisawa et al. 2014b).

Imaging features that are commonly found in other IgG4-RDs include the following. In IgG4-related sialadenitis, the submandibular glands are more commonly affected than the parotid glands. In IgG4-related dacyroadenitis, in addition to (often bilateral) lacrimal glands, other tissues, such as extraocular muscles, orbital fat tissues, eyelids, trigeminal nerve branches, and nasolacrimal duct, are sometimes involved (Koizumi et al. 2014). In IgG4-related lung disease, common imaging findings are thickening of the perilymphatic interstitium and mediastinal lymphadenopathy with or without subpleural and/or peribronchovascular consolidation (Matsui et al. 2013). In IgG4-related kidney disease, characteristic imaging findings are multiple low-density lesions on enhanced CT, diffuse kidney enlargement, hypovascular solitary mass in the kidney, and hypertrophic lesion of the renal pelvic wall without irregularity of the renal pelvic surface (Kawano et al. 2011). In IgG4-related retroperitoneal fibrosis, a soft tissue mass surrounding the aorta and/or adjacent tissues, sometimes with hydronephrosis, is observed (Chiba et al. 2013).

2.5 Histopathology

The current gold standard for the diagnosis of IgG4-RD is its characteristic histology and immunohistochemistry, which is almost the same regardless of the organs involved. Major histopathological features of IgG4-RD are dense lymphoplasmacytic infiltration with storiform fibrosis, obliterative phlebitis, and abundant infiltration of IgG4-positive plasma cells. However, some of these features can also be found in other diseases. For example, the presence of significant infiltration of IgG4-positive plasma cells in a biopsied specimen is not specific to IgG4-RD. Extensive IgG4-positive plasma cell infiltration has been described in other conditions that commonly mimic IgG4-RD, including malignancy. It is therefore important to differentiate IgG4-RD from malignant tumors of each organ and from similar diseases by additional adequate histopathological examination. One method that may help to distinguish IgG4-RD from other conditions is semiquantitative analysis of immunostaining. A frequently used cutoff value of infiltrated IgG4-positive plasma cells is more than 10 cells per high-power field (HPF), but the cutoff value varies according to the specific tissue. Measurement of the IgG4-positive cell/total IgG-positive cell ratio, in which a minimum ratio of 40% is usually used, may also be useful, especially in cases in which fibrosis is predominant. Although findings of storiform fibrosis and
obliterative phlebitis enhance diagnostic specificity, clinicopathological correlation is always essential (Deshpande et al. 2012).

However, a problem with IgG4-RD analysis based on histopathology is that IgG4-RD-related histopathology can vary according to the stage of the disease. Confirmation of a diagnosis of IgG4-RD in long-standing IgG4-RD using histopathology can be difficult, since the tissue may have become predominantly fibrotic. Although malignancies can generally be excluded by needle biopsies, such biopsies often provide insufficient quantities of tissue to allow confirmation of a diagnosis of IgG4-RD. Samples from previous biopsied or resected specimens may be diagnostic if they are reviewed along with IgG4-immunostaining of paraffin-embedded specimens (Khosroshahi et al. 2015).

2.6 Steroid Responsiveness

Response to steroids can confirm a strong suspicion of the presence of IgG4-RD in patients with appropriate collateral evidence. In cases in which sufficient biopsy specimens cannot be obtained, such as cases where specimens are obtained from the biliary tract, it is difficult to differentiate IgG4-RD from malignancy, and, in such cases, a steroid trial can be applied. However, such a diagnostic steroid trial should be conducted carefully after a negative workup for malignancy that includes a histopathological approach. Furthermore, a steroid trial should only be applied to cases in which the effect of steroid therapy can be evaluated by imaging modalities, since symptomatic and hematological improvements occur nonspecifically in response to steroids, even in malignancy (Kamisawa et al. 2014a; Shimosegawa et al. 2011).

2.7 Diagnostic Criteria

Specific diagnostic criteria have been established for IgG4-RD in each of four organs: AIP (Shimosegawa et al. 2011); IgG4-related sclerosing cholangitis (Ohara et al. 2012); IgG4-related kidney disease (Kawano et al. 2011); and IgG4-related sialadenitis and dacryoadenitis (Mikulicz’s disease) (Masaki et al. 2010). These criteria are roughly based on a combination of the following findings: typical radiological findings; elevation of serum IgG4 levels; histopathological findings of abundant infiltration of IgG4-positive plasma cells and lymphocytes, storiform fibrosis, and obliteratorive phlebitis; association with other IgG4-related diseases; and response to steroids. Comprehensive diagnostic criteria for IgG4-RD that are independent of the predominant organ involvement have been proposed for practical use by general clinicians and non-specialists (Table 1) (Umehara et al. 2012b).
Minimal criteria proposed to consider a previously unrecognized organ or site as being involved in IgG4-RD are appropriate histopathological findings (such findings are essential), with at least one additional criterion of serology, steroid responsiveness, and other organ involvement (Deshpande et al. 2012).

### 3 Treatment

Although an international consensus guidance statement on the management and treatment of IgG4-RD was proposed in 2015 (Khosroshahi et al. 2015), no international treatment guidelines exist, and currently the treatment strategy for AIP is somewhat different in Asian and Western countries. In Japan, the Japanese consensus guidelines for treatment of AIP were revised in 2014 (Kamisawa et al. 2014a). Systemic glucocorticoids are currently the first-line approach for IgG4-RD. However, several approaches to the management of AIP have been reported, including systemic steroids, steroid-sparing immunosuppressive drugs, and biological agents. A definitive treatment strategy for IgG-RD remains to be established.

#### 3.1 Indication of Treatment

It is essential that accurate diagnosis of IgG4-RD is confirmed before starting treatment.

Spontaneous improvement is observed in some cases of IgG4-RD (Kamisawa et al. 2014a). Therefore, in asymptomatic patients with focal pancreatic enlargement, mild submandibular gland enlargement, or lymphadenopathy, it may be appropriate to provide conservative follow-up.
However, uncontrolled disease in certain organs can lead to irreversible damage. Urgent treatment is therefore recommended for the following types of IgG4-RD: aortitis, retroperitoneal fibrosis, sclerosing cholangitis, tubulointerstitial nephritis, pachymeningitis, and pericarditis (Khosroshahi et al. 2015). It is generally accepted that indications for steroid therapy in IgG4-RD patients are symptoms. A recent international multicenter study of the long-term outcomes of AIP indicated that jaundice (63 %, 458/724) was the most common indication for steroid therapy in AIP patients (Hart et al. 2013a). Some cases of markedly fibrotic or advanced diseases (so-called burned-out cases) may show a poor response to steroids (Shimizu et al. 2013).

### 3.2 Induction of Remission

The first goal of therapy in IgG4-RD is to induce remission. Glucocorticoids are the first-line agent for remission induction in all patients with acute, untreated IgG4-RD unless contraindications to such treatment are present. Glucocorticoids are used since response to steroid therapy in IgG4-RD patients is dramatic and consistently leads to clinical improvement.

For treatment of AIP, the Japanese guidelines (Kamisawa et al. 2014a) indicate that, before steroid therapy, obstructive jaundice should be controlled by biliary drainage, and blood glucose levels should be controlled in patients with diabetes mellitus, generally by using insulin. The initial recommended dose of oral prednisolone for induction of remission is 0.6 mg/kg/day, administered for 2–4 weeks. This dose is gradually tapered to a maintenance dose of 2.5–5 mg/day over a period of 2–3 months (Fig. 3). Steroid pulse therapy has been reported to be useful and may prevent unnecessary surgery when oral steroid therapy is not indicated because of the required period for drug tapering (Matsushita et al. 2007).

Response to steroids is assessed by periodic biochemical and serological blood tests, such as tests of liver enzymes and IgG4 levels, respectively, as well as by imaging tests, such as CT, MRCP, and ERCP. Pancreatic size usually normalizes within a few weeks, and biliary drainage becomes unnecessary within about 1 month. A rapid response to steroids confirms the diagnosis of AIP and IgG4-SC.

![Fig. 3](image-url) Schematic illustration of standard steroid treatment in Japan (Kamisawa et al. 2014a, b)
However, if steroid effectiveness is reduced, the patient should be re-evaluated for suspected pancreatic cancer (Kamisawa et al. 2014a).

### 3.3 Relapse and Maintenance Therapy

Relapse of IgG4-RD is defined as the reappearance of symptoms with the reappearance of imaging abnormalities, and/or elevation of serum IgG4 levels.

In a Japanese multicenter survey of AIP (Kamisawa et al. 2009a), steroid therapy significantly lowered the relapse rate of AIP, with the relapse rate being 24% (110/451) in those who received steroid therapy compared to 42% (32/77; p < 0.01) in those not given steroid therapy. In the patients who received steroid therapy, relapse occurred in the pancreas (n = 57, 52%), bile duct (n = 37, 34%), and extrapancreatic lesions.

Whether maintenance steroid therapy benefits AIP patients is still unconfirmed. In a Japanese survey of AIP (Kamisawa et al. 2009a), maintenance steroid therapy was given after remission in 377 (82%) of 459 patients that were treated with steroid. The relapse rate of patients with maintenance therapy was 23% (63/273), which was significantly lower than that of patients who stopped maintenance therapy (34%, 35/104; p < 0.05). The relapse rate of AIP patients treated with steroid in Korea, where maintenance therapy was stopped completely after about 6 months, was 33% (13/40) (Park et al. 2008). The reported relapse rates of patients treated with steroid in the USA and the UK, where no maintenance therapy was given, were 38–60% (Ghazale et al. 2008; Sandanayake et al. 2009; Raina et al. 2009). Given these findings, maintenance therapy with low-dose prednisolone (2.5–5 mg/day) was recommended to prevent relapse.

However, some patients do not relapse without maintenance therapy, and some patients relapse during steroid tapering or during maintenance therapy with relatively high doses of prednisolone. Therefore, it is important to evaluate disease activity in the patient in order to judge the indications of maintenance therapy. Patients at a higher risk of relapse are those with multi-organ disease, significant elevation of serum IgG4 levels, and proximal extrahepatic/intrahepatic biliary strictures, or those with a history of relapse (Kamisawa et al. 2009a, 2014a). These patients with an elevated risk of relapse will likely benefit from maintenance therapy in an effort to minimize morbidity. However, as IgG4-RD patients are typically elderly and are at high risk of developing steroid-related complications such as osteoporosis and diabetes mellitus, cessation of the medication should be attempted. A Japanese multicenter study of AIP (Kamisawa et al. 2009a) indicated that the cumulative rate of relapse (n = 99) after starting steroid therapy was 56% at 1 year, 76% at 2 years, and 92% after 3 years. Cessation of maintenance therapy should be planned within at least 3 years in cases with radiological and serological improvement. It is necessary to evaluate disease activity when stopping medication, and after stopping medication, patients should be followed up for relapse.
For relapsed AIP, re-administration or dose up of steroid was shown to be effective.

In cases where the steroid dosage cannot be tapered due to persistently active disease, the addition of immunomodulatory drugs such as azathioprine, mycophenolate mofetil, or 6-mercaptopurine has been considered to be appropriate (Ghazale et al. 2008; Sandanayake et al. 2009; Raina et al. 2009). However, in a retrospective study that compared treatment of patients who had relapsing AIP with immunomodulatory drugs to steroid monotherapy, no significant difference in relapse-free survival was observed between the 2 groups (Hart et al. 2013b). Retrospective studies suggest that B cell depletion with rituximab (an anti-CD20 antibody) is effective, even in many patients in whom treatment with immunomodulatory drugs was unsuccessful (Topazian et al. 2008; Khosroshahi et al. 2012). A recent prospective study reported that disease response was observed in 97% of patients with IgG4-related disease who were treated with rituximab (Carruthers et al. 2015a,b). The effect of rituximab has been attributed, at least in part, to a failure of repletion of short-lived plasma blasts or plasma cells that produce IgG4 in IgG4-RD (Kamisawa et al. 2015).

3.4 Treatment–Related Side Effects

Treatment-related side effects were reported in a Japanese study of 459 AIP patients treated with steroid (Kamisawa et al. 2009a). These effects included mildly or moderately worse glucose tolerance in several patients; osteoporosis, including compression fractures of lumbar vertebrae \(n = 5\) and avascular necrosis of the femoral head \(n = 3\), in 10 patients; and pneumonia in 3 patients. However, these effects could be controlled with medical treatment and reduction in dosage or cessation of medication.

Side effects of immunosuppressive drugs were reported in a study by the Mayo Clinic (Hart et al. 2013b). In that study, nine (22%) of 41 patients treated with immunosuppressive drugs required drug discontinuation (azathioprine or 6-mercaptopurine) for nausea/vomiting \(n = 4\), transaminitis \(n = 2\), bacteremia \(n = 1\), drug rash \(n = 1\), or myelosuppression \(n = 1\). Side effects seen in three (25%) of 12 patients treated with rituximab included infusion reaction (chills and headache, \(n = 1\)), late-onset neutropenia, and probable bronchiolitis obliterans organizing pneumonia.

4 Prognosis

The short-term clinical, morphological, and functional outcomes of most IgG4-RD patients treated with steroid therapy are good, although the long-term outcomes are less clear. Thus, after steroid therapy, pancreatic endocrine and exocrine functions
improve in half of AIP patients, and salivary and lacrimal gland function improve in patients with IgG4-related sialadenitis and dacroadenitis (Kamisawa et al. 2003a, b). However, there are several unknown factors such as relapse, developed fibrosis, and associated malignancy that influence long-term outcomes. For example, pancreatic stones form in relapsing AIP patients, which might be induced by pancreatic juice stasis from intensified incomplete obstruction of the pancreatic duct system (Hart et al. 2013a, b; Kamisawa et al. 2014a, b).

It has also been reported that the risk of malignancy is high in patients with IgG4-RD (Yamamoto et al. 2012). There are a few reports of an AIP case developing pancreatic cancer, but it is unclear whether there is a relationship between AIP and pancreatic cancer (Kamisawa et al. 2014a). However, as IgG4-RD occurs predominantly in elderly males and steroid therapy is immunosuppressive, imaging and serum tumor markers should be periodically checked during follow-up.

5 Future Perspectives

Early detection of IgG4-RD requires greater awareness of this disease in the medical community. Furthermore, it is necessary to identify more reliable biomarkers than serum IgG4 levels for the assessment of longitudinal disease activity.

With respect to the initial management of IgG4-RD, there is still no consensus regarding the details of the steroid regimen to be used to induce remission, including the duration of induction therapy and the tapering schedule, and it is still unknown which patients might benefit from maintenance therapy. Additionally, the choice of medication (steroid, immunosuppressive drugs, or rituximab) and the optimal duration of maintenance therapy need to be standardized. These points need to be addressed in international, randomized, controlled clinical trials.

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IgG4-Related Disease
Okazaki, K. (Ed.)
2017, VII, 128 p., Hardcover
ISBN: 978-3-319-52541-9