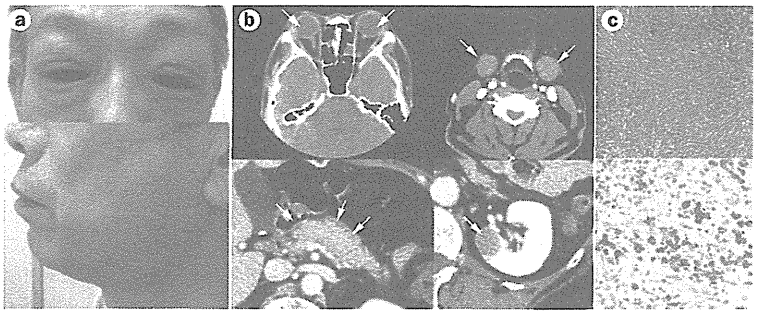

Figure 2 | A typical case with IgG4-related disease exemplifying key diagnostic features. **a** | Dacryoadenitis and sialadenitis manifest as bilateral swelling of the upper eyelids (top panel) and submandibular regions (lower panel), respectively. **b** | CT images reveal enlargement of the lacrimal gland (top left), submandibular gland (top right), and pancreas (bottom left). Multiple areas of poor contrast enhancement, representative of dense inflammation and fibrosis are seen in the kidney (bottom right). **c** | A biopsy specimen from the submandibular gland shows severe infiltration of $IgG4^+$ plasmacytes and storiform—whorled or cartwheel patterned—fibrosis (top: haematoxylin and eosin stain, 100× magnification; bottom: anti-IgG4 monoclonal antibody stain with haematoxylin counterstain, 200× magnification).

and sialadenitis, whereas type 1 AIP was decided to be the preferred term for pancreatic manifestations.

Aetiology and pathogenesis

The aetiology of IgG4-related disease remains unclear. Familial cases are rare, nevertheless, the involvement of complex genetic susceptibility factors and resultant abnormality in immune responses have been suggested to underlie development of the disease.

Susceptibility genes for IgG4-related disease

In a genetic association study comprising 40 patients with type 1 AIP and 201 healthy individuals,[32] *HLA-DRB1*0405* ($P = 2.9 \times 10^{-6}$; OR 4.97) and *HLA-DQB1*0401* ($P = 2.0 \times 10^{-6}$; OR 5.12) haplotypes were found to be associated with type 1 AIP in Japanese populations. A study in 40 Korean patients with type 1 AIP and 154 healthy control individuals revealed that *HLA-DRB1*0701* ($P = 0.033$; OR 2.519) and *DQB1*0202* haplotypes ($P = 0.023$; OR 2.68) were associated with susceptibility to type 1 AIP.[33] In similarly sized studies, the ATP-binding cassette subfamily F member 1 encoding gene (*ABCF1*; $P = 0.0076$; OR 2.96), which regulates TNF signalling,[34] the −110A/A allele of the gene encoding Fc-receptor-like protein 3 (*FCRL3*; $P = 0.012$; OR 7.45),[35] and the −318C/+49A/CT60G ($P = 0.001$, OR 8.53)[36] and +6230G/G ($P = 0.011$, OR 2.48)[37] haplotypes of *CTLA4* have been linked with type 1 AIP in Asian populations. These associations implicated genes related to immune responses in susceptibility to type 1 AIP. Furthermore, the rs2840381, rs1058184, rs2640480 and rs1319782 single nucleotide polymorphisms (SNPs) within *KCNA3*, encoding potassium voltage-gated channel subfamily A member 3, were associated with susceptibility to type 1 AIP in a Japanese population ($P < 0.007$).[38] This protein is known to be the target autoimmune reactions that result in a form of neuromyotonia, although its potential role in IgG4-related disease remains unknown.

The potential involvement of micro-organisms

Micro-organisms might represent a triggering factor for the immune, and potentially autoimmune, responses underlying IgG4-related disease. Indeed, *Helicobacter pylori* plasminogen-binding protein (PBP) has been a focus of attention because antibodies targeting this protein were detected in patients with AIP. Interestingly, PBP shares amino acid sequence homology with the human E3 ubiquitin-protein ligase UBR2, which is expressed in pancreatic acini.[39] However, PBP is not specific to *H. pylori*, and is expressed by other enterobacteria.[40] Furthermore, the study that identified anti-PBP antibodies in AIP[39] only included patients with type 2 AIP; therefore, whether a relationship exists between PBP and IgG4-related disease remains to be determined.

Innate immunity and IgG4-related disease

The contribution of innate immune responses to IgG4-related disease are increasingly recognized. In particular, foreign pathogen-associated molecular patterns (PAMPs), and potentially self-factors, damage-associated molecular patterns (DAMPs), have been implicated as possible triggers of IgG4-related disease. A study published in 2012[41] investigated the capacity of certain receptors that recognize PAMPs to induce IgG4 production; stimulation of peripheral blood mononuclear cells (PBMCs) from patients with IgG4-related disease revealed that various Toll-like receptor (TLR) and nucleotide-binding oligomerization (NOD)-like receptor (NLR) ligands induced the production of large amounts of IgG4 (Figure 3).[41] In PBMCs from healthy individuals, activation of NOD2 by muramyl dipeptide was the most robust activator of IgG4 production.[41] NOD2 activation in $CD14^+$ monocytes was shown to activate nuclear factor κB (NFκB), leading to B-cell-activating factor (BAFF)-dependent induction of IgG4 production by $CD19^+$ B cells.[41] In addition, basophils have been demonstrated to produce BAFF and IL-13 via TLR signalling, and thus maintain type 2 T-helper-(T_H2)-cell-dominant immune responses.[42] In support of a role for induction of BAFF expression downstream for TLR and/or NLR signalling in the pathogenesis of IgG4-related disease, several studies have reported that serum BAFF concentrations are elevated in this disease.[43,44]

Pathogenicity of IgG4 antibodies

High serum levels of IgG4 characterize IgG4-related disease, therefore, whether these antibodies play a part in the pathogenesis of the disease is an obvious question. Owing to the weak disulphide bonds that link the heavy chains within IgG4 antibodies, these antibodies have the unusual ability to exchange half of one IgG4 molecule (a heavy chain–light chain pair) with that of another IgG4 molecule. Thereby, the IgG4 molecule can acquire two distinct Fab arms and become bispecific (Figure 4a). Whereas other subclasses of IgG have two binding site for the target antigen, IgG4 can thus demonstrate functional monovalency and compete with other subclasses for antigen and receptor binding sites.[45] Furthermore, IgG4 shows limited capacity to activate complement cascades

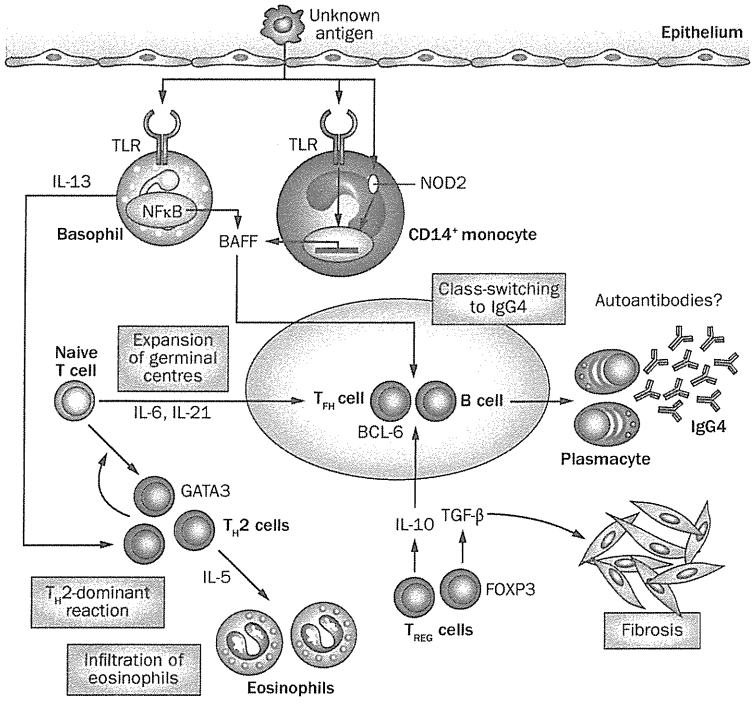

Figure 3 | Immunological responses in inflammatory lesions of IgG4-related disease. PAMPs and DAMPs are recognized by TLRs and NOD2 in monocytes and basophils initiating signalling that leads to the abundant production of BAFF, which promotes immunoglobulin class-switching and results in the production of IgG4. The specific PAMPs and/or DAMPs that are involved in the pathogenesis of IgG4-related disease remain to be determined. Activated basophils also produce IL-13, and support T_H2-cell-dominant inflammation. T_H2 cells secrete IL-4 and IL-5, which promote T_H2 cell self-propagation via differentiation of naive T cells and activation of eosinophils, respectively. Excess immunoreaction of T_H2 cells leads to recruitment of T_{REG} cells, which secrete high levels of IL-10, inducing further class-switching to IgG4, and TGF-β, driving severe fibrosis. In addition, abundant production of IL-6 and IL-21 promotes differentiation of naive T cells to T_{FH} cells, leading to formation of ectopic germinal centres, plasmacyte development and active antibody production. Autoantigens and autoantibodies might also be involved in the pathogenesis of IgG4-related disease, although this hypothesis requires clarification. Abbreviations: BAFF, B-cell-activating factor (also known as, TNF ligand superfamily member 13B, or B-lymphocyte stimulator [BLyS]); DAMPs, damage-associated molecular patterns; FOXP3, forkhead box protein P3; GATA3, GATA-binding factor 3; NFκB, nuclear factor κB; NOD2, nucleotide-binding oligomerization domain-containing protein 2; PAMPs, pathogen-associated molecular patterns; T_{FH}, follicular helper T (cell); T_H2, type 2 T-helper (cell); TGF-β, transforming growth factor-β; TLR, Toll-like receptor; T_{REG}, regulatory T (cell).

and Fcγ receptors (Figure 4b).[45,46] IgG4 antibodies are therefore considered to lack many of the effector functions shown by other IgG subclasses and, hence, IgG4 is often considered to function as an anti-inflammatory antibody,[47–49] Indeed, IgG4 functions as a blocking antibody in bee venom allergy because these antibodies can compete with other antibody subtypes for binding to both allergens and Fc receptors on mast cells, but cannot induce degranulation of these cells, in contrast with IgE.[50] In fact, evidence suggests that repeated exposure to antigen can cause a shift from IgG1 to IgG4 production, potentially reflecting a mechanism that protects against antibody-mediated damage.[45] At present, whether IgG4 antibodies are pathogenic in IgG4-related disease or are produced in excess in response to inflammatory stimuli due to their anti-inflammatory properties, thus potentially representing a byproduct of the immune response, remains unclear.

Another interesting and unique property of IgG4 is the capacity to bind to other antibodies of IgG subclasses via interactions between their Fc portions (Fc–Fc binding).[51] Thus, IgG4 could be envisaged to act similarly to rheumatoid factor (RF), in some respects. However, RF usually binds the Fc regions of other antibodies via its Fab portion, retaining functionality of its Fc regions and the ability to form immune complexes, whereas IgG4 can block Fc-mediated effector function and might dampen the inflammatory response via Fc–Fc binding (Figure 4b). Clarification is needed regarding the roles these complexes might have in the pathogenesis of IgG4-related disease.

Autoantibodies in IgG4-related disease

Hypergammaglobulinaemia and certain autoantibodies are often detected in patients with IgG4-related disease. In an analysis of patients with IgG4-related dacryoadenitis and sialadenitis,[52] ANA (titres ≥160:1) were detected in 15.7%, whereas RF was detected in 20.0%; low levels of anti-DNA antibodies were also detected in some patients.[52] However, these autoantibodies are neither associated with disease activity nor related to the clinical features seen in IgG4-related disease, and are, therefore, considered nonspecific in IgG4-related disease. In terms of other autoantibodies, anti-carbonic anhydrase II antibodies,[53] anti-lactoferrin antibodies,[54] and anti-pancreatic secretory trypsin inhibitor antibodies[55] have been reported in patients with type 1 AIP, but these findings are also not highly specific for this disease. At this point, no direct confirmation has been found that autoantibodies have a role in the pathogenesis of IgG4-related disease.

Cytokines in IgG4-related disease

The immunological characteristics of IgG4-related disease are T_H2-cell-dominant immune responses and abundant infiltration of regulatory T (T_{REG}) cells, which produce IL-10, into the organs involved.[56,57] Tanaka *et al.*[57] analysed the expression of cytokines and chemokines within the minor salivary glands in patients with SS and patients with IgG4-related dacryoadenitis and sialadenitis; immune reactions related to type 1 T-helper (T_H1) cells, T_H2 cells and type 17 T-helper (T_H17) cells were dominant in SS tissues, compared with the T_H2-cell–T_{REG}-cell-dominant responses observed in IgG4-related dacryoadenitis and sialadenitis tissue samples.[57] Indeed, IL-4 and IL-10 expression levels correlated with the ratio of $IgG4^+$:IgG^+ cells in IgG4-related dacryoadenitis and sialadenitis tissue.[57] Furthermore, IL-10 and transforming growth factor (TGF)-β produced by T_{REG} cells have been suggested to be associated with elevated serum levels of IgG4 and fibrosis.[58] Again, this finding could reflect a negative feedback response, with T_{REG} cells and possibly IgG4, which both have potential anti-inflammatory properties, being upregulated after an unknown inflammatory

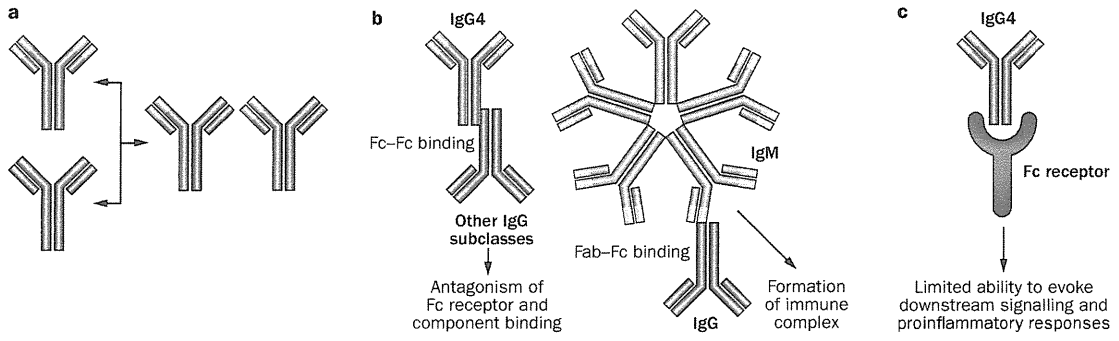

Figure 4 | IgG4 Fab-arm exchange and Fc-dependent interactions. **a** | The IgG4 antibody class demonstrates an unusual characteristic termed Fab-arm exchange, which describes exchange of half a molecule (heavy chain–light chain pair) from one IgG4 for half of a different IgG4 antibody. The IgG4 molecule can thereby acquire two distinct Fab arms, each with different epitope specificity, and thus becoming functionally monovalent, but bispecific. **b** | IgG4 Fc regions can interact with the Fc portions of other IgG subclass antibodies (Fc–Fc binding), which could, potentially, prevent immune-complex-mediated and Fc-receptor-mediated immune responses by blocking interactions with complement proteins and Fc receptors. By contrast, IgM rheumatoid factor Fab regions recognize IgG Fc regions (Fab–Fc binding), which enables immune complex formation and leaves the IgM Fc regions accessible for Fc receptor binding. **c** | The Fc region of IgG4 antibodies can also interact with various Fc receptors and complement proteins, but has minimal capacity to activate them to induce signalling; thus, these antibodies might antagonize proinflammatory responses mediated by other antibody classes via competitive interaction with these molecules.

insult to dampen the immune response. Nakashima and co-workers[59] also reported similar results in IgG4-related tubulointerstitial nephritis lesions. In addition, expression of single-stranded DNA cytosine deaminase is reportedly elevated in labial salivary gland tissue from patients with IgG4-related disease compared with patients with SS or healthy individuals.[60] Interestingly, this protein is considered to lead to active immunoglobulin class-switching.[60] With regard to class-switching in IgG4-related disease, focus has been placed on the role of IL-21 in the formation of lymphoid follicles (Figure 3), with expression of this cytokine in IgG4-related dacryoadenitis and sialadenitis tissue samples correlating with both the number of germinal centres and the $IgG4^+$:IgG^+ cell ratio.[58] Thus, abnormal T_H2-cell and T_{REG}-cell cytokine responses seem to potentiate IgG4 production and promote IgG4-related disease, although the origin of these cytokine imbalances remains unclear.

Epidemiology

The number of patients with IgG4-related disease is estimated to be about 8,000 in Japan, including around 4,300 patients with IgG4-related dacryoadenitis and sialadenitis and 2,700 patients with type 1 AIP.[2,3] Most IgG4-related disease cases have been reported in Asia, but case reports from Europe and the USA are now increasing; thus, whether racial differences in disease epidemiology exist is unknown at present. The average age of disease onset is in the seventh decade of life, with the gender ratio showing a predisposition of IgG4-related disease in men, with the exception of IgG4-related dacryoadenitis and sialadenitis, for which the gender ratio seems almost equal or slightly skewed towards female predominance.[61]

Clinical signs and laboratory findings

Swollen but painless organs are characteristic of IgG4-related disease. Moreover, patients with IgG4-related disease rarely present with general symptoms such as fever and malaise, unlike the situation observed in rheumatic diseases. Laboratory testing often reveals hypergammaglobulinaemia, sometimes positivity for ANAs and RF, but no specific autoantibody is associated with the disease, in principle. Almost all cases present with elevated serum levels of IgG4 (≥135 mg/dl [1.35 g/l]). In fact, patients with IgG4-related dacryoadenitis and sialadenitis often have serum levels of IgG4 exceeding 500 mg/dl (5.00 g/l).[12] Hypocomplementaemia and elevated levels of circulating immune complexes are often detected in patients with multiple organ dysfunction, particularly with renal involvement.

In imaging studies, enhanced CT and FDG-PET are useful tools for the diagnosis and examination of complications of IgG4-related disease (Figure 2b);[62] CT images can reveal organ enlargement, and FDG-PET can detect severe inflammation. Accumulation of FDG at sites atypical for IgG4-related disease is strongly suggestive of underlying cancers.

In the following sections we describe the organ manifestations that consensus statements[30,31] have established as characteristic of IgG4-related disease and that rheumatologists encounter frequently in daily practice. Not all of the manifestations we describe occur in all patients with IgG4-related disease. Whereas some patients present with only a single organ lesion for a prolonged period of time, other patients demonstrate multiple organ involvements simultaneously. However, the mechanism underlying the pathogenetic differences between systemic and focal IgG4-related disease remains unknown.

Lacrimal and salivary glands manifestations

Changes in facial appearance, such as continuous and painless swelling of the upper eyelids, and parotid and submandibular portions, are often an opportunity for diagnosis.[10,11] As the name suggests, IgG4-related dacryoadenitis

and sialadenitis (so-called Mikulicz disease) strictly refers to bilateral and symmetrical enlargement of both lacrimal and salivary glands (Figure 2a);[30] however, patients with only lacrimal gland,[63] or with unilateral submandibular gland involvement[64]—previously known as Küttner tumour and now termed IgG4-related submandibular gland disease[30]—have been encountered. Sicca symptoms are not apparent, or only slightly present, with sialography usually showing normal results. Nevertheless, ultrasonography of the lacrimal and submandibular glands often reveals gathered hypoechoic lesions within the septum.[65]

Pancreas and bile duct manifestations

Pancreatic (type 1 AIP; also known as IgG4-related pancreatitis[30]) and bile duct (IgG4-related sclerosing cholangitis) involvement are recognized features of IgG4-related disease.[18,19] Chief complaints in patients with these conditions are upper abdominal discomfort and obstructive jaundice. However, patients sometimes present with diarrhoea and impaired glucose tolerance due to reductions in the exocrine and endocrine functions of the pancreas.[66] Differentiation of type 1 AIP from pancreatic cancer, and IgG4-related sclerosing cholangitis from cholangiocarcinoma and primary sclerosing cholangitis, is necessary.

Low sonographic echogenicity is indicative of a swollen pancreas, which is sometimes accompanied by highly echogenic regions in type 1 AIP. Enhanced dynamic CT imaging can reveal diffuse or localized enlargement of the pancreas; such lesions have low density in the early-enhanced phase and high density in the delay phase.[67] In particular, a capsule-like rim is a CT finding characteristic of type 1 AIP (Figure 2b), with this belt-like structure around the lesions showing a lower density than lesions found in other disease in the early-enhanced phase.[67] In addition, endoscopic retrograde cholangiopancreatography can be used to assess the condition of the main pancreatic duct at the lesion and stricture of the common bile duct. These findings are useful for differentiation of IgG4-related disease from pancreatic cancer and cholangiocarcinoma.

Pituitary gland and dura mater involvement

Central nervous system involvement in patients with IgG4-related disease has been reported in the forms of hypophysitis (inflammation of the pituitary gland),[68] and pachymeningitis (inflammation of the dura mater).[69] Indeed, a number of patients diagnosed with autoimmune hypophysitis to date might actually have had IgG4-related hypophysitis. IgG4-related hypophysitis typically presents similarly to anterior hypophysitis, causing headache, visual field deficit and lactation; however, patients with this condition demonstrate various symptoms depending on the pattern of hormone failure. On the other hand, posterior hypophysitis in IgG4-related disease is often associated with diabetes insipidus. MRI can reveal enlargement of the pituitary lobes or stalk in patients with suspected IgG4-related hypophysitis. With regard to IgG4-related pachymeningitis, the patient generally presents with chronic headache and cranial neuropathy, such as visual loss and palsy of the facial nerve. Differentiation from hypertrophic pachymeningitis, associated with rheumatoid vasculitis, tuberculosis and mycosis, is necessary, with elevated serum levels of IgG4 and histopathological findings being required for differential diagnosis.

Orbital involvement

Orbital inflammation can be encountered in patients with IgG4-related disease,[70] and is termed 'IgG4-related ophthalmic disease.' In addition to dacryoadenitis, inflammation of the orbital region can manifest as ocular myositis, perineuritis of the optic nerve and trigeminal nerves, and orbital inflammatory pseudotumour.[70] These lesions can lead to ocular dysmotility and weakness or loss of vision. Furthermore, visual imperception can be associated with perineuritis of the trigeminal nerve in the orbit. Infraorbital nerve enlargement (IONE), which is specific to IgG4-related ophthalmic disease, can be detected by MRI: coronal MRI analysis can reveal substantial enlargement of the infraorbital nerves.[71]

Involvement of the thyroid gland

Certain forms of thyroiditis are on the spectrum of IgG4-related systemic disease. For example, a substantial portion of cases of Riedel thyroiditis and the fibrous variant of Hashimoto thyroiditis, which manifest as fibroinflammation of all or a portion of the thyroid as well as surrounding tissues, are considered to represent IgG4-related thyroiditis.[72,73] IgG4-related thyroiditis is often associated with massive enlargement of the thyroid due to lymphocytic infiltration, necessitating surgical treatment in some patients. Furthermore, the fibrous variant of Hashimoto thyroiditis often presents with hypothyroidism.[73]

Lung and respiratory tract manifestations

Pulmonary involvement in IgG4-related disease consists of bronchial and alveolar lesions.[74,75] Patients with bronchiolar lesions often present with asthma-like symptoms, with CT imaging revealing thickened bronchial and bronchiolar walls.[75] By contrast, patients with alveolar lesions are often asymptomatic, but CT imaging detects various patterns of inflammation suggestive of interstitial or organizing pneumonia.[75] Thus, accurate diagnosis of the involvement of lung and respiratory tract in IgG4-related disease based only on imaging findings is difficult.

IgG4-related kidney disease

IgG4-related kidney disease mainly manifests as tubulointerstitial nephritis,[76,77] whereas IgG4-related glomerulonephritis is rare. Mild, early-stage tubulointerstitial nephritis is usually asymptomatic. Thus, almost all patients with IgG4-related disease are asymptomatic with regard to kidney manifestations upon presentation, as IgG4-related kidney disease is often focal. However, contrast-enhanced CT imaging reveals enlarged kidneys with multiple areas of poor contrast

Table 1 | Diagnostic guidelines for IgG4-related disease in Japanese populations

Item in guideline	Japanese Medical Society for Sjögren's Syndrome guidelines, 2008[61]	Japanese Ministry of Health, Labour and Welfare guidelines, 2011[29]
Clinical criteria	Symmetrical swelling of the lacrimal, parotid or submandibular gland, involving at least two pairs of glands and persisting for >3 months	Diffuse or localized swelling, or masses in single or multiple organs
Serological criteria	Serum IgG4 concentrations >135 mg/dl (1.35 g/l)	Serum IgG4 concentrations >135 mg/dl (1.35 g/l)
Histopathological criteria	Substantial $IgG4^+$ plasma cell infiltrates in lacrimal and salivary gland tissues: $IgG4^+$:IgG^+ plasma cell ratio of >50%	Extensive lymphocyte and plasma-cell infiltration and tissue fibrosis: $IgG4^+$:IgG^+ plasma cell ratio of >40% and ≥10 $IgG4^+$ plasma cells per high-power field
Conditions	Diagnosis of IgG4-related disease (Mikulicz disease) requires that the clinical and either the serological or the histopathological criteria are met	Definite disease: satisfying all criteria* Probable disease: both clinical and histopathological criteria are met Possible disease: patient fulfils clinical and serological criteria only
Noted differential diagnoses that should ruled out by additional histopathological examinations	Sarcoidosis, Castleman disease, GPA (Wegener's granulomatosis) and malignant lymphoma	Malignant tumours (cancer or lymphoma), Sjögren's syndrome, primary sclerosing cholangitis, Castleman disease, secondary retroperitoneal fibrosis, GPA (Wegener's granulomatosis), sarcoidosis and Churg–Strauss syndrome

*Patients who do not meet these criteria might still be diagnosed with IgG4-related disease using organ-specific criteria.[100,101] Abbreviation: GPA, granulomatosis with polyangiitis.

(Figure 2b).[77] This abnormal CT finding is an opportunity for diagnosis; however, sporadic IgG4-related lesions have to be differentiated from kidney cancer, especially papillary renal cell carcinoma and metastatic renal tumours. Unfortunately, FDG-PET is not a useful imaging modality for examining renal involvement, because accumulation of radioisotope, which is excreted via the kidneys, is physiologically detected in normal kidneys. Hence, histological examination is recommended in patients with kidney abnormalities detected using CT imaging. In patients with IgG4-related disease, thickened lesions sometimes occur at the renal hilum (where the renal blood vessels, nerves and ureter enter or exit the kidney), and about half of patients with thickened renal hilum develop hydronephrosis due to ureteral obstruction.[77]

Retroperitoneal cavity involvement

Retroperitoneal fibrosis can be drug-induced, malignancy-related or idiopathic.[78] A proportion of cases of idiopathic retroperitoneal fibrosis are considered to represent IgG4-related retroperitoneal fibrosis.[79,80] The main affected sites in IgG4-related retroperitoneal fibrosis are the regions around the thoracic and lumbar spine, the abdominal aorta and branching arteries, and the ureters. Laboratory data often show elevated levels of C-reactive protein (CRP), indicative of inflammation, in retroperitoneal fibrosis.[81] Importantly, a relationship between periaortitis and inflammatory abdominal aortic aneurysm has been suggested;[82] thus, this complication, as well as anti-inflammatory therapy to prevent progression of the aneurysm, might be considered in patients with IgG4-related retroperitoneal fibrosis.

Effects on the prostate gland

Patients with IgG4-related disease often present with symptoms of benign prostatic hyperplasia, including frequent urination and feelings of residual urine.[83] In addition, CT imaging can disclose a severely swollen prostate gland in these individuals. Such patients are usually followed up by urologists under a diagnosis of chronic prostatitis. Histological findings in IgG4-related prostatitis are similar to those in other organ manifestations, including infiltration of lymphocytes and plasma cells accompanying dense tissue fibrosis.[83]

Involvement of lymph nodes

Bilateral hilar lymphadenopathy is often detected in patients with IgG4-related disease, with enlargement of lymph nodes frequently apparent in the regions surrounding the other organs involved.[84] In systemic lymphadenopathy, differentiation from multiple Castleman disease—a condition characterized by noncancerous tumours in lymph nodes resulting from B-cell hyperproliferation—is important, but easily achieved based on clinical symptoms and serological signs of inflammation, such as markedly elevated serum levels of CRP. Indeed, diagnosis of IgG4-related lymphadenopathy is not difficult when other lesions typical of IgG4-related disease are present; however, biopsies of enlarged lymph nodes are required in patients with only lymph node lesions.

Histopathological findings

Obtaining as much histopathological data as possible is desirable in the diagnosis of IgG4-related disease. Nevertheless, the principle histopathological findings associated with lesions in most of the tissues affected by IgG4-related disease are dense lymphoplasmacytic infiltrates, a storiform pattern of fibrosis and obliterative phlebitis.[31,85–94]

The majority of cells comprising tissue infiltrates are small lymphocytes that are distributed diffusely throughout the lesion and intermingled with plasmacytes.[31]

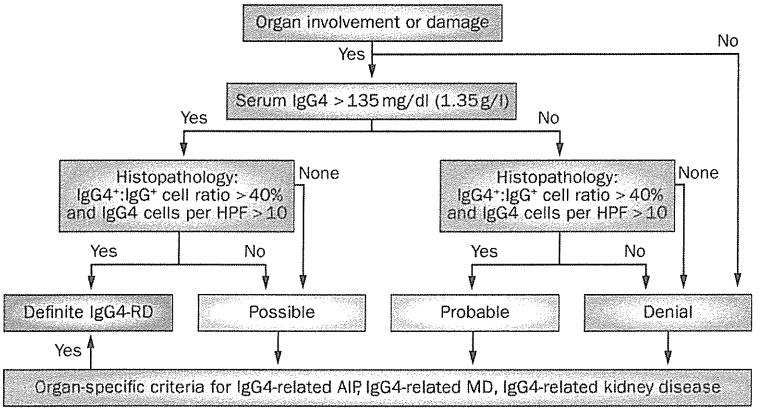

Figure 5 | Diagnostic algorithm for comprehensive diagnostic criteria for IgG4-related disease combined with organ-specific criteria. According to the Japanese Ministry of Health, Labour and Welfare's 2011 guidelines,[29] a diagnosis of IgG4-related disease is definitive in patients meeting all defined clinical (organ enlargement, mass or nodular lesions, or organ dysfunction), serological (serum IgG4 concentration >135 mg/dl [1.35 g/l]), and histopathological (>10 $IgG4^+$ cells per HPF and an $IgG4^+$:IgG^+ cell ratio >40%) criteria. A diagnosis of IgG4-related disease is possible in patients who fulfill the clinical and serological criteria, but with negative results on histopathology or without histopathologic examination, whereas a diagnosis of IgG4-related disease is probable in patients with organ involvement who fulfill the histopathologic criteria, but without serum IgG4 concentrations >135 mg/dl (1.35 g/l). Patients with organ symptoms without satisfying the serological or histopathological criteria are considered unlikely to have IgG4-related disease. Nevertheless, a diagnosis of IgG4-related disease in patients, excluding definite cases, should be confirmed or ruled out using organ-specific criteria for Mikulicz disease (IgG4-associated dacryoadenitis and sialadenitis) and IgG4-related AIP or kidney disease. Patients who fulfill the organ-specific criteria have a definite diagnosis of IgG4-related disease. Abbreviations: AIP, autoimmune pancreatitis; HPF, high-power field; IgG4-RD, IgG4-related disease; MD, Mikulicz disease.

$IgG4^+$ plasmacytes sometimes account for more than a half of the IgG^+ plasmacytes within infiltrates, but lesions with severe fibrosis tend to have a low $IgG4^+$:IgG^+ cell ratio.[79] Ectopic lymphoid follicles with germinal centres are occasionally observed in affected organs.[31] In addition, eosinophils are typically found in low-to-moderate numbers in IgG4-related disease lesions.[31]

Either fibroblasts or myofibroblasts are typically found buried within the lymphoplasmacytic infiltrate in IgG4-related disease lesions.[31] Inflammation of the affected tissues, particularly release of TGF-β by T_{REG} cells (Figure 3),[57,59] probably promotes fibroblast proliferation and deposition of connective tissue, resulting in fibrosis. Storiform fibrosis is a very specific histological feature associated with IgG4-related disease (Figure 2c).[31] The storiform-type (irregular whorled) pattern of fibrosis is often said to resemble a cartwheel, patterning in a straw mat or a Chinese arabesque (foliage-scroll) design. However, this characteristic pattern of fibrosis might not be detected in fine-needle biopsy samples; hence, use of en-bloc biopsy is recommended.

Obliterative phlebitis is another of the pathological findings characteristic of IgG4-related disease,[31] caused by obliteration of the venous channels by extensive lymphoplasmacytic cell infiltration. Lymphocytes, including plasma cells, are seen within both the wall and the lumen of affected venous channels.[31] Fully obliterated veins can necessitate the use of elastin stains for identification. The degree of obliterative phlebitis observed depends on the organ involved;[31] for example, this pathological feature is often easily identified in salivary gland or pancreatic lesions, but is seldom seen in lymph nodes.[31]

In general, inflammatory cell infiltration is observed sporadically in the involved organs in the early stages of IgG4-related disease.[95] As the disease progresses, lesions spread throughout the affected organs and sometimes new lesions appear in different organs, and, in the advance stages of the disease, inflammation is replaced by severe fibrosis.[95] As a result, the involved glands or organs become atrophic and their structures are gradually destroyed.[95]

Diagnosis of IgG4-related disease

Diagnosis of IgG4-related disease should be carried out in a comprehensive manner on the basis of physical, imaging, serological and, especially, histopathological findings. CT imaging or ultrasonography can be used to detect enlarged or thickened organs, whereas serological testing can reveal elevated levels of serum IgG4. In addition, biopsy specimens reveal specific histopathological findings, as discussed previously: abundant infiltration of $IgG4^+$ plasmacytes, storiform fibrosis and obliterative phlebitis.

In Japan, comprehensive diagnostic criteria for IgG4-related disease have been available since 2011[29] and are applied in daily practice (Table 1). The criteria consist of swelling or masses in single or multiple organs, elevated serum IgG4 concentrations (≥135 mg/dl [1.35 g/l]) and the following histopathological findings: marked lymphocyte infiltration, in particular, infiltration of IgG4-bearing plasmacytes (ratio of $IgG4^+$:IgG^+ plasma cells >40% and at least 10 $IgG4^+$ plasmacytes per high-power field); and tissue fibrosis. Definitive diagnosis requires meeting all these criteria (Figure 5), whereas a diagnosis of IgG4-related disease is deemed probable when the physical and histopathological, but not the serological criteria, are met. Meeting the physical and serological criteria, but without histopathological evidence, only supports a possible diagnosis. In patients with possible IgG4-related disease, eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) and multicentric Castleman disease, which have symptoms similar to IgG4-related disease and also present with elevated serum levels of IgG4, have to be ruled out by histological testing and presence of anti-neutrophil cytoplasmic antibodies.[96,97] Another important consideration is that, using histopathological techniques, $IgG4^+$ plasma cell infiltrates are often detected in the lymph nodes of patients with rheumatoid arthritis,[98] as well as in normal pancreatic tissues surrounding pancreatic cancers.[99] Furthermore, the same findings are sometimes observed in other carcinomas, thus, screening for cancer is important in the diagnosis of IgG4-related disease.

Diagnosis of IgG4-related disease affecting tissues that are not easy to biopsy, such as the pancreas, is difficult

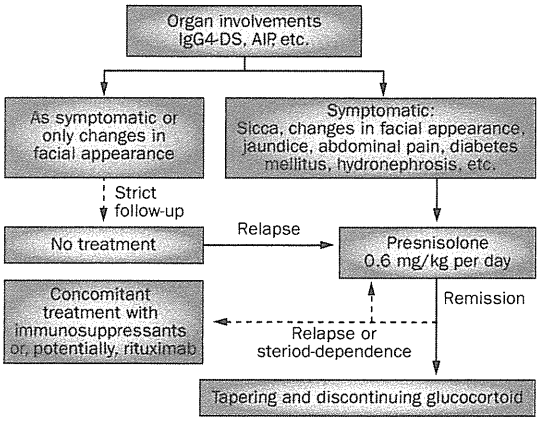

Figure 6 | Algorithm informing treatment decisions in patients with IgG4-related disease. In patients with IgG4-related disease with symptomatic organ involvement, glucocorticoid therapy with prednisolone can be initiated at a starting dose is 0.6 mg/kg per day. Patients with only asymptomatic organ involvement or patients with changes only in facial appearance are usually left untreated and strictly observed to monitor disease progression, with initiation of therapy in the event of escalation of symptoms. The initial dose of prednisolone is continued for 2–4 weeks, then tapered by 10% every 2 weeks. Although discontinuation of treatment with steroids is the ideal situation, continuation of prednisolone treatment at 5–10 mg per day is recommended to avoid relapse. The dose of glucocorticoids can be increased in the event of relapse. Concomitant rituximab is reportedly effective for inducing remission and achieving steroid-sparing effects in IgG4-related disease,[113] although further investigation of this approach is needed. Abbreviations: AIP, autoimmune pancreatitis; IgG4-DS, IgG4-associated dacryoadenitis and sialadenitis.

using the comprehensive Japanese diagnostic criteria,[29] owing to the emphasis placed on histological findings; definite diagnosis is impossible in such cases. To solve this problem, organ-specific diagnostic criteria[61,100–102] can be applied when biopsies are difficult to obtain (Figure 5). Alternatively, the organ-specific diagnostic criteria can be applied before, or in place of, the diagnostic criteria for systemic IgG4-related disease. For example, diagnosis of the lacrimal and salivary gland lesions that are associated with IgG4-related disease is possible using the diagnostic criteria for IgG4-related Mikulicz disease (approved by the Japanese Medical Society for Sjögren's syndrome in 2008),[61] without using the comprehensive diagnostic criteria (Table 1).[29] In Japan, organ-specific diagnostic criteria are now available for IgG4-related dacryoadenitis and sialadenitis (Mikulicz disease),[61] type 1 AIP,[100] IgG-related kidney disease,[101] and sclerosing cholangitis;[102] the original articles describing these guidelines should be consulted for more information on specific criteria that are used. In addition, several criteria sets for the diagnosis of AIP[103–106] and IgG4-related kidney disease[107] have been developed in various populations, but none of these criteria have been validated for use in racial or ethnic groups other than the ones in which they were formulated. Therefore, the development and validation of diagnostic criteria for IgG4-related disease that can be used worldwide is an important unmet need.

Treatment and prognosis

Glucocorticoid therapy is effective in the treatment of IgG4-related disease. Obstructive jaundice and hydronephrosis are absolute indications for treatment, whereas multiple organ dysfunction and the presence of clinical symptoms are considered to be strong indications for glucocorticoid therapy (Figure 6). In our practice, we sometimes delay initiation of therapy in asymptomatic individuals with IgG4-related disease and patients showing only changes in facial appearance, given the possibility of spontaneous remission, and place them under observation. Nevertheless, in the middle and long term, the high frequencies of recurrence of symptoms and organ dysfunction due to progressive fibrosis are matters of concern.[95] As a result, patients who are not initially treated must be observed carefully at regular intervals.

With regard to glucocorticoid therapy, daily prednisolone at a starting dose of 0.6 mg/kg is appropriate for treatment of patients with organ failures (Figure 6). The initial dose of prednisolone should be continued for 2–4 weeks, after which time, the dose should be tapered by 10% every 2 weeks. In our experience, enlarged organs generally improve rapidly after initiation of prednisolone, and gland secretions gradually increase with treatment. Indeed, reversal of gland dysfunction has been shown.[108,109] Primary nonresponders to glucocorticoid therapy are rare, but some patients with IgG4-related disease experience difficulty with steroid tapering; however, increasing the glucocorticoid back up to the starting dose is usually effective in such cases, and in cases of relapse. Indeed, although the initial prognosis of patients with IgG4-related disease is generally good, the relapse ratio after tapering or discontinuing steroids is very high. Around half of patients treated for IgG4-related dacryoadenitis and sialadenitis who relapse present with new lesions in different organs during both short-term[110] and long-term (>10 years)[111] follow-up. These results suggest that both systemic and long-term follow-up is important in IgG4-related disease. At present, whether maintenance therapy is needed in patients who achieve remission remains unclear, but continuing prednisolone at 5–10 mg per day is recommended because of the high relapse rates observed after reducing or stopping glucocorticoid therapy.

Concomitant use of immunosuppressants such as calcineurin inhibitors and azathioprine has been reported in patients with IgG4-related disease,[112] but their efficacy has not been demonstrated. Other reports have suggested that rituximab, an anti-CD20 antibody that promotes depletion of B cells, is effective in inducing remission and achieving steroid-sparing effects in patients with IgG4-related disease (Figure 6).[113–115] Considering the poor long-term prognosis associated with IgG4-related disease, the indications for therapy with biologic agents, including B-cell-depleting approaches, will be important to consider in the future.

Regarding the relationship between IgG4-related disease and malignancies, several reports have described the complication of pancreatic cancer during the follow-up of patients with type 1 AIP.[116,117] Using data from our patient database, we found that the standardized incidence rate of cancers within 3 years of diagnosis of IgG4-related disease was higher than in the rate observed for the general population (383 versus 100).[118] However, the malignancies observed in patients with IgG4-related disease were all different, and no characteristic (apart from age at diagnosis) correlated with development of cancer. Although the cause of this association therefore remains unclear, the risk of cancer in such patients is nevertheless an important consideration.

Conclusions

Although autoimmune mechanisms have not yet been confirmed in IgG4-related disease, specific immunological abnormalities have been identified. Knowledge of the pathological features and some of the underlying pathogenetic mechanisms of the disease has improved diagnosis, particularly in Asian individuals, although further efforts are needed to develop worldwide consensus diagnostic criteria. Examining for systemic organ failure and performing screening for underlying malignancies have also been identified as important procedures during the diagnosis and the follow-up of IgG4-related disease. However, many details of the pathogenic processes that result in development of IgG4-related disease, as well as the basis for differential organ involvement and increased risk of cancer in affected individuals, remain undetermined and should be the focus of research. Increased understanding of such issues might also stimulate the development of novel therapeutic interventions. Indeed, research should be aimed at the development of novel treatments for IgG4-related disease. Currently, glucocorticoids represent the first-line treatment for IgG4-related disease, but development of improved treatments, with fewer adverse effects and reduced relapse rates, can be expected in the future. Such therapies are likely to target the T_H2-cell responses that seem to be aberrant in this disease, and, if successful, could potentially be adapted to treat T_H2-cell dominant inflammation that underlies certain allergic disorders and fibrotic diseases.

Review criteria

We searched PubMed and textbooks for articles related to IgG4-related disease published between 1892 and October 2013. The search terms used were: "IgG4"; "IgG4-related disease"; "Mikulicz disease"; "autoimmune pancreatitis"; and "retroperitoneal fibrosis". The articles identified are full-text, English-language papers and abstracts apart from three articles in German and one in Japanese. The reference lists of the articles identified were searched for additional relevant papers.

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Author contributions

M. Yamamoto researched the data for the article, decided on the content and wrote the manuscript. H. Takahashi and Y. Shinomura made substantial contributions to review/editing of the manuscript before submission.

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IgG4 Disease

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Abstract: Immunoglobulin (Ig) G4–related disease (IgG4-RD) is a chronic inflammatory disorder characterized by elevated serum level of IgG4 and abundant infiltration of IgG4-bearing plasmacytes and fibrosis in various organs, typically including the lacrimal glands, salivary glands, pancreas, thyroid gland, lungs, and kidneys. Lacrimal and orbital involvements are called IgG4-related ophthalmic disease, often presenting as orbital myositis, perineuritis of the optic and trigeminal nerves, and orbital inflammation. In particular, a characteristic finding is infraorbital nerve enlargement on magnetic resonance imaging. Systemic screening is necessary to establish the diagnosis of IgG4-RD, and it must be distinguished from neoplastic disease. Corticosteroid treatment is effective in inducing remission but some patients may relapse during tapering of pharmacotherapy. This review encompasses the history, clinical profile, diagnostic criteria, treatment, and prognosis of IgG4-RD.

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Immunoglobulin (Ig) G4–related disease (IgG4-RD) is a chronic inflammatory condition characterized by elevated serum levels of IgG4 and marked infiltration of IgG4-positive plasmacytes and storiform fibrosis in a variety of organs (1,2). Whether this disease is an autoimmune disorder remains unclear, but patients with IgG4-RD often present with systemic organ dysfunction and immunological abnormalities (3). This report provides an overall review of IgG4 disease including neuro-ophthalmic involvement.

HISTORY OF IgG4-RD

The historical origins of IgG4-RD are found in the clinical descriptions of Mikulicz disease (MD) and autoimmune pancreatitis (AIP). In 1888, Johann von Mikulicz-Radecki, a surgeon, described a patient with bilateral, symmetric, and painless swelling of the lacrimal, parotid, and submandibular glands (4). Although tuberculosis and sarcoidosis subsequently were reported as causes of this clinical presentation, idiopathic cases were classified as MD, whereas cases with an identifiable cause were classified as Mikulicz syndrome (5). In the 1930s, Henrik Sjögren, a Swedish ophthalmologist, analyzed cases of keratoconjunctivitis sicca and documented an association with swollen salivary glands (6), leading to the recognition of the Sjögren syndrome (SS). In 1953, Morgan and Castleman (7) proposed that MD and SS were the same type of disorder or MD was a subtype of SS, and MD disappeared from the literature for approximately 50 years. In 2000, Tsubota et al (8) demonstrated that the frequency of apoptosis in the lacrimal glands was lower in MD than in SS. Yamamoto et al (9,10) reported a series of cases of MD and identified elevated serum levels of IgG4 and noted in other patients' infiltration of IgG4-positive plasmacytes within swollen lacrimal and submandibular glands. In 2006, MD was recognized as a clinical and pathological entity distinct from SS (11).

The history of AIP began in 1961 with a case report by Sarles et al (12) of a patient with pancreatitis and hypergammaglobulinemia. In the 1990s, characteristic histological (13) and imaging (14) features of this type of pancreatitis were reported and, soon thereafter, Yoshida et al (15) proposed the concept of AIP. Hamano et al (16,17) found elevated serum levels of IgG4 and infiltration of IgG4-positive plasmacytes in pancreatic tissue in patients with AIP. This established a link between AIP and IgG4. Additional studies led to the designation of

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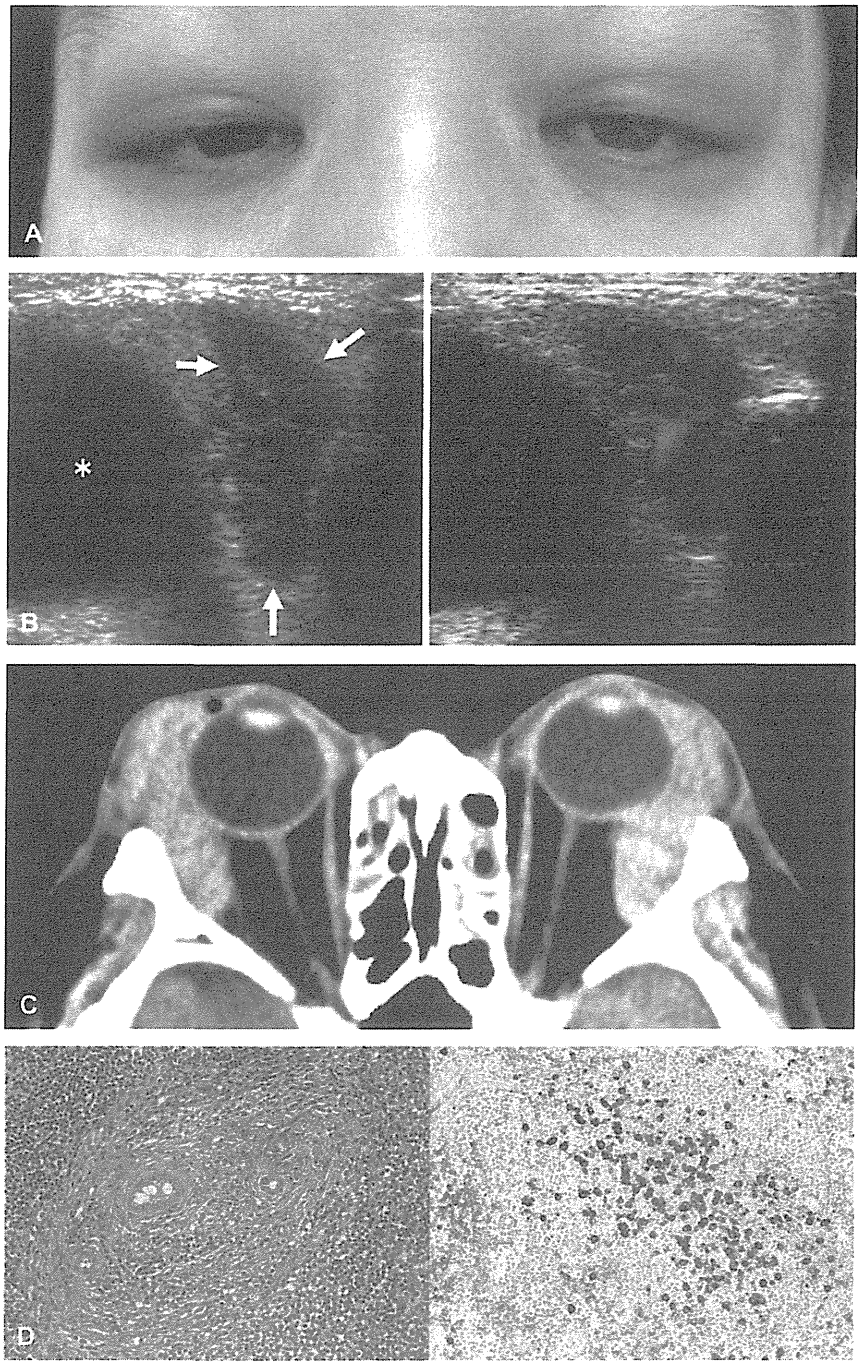

FIG. 1. Dacryoadenitis due to IgG4 disease. **A.** Bilateral upper eyelid ptosis and swelling. **B.** *Left*, echography shows low echogenic lacrimal gland (*arrows*) next to the globe (*asterisk*); *right*, Doppler study reveals highly vascular (red) tissues. **C.** Postcontrast computed tomography shows enlargement of both lacrimal glands. **D.** Lacrimal gland biopsy reveals marked infiltration of IgG4 plasmacytes and fibrosis (*left*, hematoxylin & eosin, ×200; *right*, anti-IgG4 monocolonal antibody stain, ×200).

AIP associated with IgG4 as Type 1 AIP and AIP associated with neutrophils as Type 2 (18–20).

A series of published reports began to expand the clinical manifestations associated with IgG4. IgG4-related autoimmune disease (21) and IgG4-related sclerosing disease (22) were derived from an analysis of AIP. Systemic IgG4-related plasmacytic syndrome (11,23) and IgG4-positive multiorgan lymphoproliferative syndrome (24) subsequently

were reported. It became apparent that unification of disease terminology and establishing diagnostic criteria were required (25). In 2011, comprehensive diagnostic criteria for IgG4-RD were proposed at an international symposium on IgG4-RD (26). That same year, recommendations regarding the nomenclature for IgG4-RD and its individual organ system manifestations (27) and consensus on the pathology of IgG4-RD (28) were published. MD was designated as IgG4-DS in the proposed classification.

ORGAN INVOLVEMENT

Lacrimal Gland and Orbit (IgG4-Related Dacryoadenitis and IgG4-Related Ophthalmic Disease)

Oshima et al (29) reported that IgG4-related orbital lesions comprise 22.5% of orbital lymphoproliferative disorders. Primary sites of involvement include the lacrimal glands, extraocular muscles, and orbital nerves (2). Patients with lacrimal gland disease often present with swelling of the upper eyelids and bilateral ptosis (Fig. 1A). They also may display swelling of the submandibular salivary glands (IgG4-DS). Keratoconjunctivitis sicca is apparent in a small number of cases with IgG4-related dacryoadenitis. Lacrimal gland echography (30) reveals a low-echogenic swollen gland with partitioning (Fig. 1B), whereas neuroimaging demonstrates lacrimal gland enlargement (Fig. 1C). Evaluating whether a lesion is benign or malignant based solely on imaging findings is difficult, and histopathological examination is required (Fig. 1D). This is particularly true in cases of unilateral involvement and without signs of additional organ dysfunctions (salivary or pancreatic lesions).

Extraocular myositis due to IgG4 disease frequently develops after dacryoadenitis (31,32). Pain on eye movement and diplopia are typical clinical findings. IgG4-related disease must be differentiated from thyroid eye disease, which is characterized by lid retraction and enlargement of multiple extraocular muscles.

IgG4-related disease may affect branches of the ophthalmic (supraorbital) and maxillary (infraorbital) nerves and cause sensory impairment in the area of innervation (Fig. 2A) (29,32,33). The inflammatory response is primarily perineuritis because direct infiltration of nerve fibers is not present (Fig. 2B) (34,35). Optic nerve involvement also has been described and may lead to permanent visual loss (34,36).

Salivary Glands (IgG4-Related Sialadenitis)

Inflammation of the salivary glands often occurs in IgG4-RD. The submandibular glands are most frequently involved but the parotid, sublingual, and minor salivary glands may be affected (Fig. 3). Kűttner tumor (chronic sclerosing sialadenitis) falls within the spectrum of IgG4-related sialadenitis (37). Salivary gland swelling is usually painless, and dry mouth is not a major clinical symptom (10). Differentiation from lymphoma is important and requires histopathological examination.

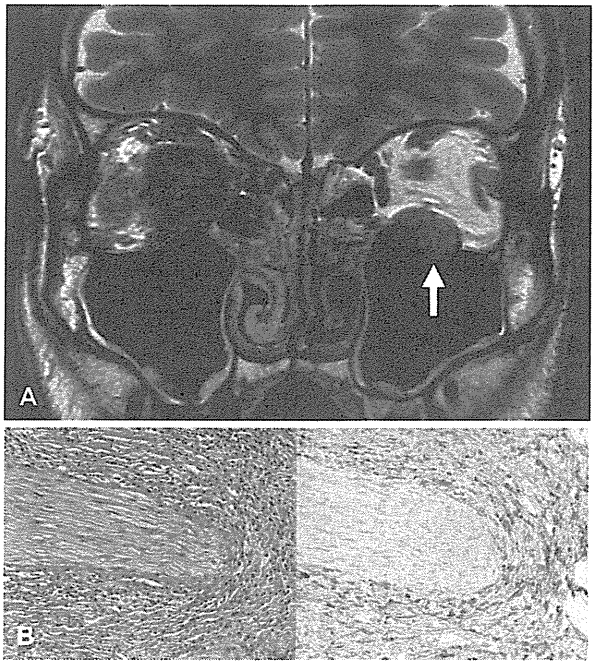

FIG. 2. Infraorbital nerve enlargement. **A.** Contrasted T1 coronal magnetic resonance imaging shows enlargement of the left infraorbital nerve (*arrow*). **B.** Biopsy of infraorbital nerve demonstrates infiltration of IGG4 plasmacytes (*left*, hematoxylin & eosin, ×200; *right*, anti-IgG4 monoclonal antibody stain, ×200).

Pancreas and Bile Duct (Type 1 AIP and IgG4-Related Sclerosing Cholangitis)

With pancreatic involvement in IgG4-RD, patients will complain of upper abdominal discomfort and develop obstructive jaundice. Pancreatic endocrine and exocrine dysfunction leads to impaired glucose tolerance (38) and gastrointestinal symptoms. Differentiation from pancreatic cancer is necessary with AIP and from bile duct cancer and primary sclerosing cholangitis in patients with IgG4-related sclerosing cholangitis. Abdominal echography in AIP shows a low-echogenic swollen pancreas, and abdominal computed tomography (CT) reveals diffuse or focal swelling of the pancreas with a capsule-like rim (Fig. 4A) (39). In cases with pancreatic or biliary involvement, endoscopic retrograde cholangiopancreatography often is performed to achieve the correct diagnosis.

Head and Neck Region (Pituitary Gland, Dura Mater, and Thyroid)

Infrequently, IgG4-RD may involve the pituitary gland (40), dura mater (41), and thyroid gland (42,43). IgG4-related hypophysitis of the anterior pituitary may cause headache, visual field loss, and galactorrhea.

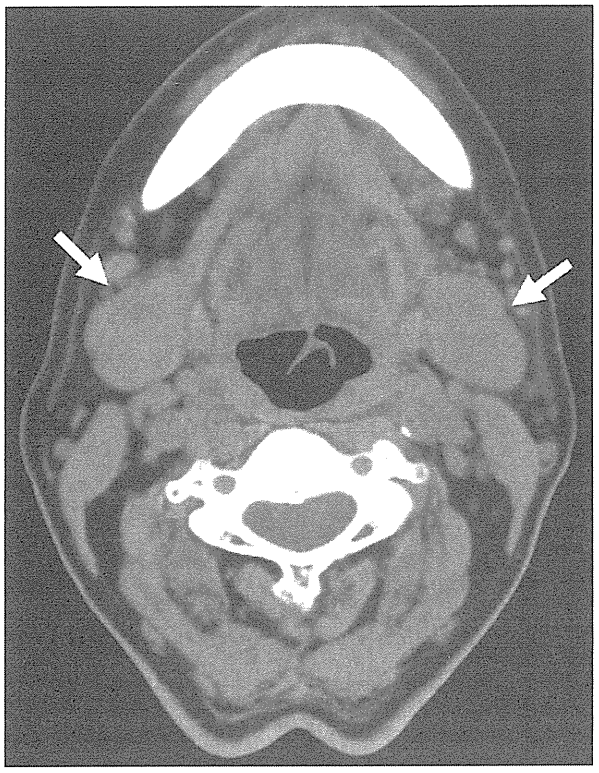

FIG. 3. IgG4-related sialadenitis. On T1 axial computed tomography, there is swelling of the submandibular salivary glands (*arrows*).

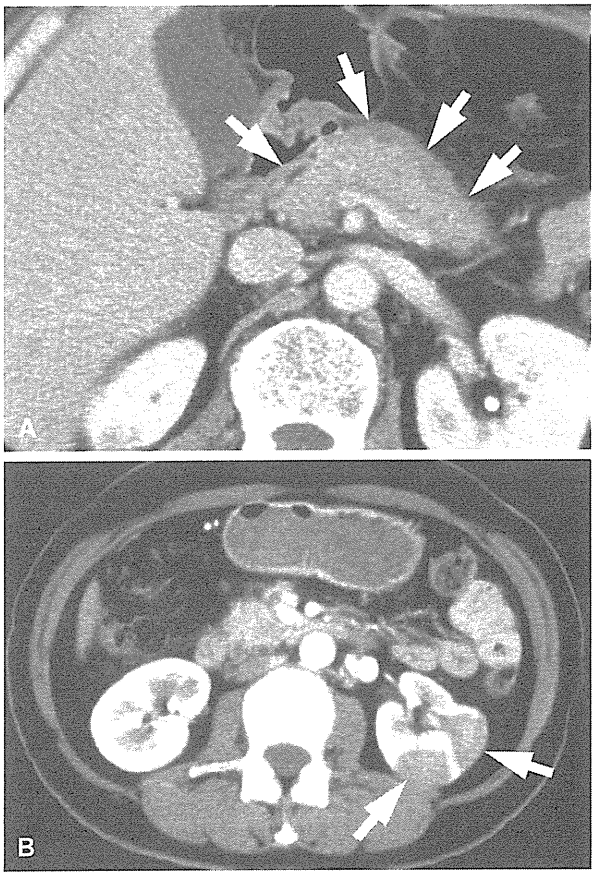

FIG. 4. Systemic organ involvement. Postcontrast axial computed tomography demonstrates involvement (*arrows*) of the pancreas (**A**) and kidneys (**B**).

Symptoms of hypopituitarism include general malaise and amenorrhea. Riedels thyroiditis and the fibrous variant of Hashimoto thyroiditis show partial overlap with IgG4-related thyroiditis. Thyroidal lesions exhibit focal or diffuse enlargement of the thyroid. Involvement at the posterior pituitary sometimes induces diabetes insipidus. Patients with IgG4-related hypertrophic pachymeningitis often present with chronic headache and cranial nerve dysfunction (visual loss and facial nerve palsy) (41).

Thoracoabdominal Region (Lung, Kidneys, Retroperitoneal Cavity, and Prostate Gland)

Pulmonary lesions in IgG4-RD are classified as bronchial or alveolar (44). Patients with bronchial lesions often present with asthma-like symptoms. CT reveals thickened bronchial and bronchiolar walls. Patients with alveolar lesions are often asymptomatic. CT detects various patterns suggestive of interstitial or organizing pneumonia. IgG4-related kidney disease mainly takes the form of tubulointerstitial nephritis, sometimes complicated by glomerulonephritis. Postcontrast CT reveals enlarged kidneys with multiple areas of mild enhancement (Fig. 4B) (45). Thickened lesions sometimes occur at the renal hilus. Approximately, one-half of cases with renal involvement develop hydronephrosis because of ureteral obstruction and some develop prostatitis (46). Regions around the thoracic and lumbar spine, aorta and branching arteries, and ureters may be involved. With periaortitis, a relationship to inflammatory abdominal aortic aneurysm has been suggested (47).

Lymph Nodes

Bilateral hilar lymphadenopathy is often detected in IgG4-RD. Enlargement of regional lymph nodes occurs around any involved organs. Patients with systemic lymphadenopathy due to IgG4 disease must be distinguished from those with Castleman disease. The diagnosis of IgG4-related lymphadenopathy is not difficult when other lesions typical of IgG4-RD are present, but biopsy of enlarged lymph nodes is required in cases with only lymph node lesions involvement (48).

Common Pathological Findings

When possible, histopathological findings should be obtained to confirm the diagnosis in IgG4-RD. Common findings include abundant infiltration of lymphocytes and IgG4-bearing plasmacytes and storiform fibrosis in the involved organs. Infiltration of eosinophils and obstructive

phlebitis are also characteristic but the degree of these findings depends on the specific organ. For example, obstructive phlebitis is easily identified in AIP but rarely apparent in IgG4-related sialadenitis (28). The ratio of IgG4/IgG-positive cells in IgG4-related retroperitoneal fibrosis tends to be lower than the other sites of involvement. In the early stage of IgG4-RD, these findings are observed sporadically in the involved organs. Although inflammation is present, the structure of the organ is retained. With progression, there is diffuse spread of inflammation leading to fibrosis and eventually failure of the organ system (49).

DIAGNOSIS OF IgG4-RD

Diagnosis of IgG4-RD is made on the basis of clinical imaging, serological, and pathological findings. Proposed diagnostic criteria include enlarged or hypertrophic affected organs, elevated serum level of IgG4 (≥135 mg/dL), and pathological findings (ratio of IgG4+ IgG+ cells >40% and ≥10 IgG4+ plasmacytes/high power field (Table 1) (26). Definitive diagnosis requires that all criteria are met, whereas probable diagnosis is determined when the clinical and histopathological criteria are met. Meeting the clinical and serological criteria warrants only possible diagnosis. It is essential to exclude eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) and multicentric Castleman disease because both disorders also may have elevated serum levels of IgG4 (50,51). Histopathologically, infiltration of IgG4-positive plasmacytes is often detected in the lymph nodes of patients with rheumatoid arthritis (52). IgG4-positive plasmacytes may be found in surrounding pancreatic cancer (53), and similar findings may be observed in other carcinomas. In patients with lesions that are difficult to be biopsied, diagnosis may be achieved using organ-specific criteria for IgG4-RD. Diagnostic criteria for IgG4-DS (MD) have been established (Table 2) (30) as well as diagnostic criteria for AIP (54–56), IgG4-related sclerosing cholangitis (57), and IgG4-related kidney disease (58,59).

TABLE 1. Comprehensive diagnostic criteria for IgG4-RD 2011 (Ministry of Health, Labour and Welfare, Japan)

1	Clinical examination reveals characteristic diffuse/localized swelling or masses in single or multiple organs
2	Hematological examination shows elevated serum IgG4 concentrations (≥135 mg/dL)
3	Histopathological examination shows marked lymphocyte and plasmacyte infiltration and fibrosis Infiltration of IgG4+ plasma cells: ratio of IgG4+ IgG+ cells >40% and 10 IgG4+ plasma cells/high power field

Definite: 1 + 2 + 3; Probable: 1 + 3; Possible: 1 + 2.

It is important to differentiate IgG4-RD from malignant tumors of each organ (e.g., carcinoma, lymphoma) and similar disease (e.g., Sjorgren syndrome, primary sclerosing cholangitis, Castleman disease, secondary retroperitoneal fibrosis, Wegener granulomatosis, sarcoidosis, Churg–Strauss syndrome) by additional histopathological examination. Even when patients cannot be diagnosed using the CCD criteria, they may be diagnosed using organ-specific criteria for IgG4-RD.

TREATMENT AND PROGNOSIS

Systemic corticosteroids are effective in inducing remission of IgG4-RD. Starting prednisone at a dose of 0.6 $mg \cdot kg^{-1} \cdot d^{-1}$ is appropriate for single organ failure, increasing to 1.0 $mg \cdot kg^{-1} \cdot d^{-1}$ for multiple organ failure. The initial dose of prednisone is continued for 2–4 weeks, followed by tapering the dose by 10% every 2 weeks. Enlarged organs improve rapidly, and gland secretions gradually increase with treatment (60). Maintaining prednisone dose at 5–10 mg/d is recommended because of the high relapse rate of IgG4-RD. Approximately, one-half of relapse patients present with lesions in other organ systems (61). With relapse, corticosteroids are increased or another immunosuppressant must be chosen. Rituximab, an anti-CD20 antibody, has been shown to be effective in inducing remission and achieving steroid-sparing effects (62). The prognosis for patients with IgG4-RD is good but the incidence of developing cancer within 3 years of diagnosing IgG4-RD is higher in the general population (63). The cause for this association is unclear but mandates careful patient follow-up.

CONCLUSIONS

IgG4-RD has only been reported since the beginning of the 21st century. Although autoimmune mechanisms have yet been elucidated, specific immunological abnormalities have been identified. Examination for systemic organ failure and screening for underlying malignancy are essential in caring for patients with this disorder and requires involvement of a wide variety of clinicians.

TABLE 2. Diagnostic criteria for IgG4-related MD, 2008 (Japanese Society for Sjögren's syndrome)

1	Persistent (>3 months), symmetrical swelling of the lacrimal, parotid, and submandibular salivary glands, involving at least 2 pairs
2	Serologically high levels of IgG4 (>135 mg/dL)
3	Marked IgG4-positive plasmacyte infiltration (>50% IgG4/IgG-positive cells in 5 high power fields) into lacrimal and salivary gland tissues

In terms of diagnosis, IgG4-related Mikulicz disease is defined as satisfying 1 and either 2 or 3.

Sarcoidosis, Castleman disease, Wegener granulomatosis, and malignant lymphoma need to be considered in the different diagnosis.

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