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REVIEW ARTICLE

A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details

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Abstract IgG4-related disease (IgG4RD) is a novel clinical disease entity characterized by elevated serum IgG4 concentration and tumefaction or tissue infiltration by IgG4-positive plasma cells. IgG4RD may be present in a certain proportion of patients with a wide variety of diseases, including Mikulicz's disease, autoimmune pancreatitis, hypophysitis, Riedel thyroiditis, interstitial pneumonitis, interstitial nephritis, prostatitis, lymphadenopathy, retroperitoneal fibrosis, inflammatory aortic aneurysm, and inflammatory pseudotumor. Although IgG4RD forms a distinct, clinically independent disease category and is attracting strong attention as a new clinical entity, many questions and problems still remain to be elucidated, including its pathogenesis, the establishment of diagnostic criteria, and the role of IgG4. Here we describe the concept of IgG4RD and up-to-date information on this emerging disease entity.

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Keywords IgG4-related diseases · Mikulicz's disease · Sjögren's syndrome · Autoimmune pancreatitis · Castleman's disease

Abbreviations

IgG4RD	IgG4-related disease
MD	Mikulicz's disease
SS	Sjögren's syndrome
MHLW Japan	Ministry of Health, Labor and Welfare Japan
LPSP	Lymphoplasmacytic sclerosing pancreatitis
AIP	Autoimmune pancreatitis
FMF	Familial multifocal fibrosclerosis
ANA	Anti-nuclear antibody

Introduction

In 1892, Dr. Johann von Mikulicz, also known as Jan Mikulicz-Radecki, published a paper describing a patient with symmetrical swelling of the lachrymal, parotid, and submandibular glands, with massive infiltration of these glands by mononuclear cells [1]. Following reports describing similar patients, this condition was called Mikulicz's disease (MD). In contrast, patients with similar symptoms, but with diseases such as leukemia, malignant lymphoma, and sarcoidosis, were reported to have Mikulicz's syndrome [2]. In 1930, Dr. Henrik Sjögren, an ophthalmologist, published a paper describing a woman with rheumatoid arthritis accompanied by keratoconjunctivitis sicca and severe swelling of the parotid glands, a condition that has been recognized as Sjögren's syndrome (SS) [3]. In 1953, Morgan and Castleman examined 18 patients with MD and concluded that this condition is one manifestation of SS [4]. Since then, MD has attracted very little interest in western countries. In Japan, however, there have been many patients with MD, such that differences between MD and SS have been clarified [5–7]. For example, their gender distribution is quite different, in that MD occurs in both men and women, whereas SS occurs mainly in women. Second, patients with MD have relatively mild xerostomia and xerophthalmia, despite significant enlargement of their lachrymal and salivary glands. Further, MD is accompanied by more complications, such as autoimmune pancreatitis (AIP). Patients with MD show a better response to glucocorticoid therapy than patients with SS. Finally, it has become clear that MD is related to elevated serum IgG4 concentrations and infiltration of IgG4-positive cells [5–9].

Following the description of a patient with chronic pancreatitis due to an autoimmune mechanism [10], lymphoplasmacytic sclerosing pancreatitis (LPSP) was found to be a characteristic histopathological finding in patients with AIP [11]. These findings led to the concept of AIP, which has characteristics similar to those of other autoimmune diseases, such as hypergammaglobulinemia, the

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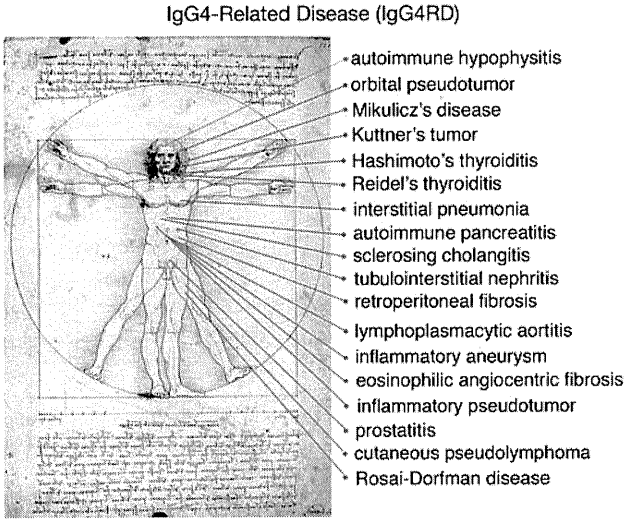


Fig. 1 IgG4-related conditions. Many diseases have been reported to be IgG4-related

Table 1 Nomenclatures of IgG-related conditions

IgG4-related autoimmune disease	Kamisawa [21]
IgG4-associated multifocal systemic fibrosis	van der Vliet [76]
IgG4-related systemic disease	Kamisawa [20]
IgG4-related sclerosing disease	Kamisawa [15]
Hyper-IgG4 disease	Neild [59]
IgG4-related disease (IgG4-RD)	Zen [77]
Systemic IgG4 plasmacytic syndrome (SIPS)	Yamamoto [22]
IgG4-related multi-organ lymphoproliferative syndrome (IgG4-MOLPS)	Masaki [29]
IgG4-associated disease	Geyer [78]

presence of various autoantibodies, lymphocytic infiltration into pancreatic tissue, and good responsiveness to steroids [12]. Following a report showing elevated serum IgG4 concentrations in patients with AIP [13], the pancreatic research team of the Ministry of Health, Labor and Welfare Japan (MHLW Japan) showed that AIP was related to IgG4 [14].

IgG4-positive plasma cell infiltration has also been observed in patients with other conditions, including retroperitoneal and mediastinal fibrosis [15, 16], inflammatory pseudotumor of the lung and liver [17], Küttner tumor [18], and interstitial nephritis [19], indicating that these diseases and conditions collectively constitute a new disease concept, IgG4-related disease (Fig. 1). These findings have led to the organization of two study groups by MHLW Japan to analyze the condition of IgG4-related disease. These groups consist of doctors and researchers in various fields, including rheumatology, hematology, gastroenterology, nephrology, pulmonology, ophthalmology, odontology, pathology, statistics, and basic and molecular immunology, from all over Japan. One of these groups, chaired by Professor Umehara of Kanazawa Medical University, is seeking to establish diagnostic criteria for IgG4-related multi-organ lymphoproliferative syndrome (IgG4-MOLPS), whereas the second group, chaired by Professor Okazaki of Kasai Medical University, is seeking to understand the etiology and pathogenesis of IgG4-related systemic disease.

Unification of different nomenclatures for IgG4-related disease (IgG4RD)

The concept of IgG4RD arose when elevated serum IgG4 concentrations were first reported in patients with sclerosing pancreatitis [13]. Autoimmune pancreatitis (AIP) is also associated with a variety of extrapancreatic lesions, including sclerosing cholangitis, sclerosing sialadenitis, and dacryoadenitis, resulting in the concept of IgG4-related systemic disease [20], also called IgG4-related autoimmune disease [21] or IgG4-related sclerosing disease [15]. The finding of elevated serum IgG4 and IgG4-positive plasma cell infiltration in MD suggested that MD was a systemic disease, which was called systemic IgG4 plasmacytic syndrome (SIPS) [22]. Further, a comparison of patients with MD and those with typical SS resulted in the formulation of a new clinical entity, IgG4+MOLPS [23]. Although many reports from Japan and other countries have described IgG4-related conditions under different names (Table 1), these may refer to the same condition, familial multifocal fibrosclerosis (FMF). Indeed, retroperitoneal fibrosis (RPF), mediastinal fibrosis, sclerosing cholangitis, Riedel's thyroiditis, and pseudotumor of the orbit may all be different manifestations of a single disease [24].

The name "IgG4-related sclerosing disease" is mainly based on the swelling of fibrous organs, such as the pancreas and retroperitoneum, whereas "SIPS" and "IgG4+MOLPS" are based on lymphoplasmacytic proliferation in glands and swollen lymph nodes without fibrosis. Although many patients with this condition (i.e., IgG4-related sclerosing disease, etc.) have lesions in several organs, either synchronously or metachronously, other patients show involvement of only a single organ. At this point, it is unclear whether the pathogenetic mechanism of this disease is systemic or whether it consists of manifestations in individual organs. In addition, several reports have described patients with IgG4-associated conditions concomitant with malignant tumors such as pancreatic [25, 26] and salivary [27] carcinomas, and ocular adnexal lymphoma [28]. Therefore, using the term 'systemic' may lead to an incorrect diagnosis of an IgG4-related condition in a patient with malignant

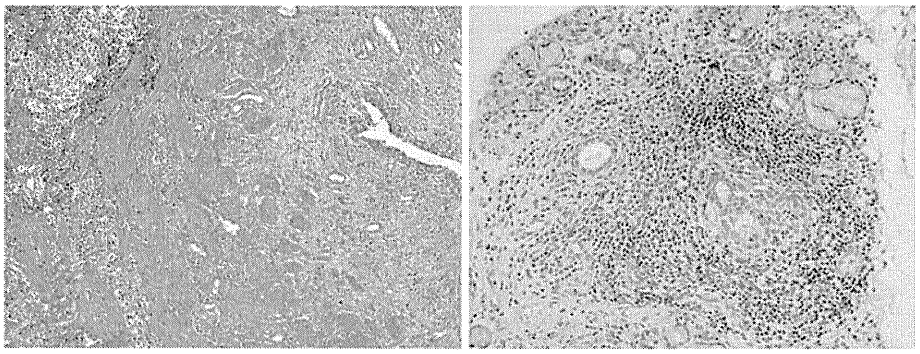


Fig. 2 Histopathology of IgG4-related disease (IgG4RD). IgG4RD is characterized histopathologically by the infiltration of IgG4-positive plasma cells and fibrosis. However, the severity of fibrosis is dependent on the individual organs involved. For example, storiform fibrosis and obliterative phlebitis are characteristic of retroperitoneal lesions, but are very seldom observed in salivary glands (×40)

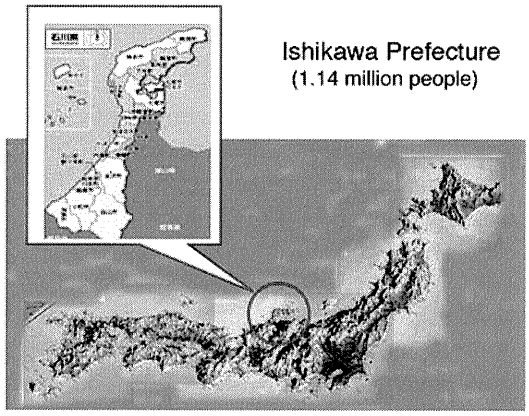
tumors in other organs. Based on these reasons, the members of the two MHLW Japan research teams agreed, at their second meeting in Kanazawa on February 11, 2010, to use the term "IgG4-related disease (IgG4RD)".

General concept of IgG4RD

After the unification of the disease name as IgG4RD, both MHLW Japan research teams have sought to determine its pathogenesis and to formulate diagnostic criteria. The two teams reached a consensus that IgG4RD can occur in various organs, including the central nervous system, salivary glands, thyroid gland, lungs, pancreas, biliary duct, liver, gastrointestinal tract, kidneys, prostate gland, retroperitoneum, and lymph nodes, but that clinical symptoms depend on the location of the lesion. IgG4RD mainly affects middle-aged to elderly men. Its clinical symptoms are relatively mild, and the condition usually comes to clinical attention due to organ swelling or damage. Many patients with IgG4RD are treated effectively by steroid therapy. Although the infiltration of IgG4-positive cells and increased serum concentrations of IgG4 are characteristic of IgG4RD, the severity of fibrosis is dependent on the individual organs involved. For example, storiform fibrosis and obliterative phlebitis are characteristic of pancreatic, biliary tract, and retroperitoneal lesions, but are very seldom found in salivary glands or lymph nodes (Fig. 2).

Prevalence of IgG4RD

It is difficult to ascertain the number of patients with IgG4RD because its diagnostic criteria have not yet been established, the awareness of this disease is low, and its symptoms vary. An attempt was made to estimate the number of individuals with IgG4RD throughout Japan by using as an example Ishikawa Prefecture, which has a population of 1.14 million people with little population inflow/outflow (Fig. 3). In Ishikawa Prefecture, there are



	KMU	KUH	total
2003	2	2	4
2004	0	1	1
2005	1	3	4
2006	1	3	4
2007	1	4	5
2008	1	3	4
2009	1	6	7
	7	22	29

Fig. 3 Prevalence of patients with IgG4RD. An attempt was made to estimate the number of individuals with IgG4RD throughout Japan by using as an example Ishikawa Prefecture (population 1.14 million people) with little population inflow/outflow. If all new patients with IgG4RD visit Kanazawa Medical University Hospital (*KMU*) or Kanazawa University Hospital (*KUH*), the incidence of this disease throughout Japan would be 0.28–1.08/100,000 population, with 336–1,300 patients newly diagnosed per year. If life expectancy after diagnosis is 20 years, then approximately 6,700–26,000 patients in Japan would have developed IgG4RD over the past 20 years. The *numbers in the table* represent the numbers of patients who visited KMU or KUH each year

two University Hospitals, Kanazawa Medical University Hospital (KMU) and Kanazawa University Hospital (KUH). Assuming that new patients with IgG4RD would visit one of these two hospitals, it was estimated that the incidence of this disease throughout Japan would be 0.28–1.08/100,000 population, with 336–1,300 patients newly diagnosed per year. Because the median age of onset of IgG4RD is 58 years and the clinical symptoms are relatively mild, with slow progression and good response to steroid therapy, life expectancy after diagnosis was estimated at 20 years. Thus, an estimated 6,700–26,000 individuals in Japan would have developed IgG4RD over the past 20 years.

Clinicopathological features of IgG4RD

Differences between IgG4-related MD and Sjögren's syndrome

Since elevated serum IgG4 was first reported in patients with MD [6], the members of the Japanese Society of Sjögren's Syndrome have assessed the clinical symptoms, laboratory findings, and detailed histopathology in patients with MD (characterized by symmetrical swelling of the lachrymal, submandibular, and parotid glands), nationwide, since 2004. Some patients did not show typical symptoms of MD such as swelling of the lachrymal, parotid, or submandibular glands but showed elevated serum IgG4 and other indices indicative of MD according to the criteria for the diagnosis of IgG4-related MD shown in Table 2 [8]. Sixty-four patients with MD or elevated serum IgG4 (>135 mg/dl) and characteristic histological findings were initially diagnosed with IgG4RD (formerly called IgG4+MOLPS) based on proposed guidelines for the diagnosis of IgG4RD (Table 3). A comparison of patients with IgG4RD and those with typical SS showed: (1) compared with SS patients, fewer patients with IgG4RD had symptoms of xerophthalmia, xerostomia, or arthralgia, whereas many had coexisting AIP, interstitial nephritis, allergic rhinitis, and/or bronchial asthma (Fig. 4a); (2) most patients with IgG4RD were negative for anti-SS-A and anti-SS-B antibodies, as well as for rheumatoid factor (RF) and anti-nuclear antibody (ANA) (Fig. 4b); (3) serum IgG4 and IgE concentrations were significantly higher in IgG4RD than in SS patients (Fig. 4c); and (4) steroid therapy was extremely effective in patients with IgG4RD but had limited effect in patients with SS [29].

The histopathological features of IgG4RD are unique, though both IgG4RD and SS show marked lymphocytic infiltration. IgG4RD is characterized by the formation of lymphoid follicles but lower levels of lymphocytic infiltration into the salivary ducts, such that their structure remains intact (Fig. 5a). Therefore, the absence of

Table 2 Diagnostic criteria of IgG4+ Mikulicz's disease [8] (approved by the Japanese Society for Sjögren's Syndrome 2008)

1. Symmetrical swelling of at least 2 pairs of lachrymal, parotid, or submandibular glands for at least 3 months
AND
2. Elevated serum IgG4 (>135 mg/dl)
OR
3. Histopathological features including lymphocyte and IgG4+ plasma cell infiltration (IgG4+ plasma cells/IgG+ plasma cells >50%) with typical tissue fibrosis or sclerosis
Differential diagnosis is necessary to distinguish IgG4+ Mikulicz's disease from other distinct disorders, including sarcoidosis, Castleman's disease, Wegener's granulomatosis, lymphoma, and cancer. The diagnostic criteria for Sjögren's syndrome (SS) may also include some patients with IgG4+ Mikulicz's disease; however, the clinicopathological conditions of patients with typical SS and IgG4+ Mikulicz's disease are different

Table 3 Guidelines for diagnosis of IgG4RD (proposed by the Research Program for Intractable Disease Ministry of Health, Labor and Welfare Japan, G4 team)

Clinical features highly suggestive of IgG4RD
1. Symmetrical swelling of lachrymal, parotid, or submandibular glands
2. Autoimmune pancreatitis
3. Inflammatory pseudotumor
4. Retroperitoneal fibrosis
5. Suspicion of Castleman's disease
Laboratory data highly suggestive of IgG4RD
1. Serum IgG4 >135 mg/dl
2. IgG4+ cells/IgG+ cells >40% in biopsy
Clinical features suggestive of IgG4RD
1. Unilateral swelling of at least one lachrymal, parotid, or submandibular gland
2. Orbital pseudotumor
3. Sclerosing cholangitis
4. Prostatitis
5. Hypertrophic pachymeningitis
6. Interstitial pneumonitis
7. Interstitial nephritis
8. Thyroiditis/hypo-function of thyroid
9. Hypophysitis
10. Inflammatory aneurysm
Laboratory data suggestive of IgG4RD
1. Hypergammaglobulinemia of unknown origin
2. Hypocomplementemia or existence of immune complex
3. Increase of IgE or eosinophils
4. Tumefactive lesions or lymph node swelling detected by gallium scan or fluoro-D-glucose positron emission tomography (FDG-PET)

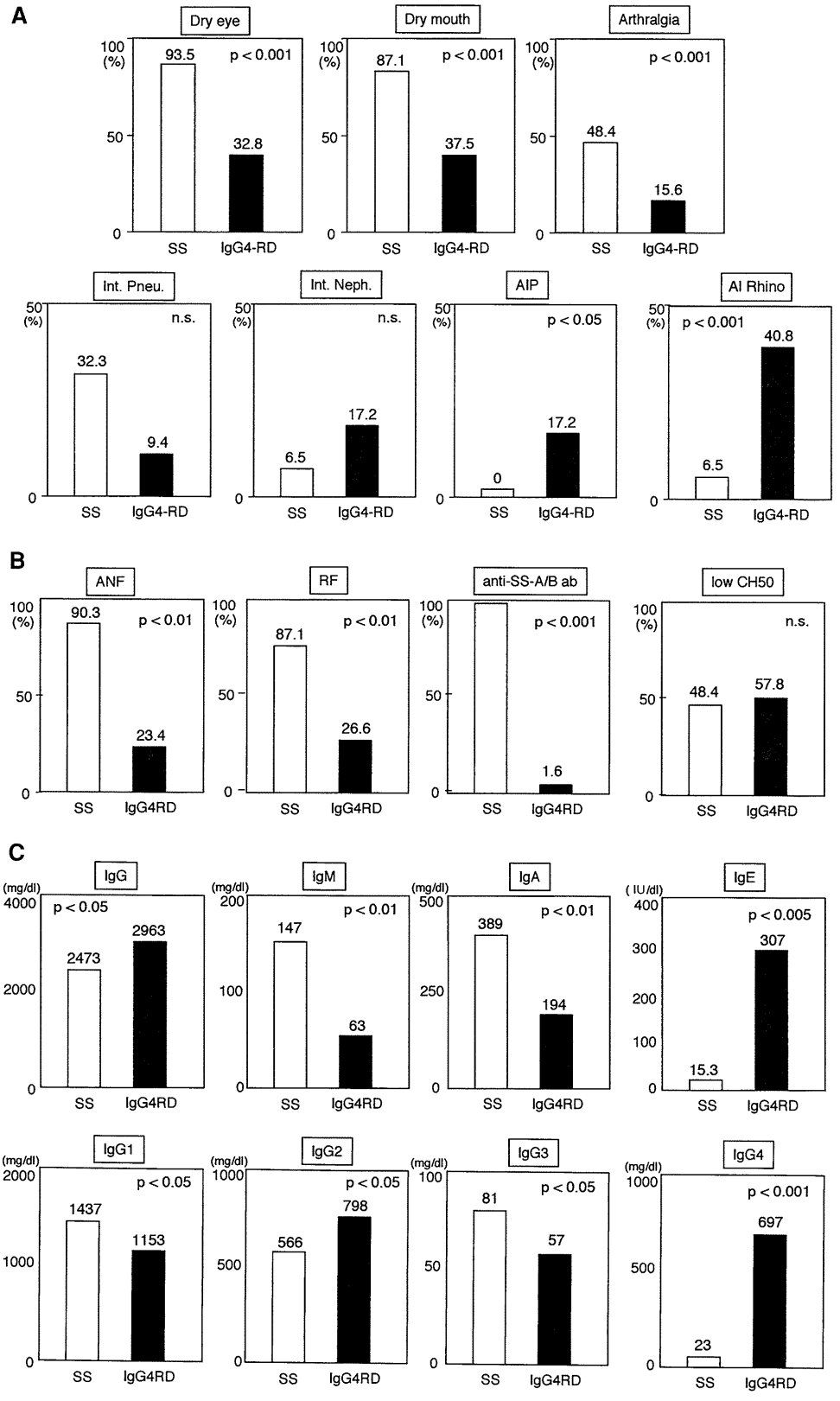


Fig. 4 Comparison of clinical symptoms and laboratory findings in IgG4RD and typical Sjögren's syndrome (*SS*) [29]. **a** Clinical symptoms, **b** immunological findings, and **c** subclasses of immunoglobulins and IgG observed in patients with IgG4RD ($n = 61$) and typical SS ($n = 31$). Data are expressed as percentages. *P* values are for comparisons of IgG4RD with typical SS. Patients with typical SS fulfilled both Japanese and European SS criteria and were positive for both anti-SSA/Ro and anti-SSB/La antibodies

lymphoepithelial lesions in patients with IgG4RD, in contrast to SS, may explain the lower rate of dryness in the former, despite the marked swelling of lachrymal and salivary glands. The most important difference between IgG4RD and SS is that the former is characterized by marked infiltration of IgG4-positive plasma cells, with a

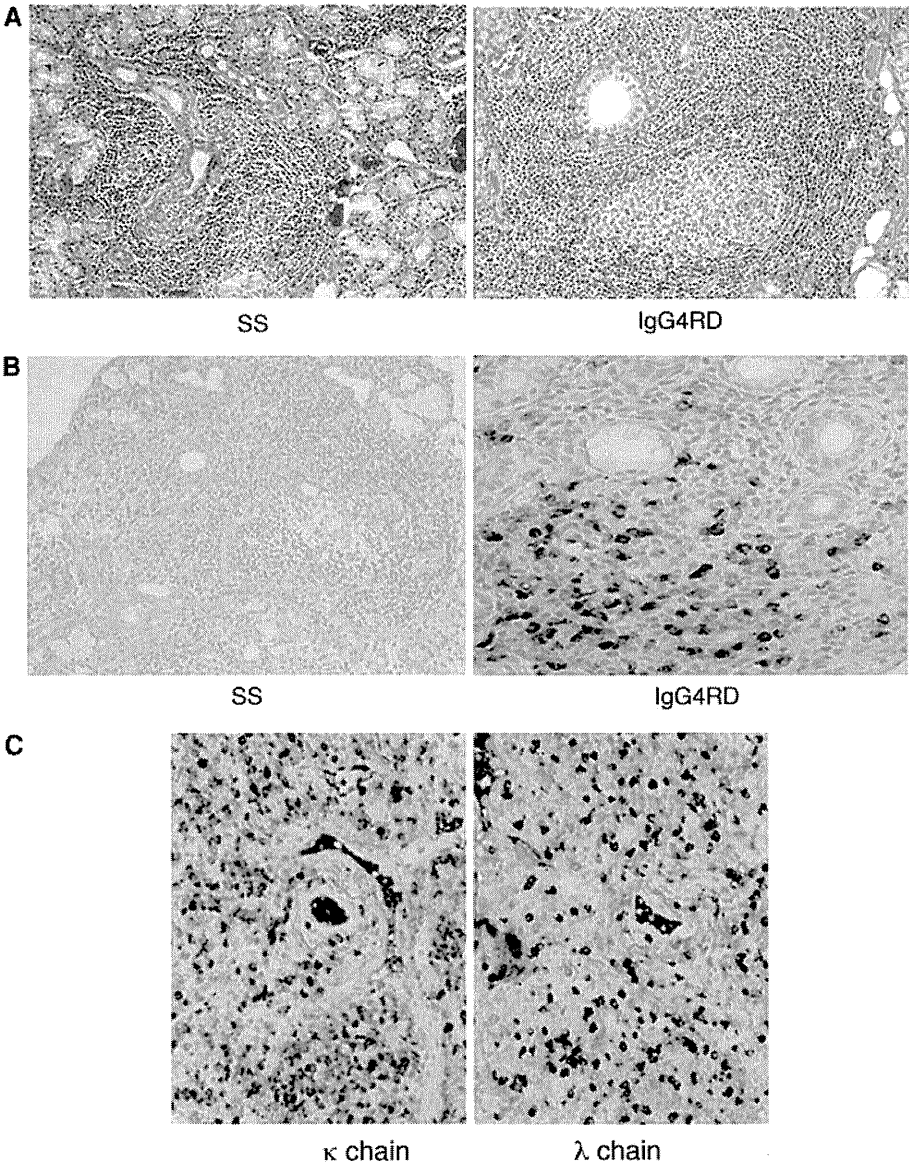


Fig. 5 Histopathological findings of minor labial salivary gland biopsies in patients with IgG4RD and typical SS. **a** Massive infiltration of lymphocytes and plasma cells was observed in patients with IgG4RD and those with typical SS (×200). IgG4RD, however, was characterized by lymphoid follicle formation but ducts were intact without lymphocytic infiltration. H&E staining. **b** IgG4RD showed scattered IgG4+ plasma cells in the periphery of the follicles (×200), whereas typical SS showed few or no IgG4+ cells. IgG4 immunostaining. **c** Staining for immunoglobulin κ- and λ-chains (×200)

ratio of IgG4-positive to IgG-positive cells of >40%, a finding almost never seen in patients with SS (Fig. 5b). Moreover, most patients with IgG4RD show polyclonal B-cell proliferation, with equal staining for immunoglobulin κ- and λ-chains (Fig. 5c). Thus, despite their similarities in organ involvement, IgG4-MD and SS are quite different conditions, with distinct clinical and pathological characteristics [7–9, 22, 29–31].

IgG4-related Küttner tumor

Küttner tumor, a unilateral sclerosing sialadenitis, is an IgG4RD [18]. A common feature of MD and Küttner tumor is that both manifest sialadenitis, as in IgG4RD. Histologically, Küttner tumors are very severe fibrous sclerotic lesions containing IgG4-positive plasma cells [32]. In contrast, fibrosis tends to be less severe in MD, although fibrosis in MD is frequently not examined extensively, because MD is generally diagnosed by the biopsy of minor labial salivary glands. Therefore, at present, it is difficult to set a strict boundary between MD and Küttner tumor.

IgG4-related autoimmune pancreatitis (IgG4-related AIP)

Recent studies have suggested that AIP manifests as two distinct subtypes, called types 1 and 2 (Table 4) [33]. Clinically, type 1 AIP seems to be the pancreatic manifestation of IgG4RD, characterized by: (1) mild abdominal symptoms, usually without acute attacks of pancreatitis; (2) occasional occurrence of obstructive jaundice; (3) increased serum gammaglobulin, IgG, and/or IgG4 concentrations; (4) presence of autoantibodies; (5) diffuse enlargement of the pancreas with a capsule-like low-density rim; (6)

Table 4 Subtypes of autoimmune pancreatitis (AIP) [33]

Subtype of AIP other nomenclatures	Type 1 AIP without GEL IgG4-related, LPSP	Type 2 AIP with GEL IgG4-unrelated IDCP
Prevalence	Asia > USA, Europe	Europe > USA > Asia
Age	High age	Younger
Gender	Male ≫ female	Male = female (NS)
Symptoms	Often obstructive jaundice	Often obstructive jaundice
Jaundice	Rare abdominal pain	Abdominal pain like acute pancreatitis
Pancreas images	Swelling/diffuse	Swelling/diffuse
	Segmental/focal	Segmental/focal
	Mass-forming	Mass-forming
Serology	High serum IgG	Normal IgG
	High serum IgG4	Normal IgG4
	Auto antibodies (+)	Auto antibodies (−)
Other organ involvement (OOI)	Sclerosing cholangitis	Unrelated to OOI
	Sclerosing sialadenitis	
	Retroperitoneal fibrosis	
	Other characteristics	
Ulcerative colitis	Rare	Often
Steroid response	Responsive	Responsive
Relapse	High rate	Rare

GEL, granulocyte epithelial lesion; *LPSP*, lymphoplasmacytic sclerosing pancreatitis; *IDCP*, idiopathic duct-centric chronic pancreatitis; *NS*, not significant

irregular narrowing of the pancreatic duct (sclerosing pancreatitis on endoscopic retrograde cholangiopancreatography [ERCP] images); (7) lymphocyte and IgG4-positive plasmacyte infiltration and fibrosis, and obliterative phlebitis; (8) occasional association with extrapancreatic lesions, such as sclerosing cholangitis similar to primary sclerosing cholangitis (PSC), sclerosing cholecystitis, sclerosing sialoadenitis, RPF, interstitial renal tubular disorders, enlarged celiac and hilar lymph nodes, chronic thyroiditis, and pseudotumor of the pancreas, liver, or lung; and (9) responsiveness to steroid therapy. Older males with IgG-related AIP often have obstructive jaundice, with both pancreatic and extrapancreatic manifestations responding to steroid therapy [12–15, 21, 33, 34].

Histological examination by American and European pathologists of the resected pancreases of patients with chronic non-alcoholic pancreatitis revealed another histopathological pattern, called idiopathic duct-centric pancreatitis (IDCP) or AIP with granulocytic epithelial lesions (GELs), later called type 2 AIP [35, 36]. Type 2 AIP is characterized primarily by these GELs, often accompanied by destruction and obliteration of the pancreatic duct [36]. Patients with type 2 AIP show swelling of the pancreas, but no or very few IgG4-positive plasma cells. Type 2 AIP has different clinicopathological features than type 1 AIP. Type 2 AIP shows no elevations in serum IgG4 or IgG, no autoantibodies, and no involvement of other organs, except for inflammatory bowel disease. Inflammatory bowel disease has been observed in approximately 30% of patients with type 2 AIP. Although type 1, or IgG4-related, AIP (LPSP type) often occurs in older men and is accompanied by a variety of extrapancreatic lesions, type 2, or neutrophil-related pancreatitis (IDCP/GEL type), has no gender bias, younger age at onset (often <40 years), and is frequently associated with inflammatory bowel disease. Thus, after a worldwide debate over the diagnostic criteria for AIP, IgG4-related pancreatitis has been defined as type 1 (LPSP type) and neutrophil-related pancreatitis has been defined as type 2 (IDCP/GEL type) [34].

IgG4-related sclerosing cholangitis (IgG4-related SC)

Extrapancreatic bile duct lesions are frequently associated with AIP. For example, 73% of patients with AIP have shown wall thickening or sclerosing changes in extrapancreatic bile ducts on endoscopic ultrasonography (EUS) and intraductal ultrasonography (IDUS), though only 26% of patients with AIP demonstrated sclerosing changes by ERCP [37]. However, many individuals without AIP have shown IgG4-related SC with isolated biliary tract involvement [38, 39]. In IgG4-related SC, stenosis is usually observed in the lower part of the common bile duct. The cholangiographic appearance of stenosis in the intrahepatic or hilar hepatic bile duct is very similar to that observed in PSC [40], a progressive disease of unknown etiology that ultimately results in liver cirrhosis. IgG4-related SC is associated with older age, male predominance, obstructive jaundice, weight loss, and abdominal discomfort [40]. Although steroid therapy has shown mixed results in patients with PSC, IgG4-related SC

responds dramatically to steroid therapy, as does IgG4RD [41]. The histopathological features of IgG4-related SC are similar to those of AIP and include diffuse plasmacytic infiltration, marked interstitial fibrosis with a focal storiform-like pattern, and obliterative phlebitis.

IgG4-related kidney disease (IgG4-related KD)

The kidney is a frequent target organ in IgG4RD, with tubulointerstitial nephritis (TIN) and fibrosis and abundant IgG4-positive plasma cell infiltration being diagnostically important histopathological features of this disease [42–44]. Recently, the clinicopathological features of 23 patients with IgG4-related TIN were reported to be quite uniform and similar to those observed in patients with IgG4-AIP, including high serum concentrations of IgG4 and IgE, hypocomplementemia, and TIN with infiltration of large numbers of IgG4-positive plasma cells plus fibrosis [45].

Kidney diseases in IgG4RD include conditions other than renal parenchymal lesions, such as hydronephrosis associated with RPF and tumors of the renal pelvis and urethra. However, IgG4-related TIN is considered to be representative of IgG4 renal parenchymal lesions [19]. Compared with other types of interstitial nephritis, IgG4-related TIN is often associated with extrarenal lesions, such as pancreatitis, sialadenitis, and lymphadenitis, and a high incidence of hypocomplementemia [46]. Imaging often shows heterogeneous shadows in the kidneys, such as a mass or multiple nodules (findings that are not observed in other types of interstitial nephritis). Histopathologically, the renal tubulointerstitium shows the infiltration of many lymphocytes and plasmacytes, as well as fibrosis, and IgG4 immunostaining shows a number of IgG4-positive plasma cells [47]. Although many studies have found no significant changes in the glomeruli, others have reported an association with glomerular lesions, including membranous nephropathy [46]. In the near future, the Japanese Kidney Society expects to develop diagnostic criteria for IgG4-related KD.

IgG4-related pulmonary diseases (IgG4-related PD)

IgG4-related PD has been described as inflammatory pseudotumor, interstitial pneumonitis, organizing pneumonia, and lymphomatoid granulomatosis [48]. Most (81%) patients with IgG4-related PD have been reported to be men, with a median age at diagnosis of 69 years [48], features similar to those of IgG4RD. Some patients present initially with respiratory symptoms, such as dry cough or dyspnea, whereas 75% of patients are asymptomatic and the disease is found incidentally by abnormal shadows on chest X-rays. Although IgG4-related PD is associated with a variety of radiologic abnormalities [49], diffuse lymphoplasmacytic infiltration has been observed in all lesions, with irregular fibrosis and obliterative vascular changes being more common in solid areas [48]. Hilar and pancreatic accumulation of gallium-67 has been reported as characteristic of the active stage of AIP when serum IgG4 concentrations are high [50].

Radiographically, IgG4-related PD can be divided into two types, inflammatory pseudotumors and interstitial pneumonitis. Inflammatory pseudotumors have been described as nodular or mass lesions, or infiltration, and are characterized by radiating reticular shadows surrounding the tumor. Interstitial pneumonitis presents in most patients with reticular shadows, ground-glass opacity, and interstitial fibrosis in both lower lung fields [17].

Histopathologically, inflammatory pseudotumor is a plasma cell granuloma, with infiltration mainly by plasma cells and lymphocytes, irregular fibrosis, lymphoid follicle formation, findings of interstitial pneumonitis at the periphery of the nodule, obliterating phlebitis and arteritis, and eosinophilic infiltration [17]. Interstitial pneumonitis is characterized by thickening of the alveolar septa due to infiltration by plasma cells and lymphocytes, and by diffuse fibrosis. Histopathologically, interstitial pneumonitis often shows a pattern previously classified as non-specific interstitial pneumonia (NSIP) [51]. The diagnostic criteria for IgG4-related PD are now under consideration by the Japanese Respiratory Association.

IgG4-related Hashimoto's thyroiditis (IgG4-related HT)

Hashimoto's thyroiditis (HT) has been considered a well-defined clinicopathological entity, characterized by the presence of goiter and serum thyroid autoantibodies. Recently, a unique subtype of HT was described, characterized by the presence of prominent fibrosis such as storiform fibrosis and swirling fibrosis, numerous IgG4-positive plasma cells, and elevated serum IgG4 [52], and called IgG4-related HT [53]. Among 23 patients with HT who underwent total thyroidectomy, 14 cases (60.8%) were IgG4-related HT, but there were no significant differences in positivity for thyroid and microsome tests between IgG4-related HT and non-IgG4 HT [54].

Riedel's thyroiditis was first described in 1896 in two patients with hard goiter and tracheal compressive symptoms. One-third of patients with Riedel's thyroiditis have multifocal fibrosclerosis, including sclerosing cholangitis, salivary gland fibrosis, RPF, or fibrotic orbital pseudotumor. Therefore, despite the lack of immunohistochemical staining for IgG4, certain proportions of Riedel's thyroiditis were considered a type of IgG4RD. Although one patient with IgG4RD showed involvement of the lachrymal gland and pulmonary and biliary tracts as well as Riedel's

thyroiditis [32], it is still unclear whether Riedel's thyroiditis is a type of IgG4RD.

IgG4-related lymphadenopathy and Castleman's disease

Concomitant lymphadenopathy is common in patients with IgG4RD, and there have been several reports dealing with the morphological and immunohistological findings of lymph node lesions [55–57]. Although IgG4-related lymphadenopathy is occasionally characterized by systemic lymphadenopathy, polyclonal hyperimmunoglobulinemia, especially elevated IgG and IgE concentrations, and positivity for various autoantibodies, patients with IgG4RD with generalized lymphadenopathy should only be evaluated for lymphoma, sarcoidosis, multicentric Castleman's disease, and other malignancies.

IgG4-related lymphadenopathy can be characterized into five histological subtypes: Castleman's disease-like morphology (type I), reactive follicular hyperplasia (type II), interfollicular plasmacytosis and immunoblastosis (type III), progressive transformation of germinal center-like (type IV), and inflammatory pseudotumor-like morphology (type V) [57]. In addition, IgG4-related lymphadenopathy can be classified into two types based on the infiltrative patterns of IgG4-positive cells: interfollicular plasmacytosis (types I, II, III, and V) and intragerminal center plasmacytosis (type IV). Patients with systemic IgG4-related lymphadenopathy were significantly older (68.8 vs. 43.3 years) and had significantly lower C-reactive protein (0.29 vs. 8.71 mg/dl) and interleukin (IL)-6 (8.45 vs. 34.82 pg/ml) concentrations than patients with multicentric Castleman's disease [56].

IgG4-related retroperitoneal fibrosis (IgG4-related RPF)

RPF is a chronic inflammatory condition with marked fibrosis in retroperitoneal tissue. In patients with advanced RPF a retroperitoneal mass covers the abdominal aorta and compresses the ureters, leading to urinary obstruction. Its etiology is unknown, but it has many causes, including infection, radiation, drugs, malignant tumor, and trauma. Three patients with RPF and elevated serum IgG4 have been described [58], and the histology of all 12 patients with RPF was reported to be similar to that seen in AIP, including fibrosis, intense inflammatory cell infiltration with plasma cells, venulitis, and obliterative arteritis [59]. Of 17 patients with RPF, 10 had both elevated serum IgG4 and histopathological features typical of IgG4RD, suggesting that RPF could be categorized as IgG4-related [60]. However, in RPF, fibrosis gradually progresses during chronic inflammation, with lymphocyte infiltration predominant during the early stages and a fibroinflammatory process occurring later. Therefore, determining the stage of illness seems important for diagnosis and prediction of response to steroid treatment [61].

IgG4-related aortitis

There have been several recent reports of inflammatory aneurysms in the abdominal or thoracic aorta [62–64]. For example, 40% of inflammatory abdominal aortic aneurysms (AAAs) were IgG4RD, with elevated IgG4 in serum and abundant infiltration of IgG4+ plasma cells and obliterative phlebitis [62]. These findings suggested that inflammatory AAAs can be classified into 2 groups: IgG4-related and IgG4-unrelated [62]. Although IgG4RD shows good response to steroid therapy, treatment with the anti-CD20 monoclonal antibody, rituximab, may result not only in clinical improvement, but in the tapering or discontinuation of steroids or other drugs [65].

Pathogenesis and pathophysiology of IgG4RD

At present, the pathogenetic mechanism and underlying immunological abnormalities in IgG4RD remain unclear. The elevated serum IgG4 concentration and tissue infiltration of IgG4-positive plasma cells are characteristic features of IgG4RD. Because IgG4 antibodies are dynamic molecules that can exchange Fab arms by swapping a heavy chain and attached light chain, IgG4 can form bi-specific antibodies, as well as functioning as a monovalent molecule [66, 67]. These properties may protect against type I allergy by inhibiting IgE functions, and may prevent type II and III allergy by blocking the Fc-mediated effector functions of IgG1 and inhibiting the formation of large immune complexes. The predominant expression of IgG4 under conditions of chronic antigen exposure is compatible with the clinical features of IgG4RD, including its slow progression and relatively weak immune response.

Some autoantibodies, including those to pancreatic trypsin inhibitor (PSTI), lactoferrin (LF), and carbonic anhydrase (CA), have been detected in patients with IgG4RD, especially in those with IgG4-related AIP [34]. Although IgG4 from the patients was able to bind the normal epithelia of the pancreatic ducts, gallbladder, and salivary gland ducts [68], IgG4-type autoantibodies have not been detected in patients with IgG4RD.

Aberrant immunological findings have been observed in patients with IgG4RD. For example, the Th2-dominant immune response and the production of Th2-type cytokines, such as IL-4, IL-5, IL-10, and IL-13, are increased [69–71]. Furthermore, the numbers of regulatory T cells (Treg) expressing CD4+CD25+Foxp3 are significantly higher in the affected tissues and peripheral blood of

patients with IgG4RD than the numbers in patients with autoimmune and nonautoimmune diseases [72–74]. Overexpression of the regulatory cytokines IL-10 and transforming growth factor β (TGF-β) has also been reported in patients with IgG4RD [74, 75]. IL-10 and TGF-β have potent activities in directing B cells to produce IgG4 and induce fibroplasia, respectively. IL-4, IL-5, and IL-13 are important for class switching to IgE production and eosinophil migration. Therefore, abnormalities in the production of these cytokines may be involved in the pathogenesis of IgG4RD.

Perspectives on IgG4RD

Although IgG4RD is a novel clinical entity, it is not a rare disease. Despite the effectiveness of steroid therapy, for IgG4RD, the condition has often been misdiagnosed as a malignant tumor, lymphoma, Sjögren's syndrome, or other diseases. To date, the clinical diagnostic criteria for IgG4RD have not been established. Because IgG4RD may occur in a variety of organs throughout the body, comprehensive discussions with the cooperation of many clinicians from various specialized fields is needed to establish uniform diagnostic criteria. At present, the diagnostic criteria for IgG4-MD (Table 2) [8] and those for IgG4-AIP type 1 (Table 5) [14] have been established.

Consensus has been reached on two diagnostic criteria for IgG4RD: (1) serum IgG4 concentration >135 mg/dl, and (2) >40% of IgG-positive plasma cells being IgG4-positive. The MHLW Japan team has proposed guidelines for the diagnosis of IgG4RD; these are shown in Table 3. The formulation of organ-specific (i.e., kidney and pulmonary) diagnostic criteria for IgG4RD requires cooperation with the relevant societies. Although IgG4RD responds well to steroid therapy, recurrence and relapse occur following the early reduction or withdrawal of prednisone. Therefore, it is necessary to develop treatment guidelines to establish initial doses of steroids, tapering procedures, and maintenance doses. The MHLW Japan team is currently pursuing a "Prospective study for creating IgG4-related disease treatment guidelines", and unified clinical guidelines are expected in the near future.

Table 5 Clinical diagnostic criteria of autoimmune pancreatitis; revised proposal in Japan (2006) [79]

1. Diffuse or segmental narrowing of the main pancreatic duct with irregular wall and diffuse or localized enlargement of the pancreas on imaging modalities, such as abdominal ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI)
2. High-serum F-globulin, IgG, or IgG4, or the presence of autoantibodies, such as antinuclear antibodies and rheumatoid factor
3. Marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells into the periductal area, with occasional lymphoid follicles in the pancreas

For diagnosis, criterion 1 must be present, together with criteria 2 and/or 3

However, it is necessary to exclude malignant diseases such as pancreatic and biliary cancers

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Conflict of interest None.

Appendix

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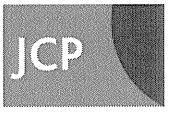

Multicentric Castleman's disease with abundant IgG4-positive cells: a clinical and pathological analysis of six cases

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Multicentric Castleman's disease with abundant IgG4-positive cells: a clinical and pathological analysis of six cases

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ABSTRACT

Background Differentiation between multicentric Castleman's disease and systemic immunoglobulin (Ig) G4-related lymphadenopathy is sometimes difficult. It has been suggested that measurement of the IgG4-/IgG-positive cell ratio is useful for the differential diagnosis of the two diseases. However, the authors present a detailed report of six patients with multicentric Castleman's disease with abundant IgG4-positive cells (IgG4-/IgG-positive cell ratio, >40%).

Results In the present series, the patients showed systemic lymphadenopathy, polyclonal hypergammaglobulinaemia and elevated serum interleukin-6 (IL-6) and C-reactive protein levels. Further, anaemia, hypoalbuminaemia, hypocholesterolaemia and thrombocytosis were observed. These findings were consistent with those of multicentric Castleman's disease. Although five patients showed elevated serum IgG4 levels, only two patients showed an increased serum IgG4/IgG ratio. However, the two patients showed highly elevated serum IgG4 levels, but the serum IgG4/IgG ratios were, although increased, not very high. Also, a patient with increased serum IgG4/IgG ratio showed a good response to antihuman IL-6 receptor monoclonal antibody (tocilizumab). Histologically, the germinal centres were mostly small and regressive, and frequently penetrated by hyalinised blood vessels, and there was no eosinophil infiltration. These findings were different from those of IgG4-related lymphadenopathy.

Conclusions The authors conclude that multicentric Castleman's disease sometimes occurs with abundant IgG4-positive cells and elevated serum IgG4 levels. Therefore, the two diseases cannot be differentially diagnosed by immunohistochemical staining alone. Laboratory findings, especially IL-6 level, C-reactive protein level and platelet count, are important for the differential diagnosis of the two diseases.

INTRODUCTION

Castleman's disease is a rare atypical lymphoproliferative disorder[1] classified according to the histopathological findings of the affected lymph nodes as plasma-cell type, hyaline-vascular type or a mixed-type variant of the former two types.[2 3] Patients with the plasma-cell type or mixed-type Castleman disease frequently show systemic manifestations (multicentric Castleman's disease (MCD)) such as fever, fatigue and loss of appetite and weight. Abnormal laboratory and clinical findings include elevated C-reactive protein (CRP) level, hypergammaglobulinaemia, anaemia, hypoalbuminaemia, hypocholesterolaemia and thrombocytosis.[2–5] These symptoms are closely related to high interleukin (IL)-6 levels, and therefore MCD is considered as a hyper-IL-6 syndrome. Idiopathic plasmacytic lymphadenopathy with polyclonal hypergammaglobulinaemia is considered the same as MCD in Western countries.[6 7] Although idiopathic plasmacytic lymphadenopathy and MCD have a similar clinicopathology, the former has a significantly better 5-year survival rate than the latter.[6 7]

Immunoglobulin (Ig) G4-related diseases have recently been confirmed, which show unique and interesting clinicopathological features.[8] Together with a group of researchers, we revealed that IgG4-related lymphadenopathy sometimes shows systemic lymphadenopathies and polyclonal hypergammaglobulinaemia,[8 9] and is often clinically and/or histologically suspected to be MCD.[8] Recently, we reported the clinical and pathological findings of systemic IgG4-related lymphadenopathy; these findings overlapped only partially with those of MCD.[8]

On the basis of immunohistochemical findings, Cheuk *et al*[9] previously suggested an IgG4-/IgG-positive cell ratio of >40% to be the diagnostic criterion for IgG4-related lymphadenopathy. However, we experienced six patients with MCD with abundant IgG4-positive cells (IgG4-/IgG-positive cell ratio, >40%).

In the present study, we conducted a detailed examination of six patients with MCD with abundant IgG4-positive cells to further clarify the differences in the clinicopathological findings of the present study on MCD and those presented in previous reports on IgG4-related lymphadenopathy, and sought to establish differential diagnostic criteria for the two diseases.

MATERIALS AND METHODS

Patients and materials

We clinicopathologically examined six Japanese patients with MCD with abundant IgG4-positive cells (IgG4-/IgG-positive cell ratio, >40%). The cases were retrieved from the surgical pathology consultation files of the authors (YS, MK and TY).

Clinical information was obtained from the patient medical records, referring pathologists or clinicians.

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All data and samples from the patients were collected with their informed consent.

Histological examination and immunohistochemistry

Surgically biopsied lymph node specimens were fixed in 10% formaldehyde and embedded in paraffin. Serial sections (4 μm) were cut from each block of paraffin-embedded tissue, and several selected sections were stained with H&E. The sections were immunohistochemically stained using an automated BenchMark XT slide stainer (Ventana Medical Systems, Tucson, Arizona). The tissue sections were subjected to standardised heating pretreatment for antigen retrieval prior to the immunohistochemical procedure. The following primary antibodies were used: CD20 (L26; 1:200; Novocastra, Newcastle, UK), CD3 epsilon (PS1; 1:50; Novocastra), CD5 (4C7; 1:100; Novocastra), CD10 (56C6; 1:50; Novocastra), CD21 (1F8; 1:20; Dako, Carpinteria, California), CD138 (MI15; 1:100; Dako), Bcl-2 oncoprotein (3.1; 1:200; Novocastra), IgG (polyclonal; 1:20000; Dako), IgG4 (HP6025; 1:400; The Binding Site, Birmingham, UK), κ light chain (kp-53; 1:100; Novocastra), Lambda light chain (HP-6054; 1:200; Novocastra) and human herpesvirus type 8 (137B10; 1:50; Novocastra).

The number of IgG4- or IgG-positive cells was estimated in areas with the highest density of IgG4- or IgG-positive cells, respectively. Five different high-power fields (HPFs; eyepiece, ×10; lens, ×40) were examined in each section, and the average number of IgG4- or IgG-positive cells per HPF was calculated.[8]

PCR for the detection of Ig heavy-chain gene rearrangement

Ig heavy-chain gene rearrangement was analysed by PCR. The reaction was performed according to the standard procedures described previously.[8 10 11] The primers used for Ig heavy-chain gene amplification were as follows[8 10 11]: 5′-TGG [A/G]TC CG[C/A] CAG [G/C]C[T/C] [T/C]C[A/C/G/T] GG-3′ as an upstream consensus V-region primer; 5′-TGA GGA GAC GGT GAC C-3′ as a consensus J-region primer; and 5′-GTG ACC AGG GT[A/C/G/T] CCT TGG CCC CAG-3′ as a consensus J-region primer.

Statistical analyses

All statistical analyses were performed using the Mann–Whitney U test with SPSS software (version 14.0). A p value of <0.05 was considered statistically significant.

RESULTS

Clinical and laboratory findings

The clinical and laboratory findings are summarised in tables 1, 2 respectively. The study subjects comprised five men and one woman with a median age of 52.0 years (range 43.0–68.0 years). All the patients showed systemic lymphadenopathy and were clinically and/or histologically suspected to have MCD, and/or malignant lymphoma previously. The size of the lymph nodes ranged from 1.0 to 2.5 cm. Analysis of the lifestyles of the patients did not indicate any risk factors for HIV infection; antihuman immunodeficiency virus 1 antibody was negative in the three patients examined. Various autoantibodies were detected in three of the six patients examined (table 1). Hypergammaglobulinaemia was detected in all the patients. The IgG level (mean±SD 5354.33±2278.67 mg/dl) was elevated in all the patients. The serum IgA level (mean±SD 708.35±241.65 mg/dl) was elevated in five patients, and the serum IgM level (mean±SD 172.37±241.65 mg/dl) was elevated in two patients. Further, five patients showed elevated serum IgG4 levels (mean±SD 492.83±538.40 mg/dl). However, only two patients showed an increased serum IgG4/IgG ratio; this was because the patients showed significantly elevated levels of other IgG subclasses. The IL-6 level (mean±SD 22.35±8.77 pg/ml) and CRP level (mean±SD 7.50±2.70 mg/dl) were significantly elevated in all the patients. Moreover, our patients showed anaemia (haemoglobin level: mean±SD 10.30±2.37 g/dl), hypoalbuminaemia (albumin level: mean±SD 2.7±0.73 g/dl), hypocholesterolaemia (total cholesterol: mean±SD 113.40±18.98 mg/dl) and thrombocytosis. Lactate dehydrogenase level was not found to be elevated (mean±SD 116.50±19.26 IU/l) in any patient. In contrast, the soluble IL-2 receptor level was significantly elevated (mean±SD 2111.67±918.87 U/ml) in all patients.

Compared with our previous study on systemic IgG4-related lymphadenopathy,[8] the present study on MCD showed significantly elevated IL-6 and CRP levels, anaemia, hypoalbuminaemia and hypocholesterolaemia. The differences in the above-mentioned findings between the groups were statistically significant (table 3).

Pathological and immunohistological findings of lymph nodes

Histopathological findings of the biopsied lymph nodes of the patients were very similar (figures 1–3). Lymphoid follicles were

Table 1 Clinical findings and IgG4-/IgG-positive cell ratio in six patients with multicentric Castleman's disease

Patient no	Age/sex	Presentation	Autoantibodies	Treatment and clinical outcome (follow-up period in months)	IgG4-/IgG-positive cell ratio (%)
1	43/M	Fatigue, systemic lymphadenopathy, thrombocytosis	ANA (borderline) RF (+)	Follow-up; stable disease (10)	45.2
2	68/M	No subjective symptoms, systemic lymphadenopathy, thrombocytosis	ANA (borderline) RF (−) Anti-SS-A/anti-SS-B (−) Anti-dsDNA (−)	Follow-up; stable disease (11)	54.7
3	47/F	Fatigue, skin purpura, renal dysfunction, systemic lymphadenopathy, thrombocytosis	ANA (+) RF (+) Anti-SS-A/anti-SS-B (+) Anti-dsDNA (+)	Steroid; partial remission, worsening of symptoms on reduced dose of steroid (26)	46.5
4	50/M	Fever, renal dysfunction, systemic lymphadenopathy, multiple lung nodules, bone marrow plasmacytosis, thrombocytosis	ANA (+) Anti-dsDNA (+)	Steroid; complete remission, disapperance of lymph node swelling and multiple lung nodules, negative test results for autoantibodies (31)	48.8
5	65/M	No subjective symptoms, incidental finding of systemic lymphadenopathy since several years	ANA (borderline)	Follow-up; stable disease (10)	76.6
6	54/M	No subjective symptoms, incidental finding of systemic lymphadenopathy since 15 years, multiple lung nodules, thrombocytosis	ANA (−) RF (−) Anti-SS-A/anti-SS-B (−) Anti-Sm (−)	Tocilizumab; complete remission, disappearance of lymph node swelling and multiple lung nodules, improvement in laboratory data (13)	43.4

ANA, antinuclear antibody; dsDNA, double-stranded DNA; F, female; Ig, immunoglobulin; M, male; RF, rheumatoid factor; SS, Sjögren syndrome; Sm, Smith antigen; Tocilizumab, anti-human interleukin-6 receptor monoclonal antibody.

Table 2 Laboratory data on patients with multicentric Castleman's disease

Patient no	IgG1 (mg/dl) (320–748)*	IgG2 (mg/dl) (208–754)*	IgG3 (mg/dl) (6.6–88.3)*	IgG4 (mg/dl) (4.8–105)*	IgG4/IgG (%) (3–6)*	IgG (mg/dl) (870–1700)*	IgA (mg/dl) (110–410)*	IgM (mg/dl) (35–220)*	IgE (IU/ml) (<170)*	CRP (mg/dl) (<0.3)*	IL-6 (pg/ml) (<4.0)*	LDH (IU/l) (119–229)*	sIL-2R (U/ml) (220–530)*	Hb (g/dl) (male, 13.5–17.6)* (female, 11.3–15.2)*	Alb (g/dl) (4.0–5.0)*	T-cho (mg/dl) (150–219)*
1	1830	1810	270	93	2.3	4003	620.1	139.2	ND	2.84	8.6	119	1812	12.7	3.4	142
2	2080	1270	94	147	4.1	3591	1049	135	1670	9.3	19.6	143	1080	13.2	3.6	103
3	ND	ND	ND	154	4.9	3113	352	106	ND	7.21	27.4	103	2137	7.5	2.2	117
4	3290	1310	168	314	6.2	5082	898	229	ND	9.3	31.2	133	3797	8.1	1.8	114
5	ND	ND	ND	1460	17.4	8380	638	263	ND	10.06	30	91	1644	10.9	2.2	ND
6	3810	2210	55.8	789	11.5	7957	693	162	ND	6.26	17.3	110	2200	9.4	3.0	91

*Normal range or value (in the respective unit).
Alb, albumin; CRP, C-reactive protein; Hb, haemoglobin; Ig, immunoglobulin; IL-6, interleukin-6; LDH, lactate dehydrogenase; ND, not determined; sIL-2R, soluble interleukin-2 receptor; T-cho, total cholesterol.

diffused throughout the cortex of the lymph node. The follicles showed variable degrees of regressive changes in the germinal centres with a distinct mantle zone, decreased number of centroblasts and tangible body macrophages. The germinal centres were mostly small and regressive, and frequently penetrated by hyalinised blood vessels. These findings were different from those of IgG4-related lymphadenopathy.[8 12 13] The interfollicular area was characterised by sheets of proliferating mature plasma cells with a slight-to-moderate increase in vascular proliferation, and there was no eosinophil infiltration. These histological findings were consistent with those of MCD rather than of IgG4-related lymphadenopathy.[8 12–16]

The majority of CD21-positive follicular dendritic cells formed networks similar to those in the germinal centres.

The IgG4-/IgG-positive cell ratio ranged from 43.4% to 76.6%, with an average of 52.0%.

There were no human herpesvirus type 8 antibody-positive cells and no Ig light-chain restriction.

Ig heavy-chain gene rearrangement

No Ig heavy-chain gene rearrangement was observed in any case.

DISCUSSION

MCD is a rare lymphoproliferative disorder and often refractory to even corticosteroid treatment or chemotherapy; consequently, the prognosis of patients with this disease is poor.[5–7] In Japan, some patients showed a less aggressive or sometimes self-limiting clinical course of a disease. Moreover, the disease is often sensitive to conventional therapies such as those with corticosteroids and cytotoxic agents.[6 7 17 18] These cases befit the disease entity of idiopathic plasmacytic lymphadenopathy with polyclonal hypergammaglobulinaemia. Our patients showed an indolent or good clinical course and tested negative for human herpesvirus type 8 antibody. Thus, our patients might have idiopathic plasmacytic lymphadenopathy with polyclonal hypergammaglobulinaemia rather than multicentric Castleman disease.[6 7 18]

In our present study, the patients showed abundant IgG4-positive cells (IgG4-/IgG-positive cell ratio, >40%), and the histological findings were partially similar to those of IgG4-related lymphadenopathy. However, our patients showed elevated serum IL-6 levels and the related biological effect, that is, elevated CRP levels, and thrombocytosis. Therefore, they were considered to have hyper-IL-6 syndrome.[5 8 16–19] Moreover, the patients showed anaemia, hypoalbuminaemia, hypocholesterolaemia and elevated serum IgA levels. These findings were consistent with those of MCD and quite different from those of IgG4-related lymphadenopathy.[5 8 16–19] IgG4-related lymphadenopathy is not characterised by elevated serum IL-6 and CRP levels.[8 16 19] Moreover, histological findings show normal-to-hyperplastic germinal centres and eosinophil infiltration.[8 12 13 16] However, our cases usually showed small and regressive germinal centres, and no eosinophil infiltration was observed there (table 3). These histological findings were consistent with those of MCD.[8 12–16]

IL-6 is an interleukin produced by a variety of cells, including T cells, macrophages and B cells, and has multiple biological functions.[5 17] It induces the final maturation of activated B cells to produce plasma cells (Ig-producing cells).[5 17] Continuous IL-6 production induces polyclonal hypergammaglobulinaemia.[20–22] Moreover, IL-6 increases the serum levels of IgG4 and other IgG subclasses.[22–24] A previous study reported a case of MCD with elevated serum IgG4 level.[25] Therefore, we suggest that the number of IgG4-positive cells increases in MCD. In our study, although five patients showed elevated serum IgG4 levels, three

Table 3 Clinical and pathological findings of multicentric Castleman's disease and systemic IgG4-related lymphadenopathy

Findings	Multicentric Castleman's disease (present series)	Systemic IgG4-related lymphadenopathy (data from Sato *et al*[8])	p Value*
Clinical findings			
Systemic lymphadenopathy	Yes	Yes	–
Polyclonal hypergammaglobulinaemia	Yes	Yes	–
Elevated serum IgG level	Yes (mean±SD 5354.33±2278.67 mg/dl)	Yes (mean±SD 3651.8±1214.1 mg/dl)	NS
Elevated serum IgA level	Yes (mean±SD 708.35±241.65 mg/dl)	No (mean±SD 228.5±135.73 mg/dl)	0.003
Elevated serum IL-6 level	Yes (mean±SD 22.35±8.77 pg/ml)	No (mean±SD 8.45±11.61 pg/ml)	0.039
Elevated CRP level	Yes (mean±SD 7.50±2.70 mg/dl)	No (mean±SD 0.29±0.25 mg/dl)	0.001
Anaemia	Yes (haemoglobin level: mean±SD 10.30±2.37 g/dl)	No (haemoglobin level: mean±SD 12.96±1.61 g/dl)	0.034
Hypoalbuminaemia	Yes (albumin level: mean±SD 2.7±0.73 g/dl)	No (albumin level: mean±SD 3.71±0.48 g/dl)	0.011
Hypocholesterolaemia	Yes (total cholesterol: mean±SD 113.40±18.98 mg/dl)	No (total cholesterol: mean±SD 163.1±28.11 mg/dl)	0.009
Thrombocytosis	Yes	No	–
Pathological findings			
Germinal centre	Small and regressive	Normal—hyperplastic	–
Interfollicular area	Sheets of proliferating mature plasma cells	Proliferation of mature plasma cells with plasmacytoid cells and immunoblasts	–
Eosinophil infiltration	No	Yes	–

*p<0.05 was considered statistically significant.
CRP, C-reactive protein; Ig, immunoglobulin; IL-6, interleukin-6; NS, not significant.

of these patients (patient nos 2, 3 and 4) did not show an increased serum IgG4/IgG ratio. The remaining two of the five patients (patients no 5 and 6) showed highly elevated serum IgG4 levels (1460 mg/dl and 789 mg/dl, respectively), but the serum IgG4/IgG ratios were, although increased, only 17.4% and 11.5%, respectively. This was because the patients had elevated levels of not only IgG4 but also IgG1, IgG2 and IgG3 (table 2). Serum IgG1 levels, in particular, were significantly elevated.

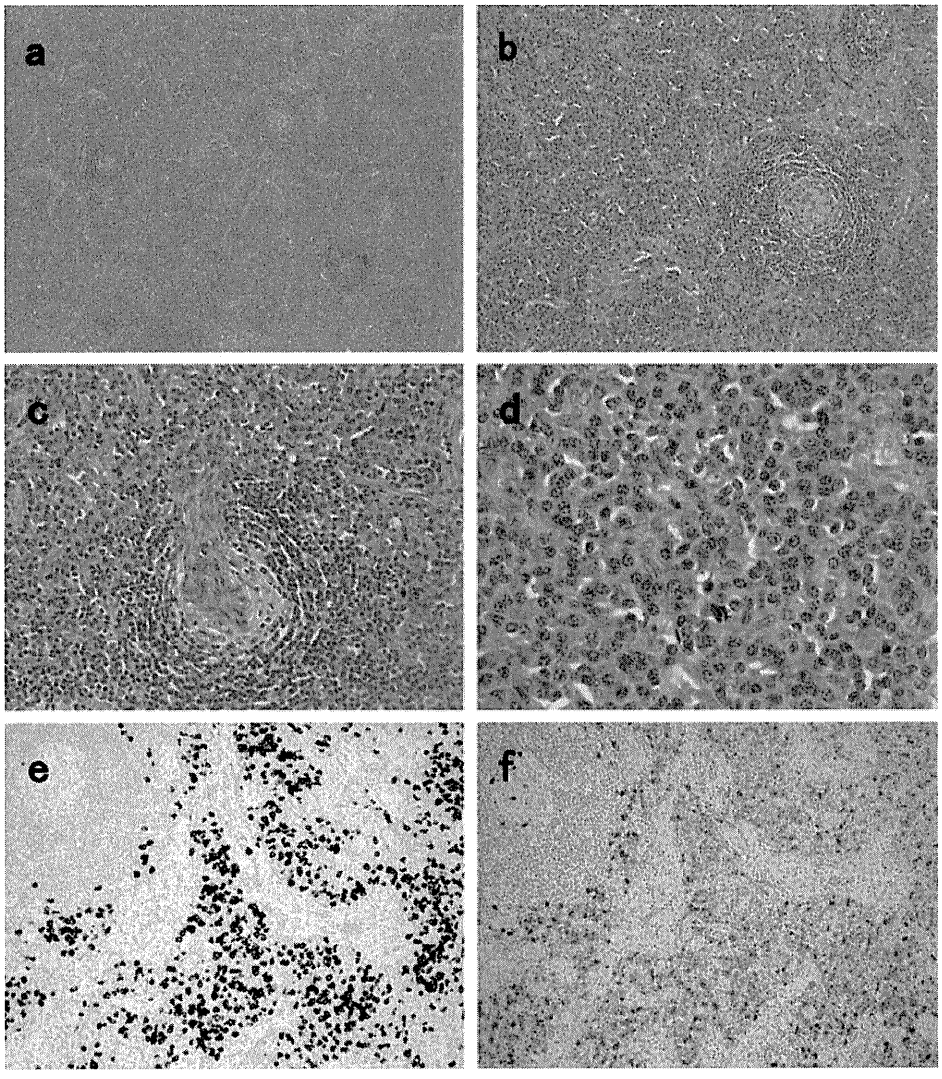

Figure 1 Histopathological findings of patient no 1. Expansion of the interfollicular area was observed, and lymphoid follicles showed variable degrees of regressive changes in the germinal centres with a distinct mantle zone (A, B). Blood vessels penetrated into the germinal centres (C). The interfollicular area was characterised by sheets of proliferating mature plasma cells, and there was no eosinophil infiltration (D). (E) Immunostaining of IgG4. (F) Immunostaining of IgG. The IgG4-/IgG-positive cells ratio was 45.2%, but the serum IgG4 level was not elevated. (A–D) H&E staining; (A) ×40, (B) ×100, (C) ×200, (D) ×400, (E, F) ×100.