levels in MD patients, and only 2.6% in SS patients (Fig. 4b). The relative serum levels of human IgG subclasses in healthy adults are as follows: IgG1 > IgG2 > IgG3 > IgG4 [34,35]. In normal human subjects, the mean levels of IgG subclasses are as follows: IgG1, 64%; IgG2, 20%; IgG3, 13%; and IgG4, 3% [36]. The Japanese population does not differ from other populations with regard to the connections of the IgG subclasses relative to the total IgG levels. IgG4 levels generally do not vary with sex and age, and both IgG4 levels and the IgG4/total IgG ratio are generally constant [2]. The noninflammatory role of IgG4 can be attributed to the unique structural features in the IgG4 hinge region that result in low affinity for certain Fcγ receptors and also to the ability of separating and pairing again, leading to bi-specific antibodies that are functionally monomeric [37]. However, the antigen responsible for increased IgG4 levels in MD patients remains unidentified. Moreover, the IgG4 levels may be increased only in some cases.

Immunohistochemically, the infiltration of numerous IgG4-positive plasmacytes near acinar and ductal cells and around lymphoid follicles has been confirmed in MD (Fig. 5a); however, the specimens from SS patients showed no IgG4-positive plasmacytes (Fig. 5b). We also detected abundant IgG4-positive plasmacytes in the stomach, colon, and kidney as well as in lymphoid tissues such as the cervical lymph nodes and bone marrow in patients with MD [29,38]. Thus, MD can constitute a singular systemic IgG4-related plasmacytic disease.

IgG4 levels are elevated in pemphigus vulgaris [39], pemphigus foliaceus [40], certain types of sclerosing pancreatitis [30], and surprisingly, in Churg-Strauss syndrome [41]. Oliveira found that IgG4-related immune complexes were involved in the pathogenesis of some membranous nephropathies [42]. Recent analyses of IgG4 antigens have revealed that the desmoglein 3 antigen is found in patients with pemphigus vulgaris, while desmo-

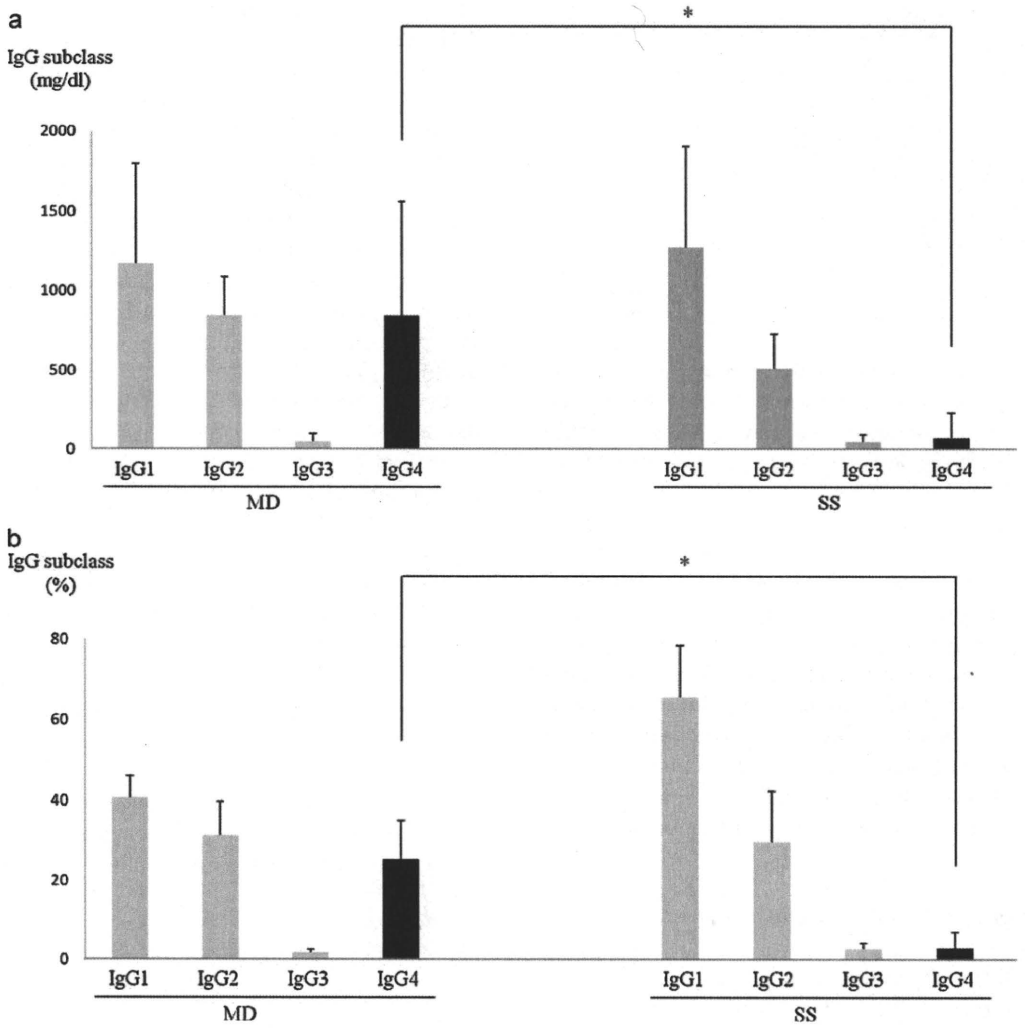

Fig. 4. Comparison of serum levels of IgG subclasses (a) and ratios of each IgG subclass/total IgG (b) between MD and SS. The statistical significance was determined by the Mann–Whitney *U* test. Serum IgG4 levels were significantly higher in MD than in SS for levels (a) as well as ratios (b). *P values of <0.005 compared to the IgG4 level of SS.

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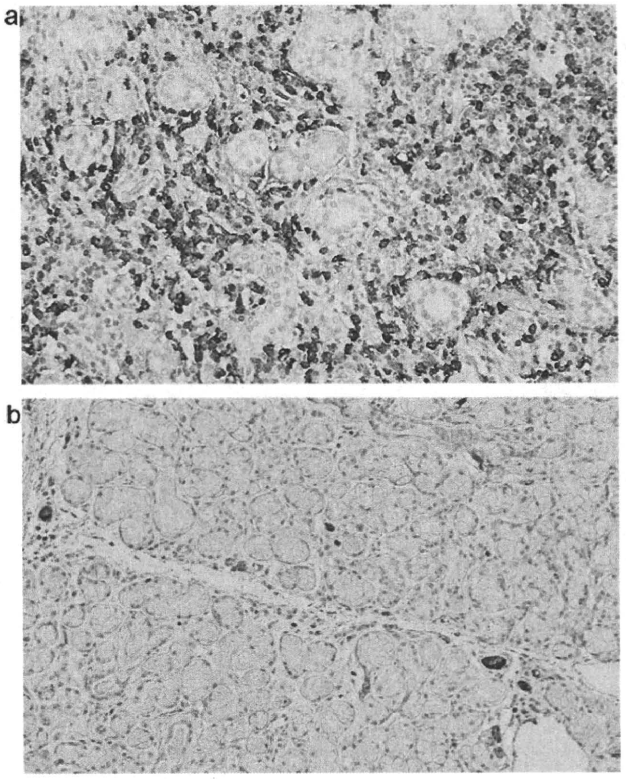

Fig. 5. Immunohistochemistry for IgG4 in salivary glands in MD (a) and SS (b). Immunoperoxidase stain, hematoxylin counterstain, ×200. Abundant IgG4-postive cells infiltrate around acinar and ductal cells in the submandibular glands of MD patients (a), whereas no infiltrating IgG4-positive cells are observed in the labial salivary glands of SS patients (b).

glein 1 is found in patients with pemphigus foliaceus [39,40]. These antigens are adhesion molecules that aid the maintenance of skin structures. IgG4 can act as a pathogenic antibody [39,40], and IgG4 levels may reflect the severity of pemphigus vulgaris [43].

On the other hand, we observed that MD patients often complained of olfactory disturbance [5]. Of the 44 MD patients who were interviewed, 20 (45.5%) cases complained of olfactory disturbance, even though no abnormalities, such as obstructive or inflammatory disease, were detected in their nasal cavities and sinuses. We were unable to determine the pathogenesis of this symptom in our study; however, we found abundant IgG4-positive plasmacytes in the nasal mucosa of MD patients who complained of olfactory disturbance [44]. This indicates that olfactory disturbance may be associated with infiltration of IgG4-positive cells.

3.3. Association of extrasalivary gland lesions

The extrasalivary gland lesions observed in our patients with MD are shown in Table 4a. AIP was observed in 7 patients with MD. Interstitial tubulointerstitial nephritis and retroperitoneal fibrosis were also observed in 7 patients with MD. Overall, extrasalivary gland lesions were seen as

Table 4a
Extrasalivary gland lesions.

	Mikulicz's disease ($n = 44$)
Autoimmune pancreatitis	7 (15.9%)
Tubulointerstitial nephritis	7 (15.9%)
Retroperitoneal fibrosis	6 (13.6%)
Sclerosing cholangitis	1 (2.3%)
Glomerulonephritis	1 (2.3%)
Hypophysitis	1 (2.3%)
Interstitial pneumonia	1 (2.3%)
Overall	20 (45.5%)

complications in 20 patients (45.5%). The relationship of serum IgG4 levels and frequency of the occurrence of extrasalivary gland lesions is shown in Table 4b. Significant relationships between IgG4 levels and the occurrence of complications were absent in our study.

AIP has recently drawn attention in the field of pancreatology as a newly proposed clinicopathological entity. Abdominal computed tomography reveals diffuse or limited swelling of the pancreas, and endoscopic retrograde cholangiopancreatography shows sclerosing pancreatic ducts. Unlike cases of chronic pancreatitis, steroid treatment is usually effective for decreasing pancreatic swelling as well as inhibiting pancreatic endocrine and exocrine secretion [45]. AIP also exhibits hypergammaglobulinemia, particularly with regard to IgG4, and severe infiltration of IgG4-positive plasmacytes into the pancreas [30,46]. These characteristics are similar to those of MD, i.e., elevated serum IgG4 levels, infiltration of IgG4-positive plasmacytes into the glands, and recovery of secretion by steroid treatment. Thus, MD and AIP are considered to be related.

Other complications associated with MD include autoimmune hypophysitis [47], Riedel's thyroiditis [48], interstitial pneumonia [29,36], sclerosing cholangitis [49], retroperitoneal fibrosis [46,49,50], and interstitial tubular nephritis [51]. In our study, the serum IgG4 levels tended to be proportional to the frequency of occurrence of these complications (Table 2). Thus, serum IgG4 levels may reflect disease activity in systemic IgG4-related plasmacytic syndromes such as MD and KT.

3.4. Similarities between Mikulicz's disease and Küttner's tumor

We also examined 6 patients with KT (2 males, 4 females) [5]. KT was diagnosed according to the following criteria: (1) persistent (>3 months) unilateral or bilateral

Table 4b
Relationships of serum IgG4 levels and extrasalivary gland lesions.

	IgG4 (mg/dl) ± SD	IgG4 (%) ± SD
Complications (+)	1185.8 ± 978.7	28.1 ± 10.8
Complications (−)	651.1 ± 402.8	24.0 ± 9.7
P value	0.10	0.16

hard swelling of the submandibular glands only; (2) histological findings similar to those reported in previous studies [18,20–22,52,53]; (3) absence of preceding lesion(s) such as sialolith or mechanical obstruction of the salivary duct. The IgG4 level was 756.6 ± 449.2 mg/dl, and the IgG4 levels accounted for 26.4 ± 10.5% of the total IgG level in KT patients. In addition, salivary gland specimens collected from KT patients also showed IgG4-producing cells. We observed extrasalivary gland lesions in KT patients complicated with AIP and tubulointerstitial nephritis [5]. Steroid treatment leads to rapid improvement in glandular swelling as well as in salivary gland lesions.

Similarly, Kitagawa et al. [4] analyzed 12 patients with KT and found that 5 cases were associated with sclerosing lesions in the extrasalivary gland tissues. Immunohistochemically, the proportion of IgG/IgG4-producing cells was more than 45% in KT, while it was less than 5% in SS.

These characteristics suggest that the serological and histopathological findings in MD and KT are very similar, and that both these diseases are related to IgG4. The abundance of IgG4-positive plasmacytes in the affected salivary glands might be related to the pathogenesis of these diseases; however, the pathogenesis of MD and KT at the cellular and molecular levels should be studied further. We recognize the need to identify and manage the systemic complications of MD and KT.

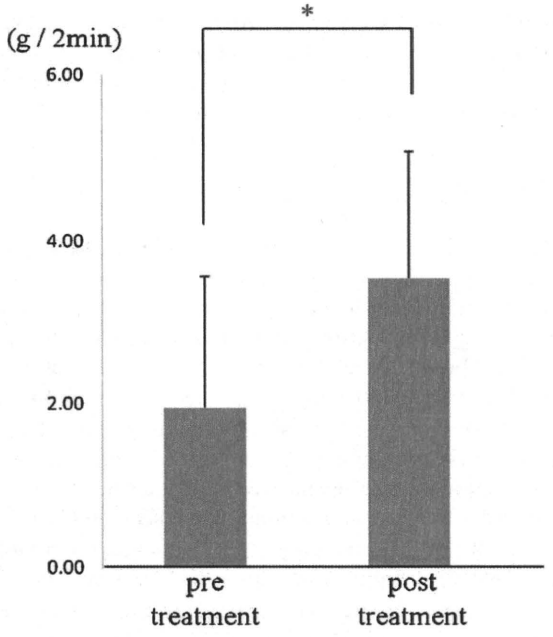

Fig. 6. Changes in salivary secretion by Saxon's test after steroid treatment. Administration of glucocorticoids for 2 months increases salivary secretion from 1.95 g/2 min to 3.55 g/2 min. *P values of <0.01 compared to pre-treatment salivary secretion ($P < 0.01$).

4. Treatment of Mikulicz's disease

MD is mainly treated by the administration of steroids. We initiated treatment with prednisolone at 30–40 mg/day against MD without encountering organ failure. The treatment led to rapid improvement in glandular swelling as well as in salivary secretion. Prednisolone administration for 2 months increased the salivary secretion from 1.95 g/2 min to 3.55 g/2 min in Saxon's test ($n = 14$) (Fig. 6). Glucocorticoid treatment also improves hypergammaglobulinemia [54]. However, when steroids were discontinued, swelling of the lacrimal and salivary glands was observed and the serum IgG4 levels were increased. Thus, it is necessary to continue administering prednisolone at 5–10 mg/day or to combine it with an immunosuppressant.

5. Controversies regarding Mikulicz's disease

To date, worldwide attention has been drawn to the new concept "systemic IgG4-related plasmacytic syndrome (SIPS)" [55], which originated in Japan. Although this disease was referred to by various names including "IgG4-positive multiorgan lymphoproliferative syndrome (IgG4+ MOLPS)" [56] and "IgG4-related sclerosing disease" [57], of late, the tendency is to label all pathological conditions presenting with elevated serum IgG4 levels and infiltration of IgG4-bearing plasmacytes in the involved organ as IgG4-related disease [58,59]. The confusion that occurs is mainly with respect to the diagnosis and interpretation of this disease. We believe that IgG4-related disease exists in both a narrow and a wide sense. MD is assumed to be included in the original IgG4-related disease in the narrow sense. The basic characteristics of MD, except for the involvement of IgG4, are swelling of the involved organ, such as salivary and lacrimal glands, and lack of systemic inflammation.

It has been suggested that T-helper-2 (Th2) immune reaction is predominant in IgG4-related disease [60,61]. Regulatory immune reactions are activated in IgG4-related disease, and interleukin (IL)-10, a regulatory cytokine, promotes IgG4 production [62]. IL-10 is a potent suppressor of total and allergen-specific IgE, but it simultaneously increases IgG4 production [63]. Allergy related to Th2 cytokines is thought to be important in the pathogenesis of IgG4-related diseases, including MD. We must further analyze the mechanisms by which regulatory T cells promote IgG4 production and the relationship between IgG4 and cytokine profiles.

More recently, Yamamoto et al. reported that IgG4-positive plasmacytes are possibly involved in the pathogenesis of Churg-Strauss syndrome, a rare systemic necrotizing vasculitis involving small vessels [41]. This syndrome is clinically different from MD and is not included in "IgG4-related disease" in the narrow sense. This report was surprising because only elevated serum IgG4 levels and infiltration of IgG4-positive plasmacytes in the involved organs were assumed to be essential for the diagnosis of IgG4-related disease. IgG4 itself is not the fundamental cause of

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IgG4-related diseases, such as MD, and that the elevated serum IgG4 levels and infiltration of plasmacytes expressing IgG4 are only contributing factors and not the sole etiological factors promoting immunological reactions [41].

6. Conclusions

We have discussed the differences between MD and SS and the similarities between MD and KT, including the elevated serum IgG4 levels and infiltration of plasmacytes expressing IgG4 in lacrimal and salivary glands observed in MD. The abundance of IgG4-positive plasmacytes in the affected salivary glands might be related to the pathogenesis of the above diseases; however, the pathogenesis of IgG4-related diseases, including MD, should be studied further at cellular and molecular levels. Recent studies have identified that in order to make an accurate diagnosis of IgG4-related diseases, such as MD, not only on IgG4 but also other factors such as physical findings and images should be taken into account. Based on the evidence presented in this study, otolaryngologists should recognize the need to identify and manage the systemic complications of MD.

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Review

The birthday of a new syndrome: IgG4-related diseases constitute a clinical entity

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ABSTRACT

IgG4-related disease is a distinct clinical entity, whose characteristic features are the following; Serum IgG4 is prominently elevated, IgG4-positive plasma cells infiltrate in involved tissues, various mass-forming lesions with fibrosis develop in a timely and spatial manner and the response to corticosteroids is prompt and good. IgG4-related diseases mainly target two organs. One is the pancreas (autoimmune pancreatitis; AIP), and the other comprises the lacrimal and salivary glands, the clinical phenotype is Mikulicz's disease (MD). MD has long been considered a manifestation of Sjögren's syndrome (SS). However, we noticed several clinical differences in case of MD from SS; no deflection of female sex differences, mild sicca syndrome, good response to corticosteroids, no positivity of anti-SS-A/SS-B antibodies. In addition, elevated level of serum IgG4 and abundant infiltration of plasma cells expressing IgG4 were reported in MD patients. Those are common features of IgG4-related diseases. MD often coexisted with IgG4-related diseases such as AIP, retroperitoneal fibrosis, and IgG4-associated nephropathy. Based on those findings, it has been considered to recognize IgG4-related diseases including MD as a new clinical entity. The etiology of IgG4-related systemic diseases remains to be elucidated. It is necessary to accumulate and analyze larger data from patients worldwide.

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1. Introduction

IgG4-related disease is a new clinical entity which has been recently proposed from Japan [1]. Characteristic features of IgG4-related disease are elevated serum IgG4 level, infiltration of IgG4 positive cells, mass-forming lesion with fibrosis, and good response to corticosteroid. IgG4-related disease mainly targets two organs. One is the pancreas, and that clinical phenotype is autoimmune pancreatitis (AIP) [2]. The other target organ comprises the lacrimal and salivary glands, and the clinical phenotype is so-called Mikulicz's disease (MD) [3]. These are the same organs that are involved in Sjögren's syndrome (SS) and, until recently, MD was considered a subtype of SS. However, recent data indicate that MD is actually an IgG4-related disease [4]. Therefore, MD is an important condition that is differentiated from SS. To help understand this new disease entity, the author will discuss it in the context of its historical background including its relationship with SS.

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2. Historical background regarding IgG4 related diseases

Johann von Mikulicz-Radecki reported the first case of MD in 1888 [5]. That 42 year-old male patient exhibited persistent and symmetrical enlargement of the lacrimal and salivary glands in the absence of infectious or neoplastic origins. Afterwards, many patients with enlarged lacrimal and salivary glands have been described as having MD regardless of cause, so Schaffer proposed in 1927 that swelling of the lacrimal and salivary glands caused by known diseases such as tuberculosis or lymphoma should be called Mikulicz's syndrome, and idiopathic cases only should be referred to as MD [6]. On the other hand, Swedish ophthalmologist, Sjögren proposed the concept of systemic disease characterized with keratoconjunctivitis sicca, xerostomia, and arthritis in 1933 [7]. Because Hamilton introduced this as a new clinical entity during 1943 in English, SS became well-known worldwide [8]. Morgan and Castleman reported in 1953 that MD and SS were pathologically identical and that MD is a subtype of SS [9]. Thereafter, no reports appeared in the western countries about MD.

3. Clinical characteristics of Mikulicz's disease

The research on the relationship between MD and SS continued in Japan, and has discussed regarding whether both disease should be considered as the same. We experienced the case of male patient presenting typical characters of MD who focused our attention to this new clinical entity in the 1990s. We started to collect similar cases according to the following criteria; 1) persistent (more than 3 months) symmetrical swelling of more than two lacrimal and major salivary glands, 2) prominent mononuclear infiltration of lacrimal and salivary glands, and 3) exclusion of other diseases presenting glandular swelling, such as sarcoidosis and lymphoproliferative disease. Table 1 showed summary of clinical characteristics of MD according to our study [4]. Compared with SS, male dominance, being negative for anti-SS-A/SS-B antibodies despite hypergammaglobulinemia, having mild dry syndrome and good responsiveness to corticosteroid were considered to be features of MD. In addition, we found low expression of Fas, and a low frequency of apoptosis in the salivary glands of patients with MD that was attributed to the reversibility of gland functions induced by corticosteroid as Tsubota reported in the lacrimal glands [10]. These findings seemed insufficient to support of the notion of MD as an independent entity. However, an epochal discovery in a field outside of rheumatology positioned MD as a new established clinical entity.

4. Autoimmune pancreatitis and IgG4

AIP is a unique form of chronic pancreatitis. The characteristic features are diffuse enlargement of pancreas and narrowing of the pancreatic duct, associated with increased level of gammaglobulin and IgG, the presence of autoantibody, and good response to corticosteroid therapy. AIP was originally described in 1961 by Sarles [11] and it attracted considerable attention in Japan during the 1990s because of its good responsiveness to corticosteroids. Autoimmunity was presumed as part of the mechanism, and idiopathic pancreatitis with these features was designated as autoimmune pancreatitis in 1995 [12]. Clinical diagnostic criteria had already been established by Japan Pancreas Society Japan in 2002 and revised in 2006 [13] and at present AIP is internationally recognized as a distinct type of pancreatitis [2]. The most difficult issue in the diagnosis of AIP was differentiation from pancreatic cancer. Hamano reported in 2001 that the serum IgG4 concentration was elevated specifically in AIP [14]. The mean IgG4 concentration in healthy donors, as well as cancer patients was around 50 mg/dl, whereas the mean IgG4 concentration in patients with AIP was 663 mg/dl, which allowed differentiation from cancer. Moreover Hamano reported in the following year that IgG4-positive plasma cells prominently infiltrate pancreatic lesions in AIP [15]. Thus, IgG4 suddenly became an important tool in the diagnosis of AIP.

Table 1
Clinical characteristics of Mikulicz's disease and Sjögren's syndrome.
Yamamoto M: Modern Rheumatol 16: 335, 2006.

	Mikulicz's disease	Sjögren's syndrome
Age of disease onset	from 50s to 60s	from 40s to 50s
Sex ratio (M:F)	1:3	1:20
Gland swelling	Persistent	Recurrent
Keratoconjunctivitis sicca	None to slight	Mild to severe
Decreased salivary secretion	None to slight	Mild to severe
Response to steroid	Rapid and very good	Partial response
Serum IgG	Normal to very high	Normal to high
Antinuclear antibody	Negative dominantly	Positive
Anti SS-A/SS-B antibodies	Negative	Positive (70%/30%)

5. Mikulicz's disease as IgG4-related disease

We found similarities between MD and AIP, in terms of mass-forming lesions and good responsiveness to corticosteroids. We measured serum IgG subclasses in preserved samples from patients with MD by nephelometry. The mean serum IgG4 concentration was 1111 mg/dl and the mean IgG4/total IgG ratio was 28.6% in patients with MD, compared with respective values of 89 mg/dl and 2.8% in patients with SS [1,16]. Thus, it was demonstrated that MD was associated with prominently elevated serum IgG4, which was also a feature of AIP. We also confirmed that histopathological findings of biopsy specimens from patients with MD are very similar to those found in AIP. Fig. 1A and B demonstrated biopsy specimens of labial salivary glands from patients with MD. Conventional hematoxylin/eosin staining did not differ from SS. However, immunostaining with anti-IgG4 antibody revealed infiltration with numerous IgG4-positive cells in MD. Those findings were the same in AIP, namely diffuse infiltration of mononuclear cells including numerous IgG4-positive plasma cells, lymphoid follicles and interfollicular fibrosis. The pathological changes in the salivary glands and the pancreas were also identical, indicating the possibility that MD and AIP have a common pathogenesis. Although AIP had been often reported to be complicated with SS-like salivary gland disease, it was assumed that salivary gland involvement in AIP would correspond to MD. Our analysis of reported cases of sialoadenitis in AIP in the literature revealed that the sex ratio was 1 to 2 in favor of females, and the rate of antinuclear antibody positivity was at most only half, and the results with anti SS-A/SS-B antibodies were negative except for few patients [17]. Those clinical findings are obviously different from typical SS. Therefore, we assumed that many patients diagnosed with SS as a complication of AIP in the past would have MD. It is currently reported that AIP is complicated with MD in 10 to 30% of patients [18], and MD is accompanied by AIP in approximately 10% of patients [1].

6. IgG4-related disease as a systemic clinical entity

MD and AIP seemed to have a common pathogenesis and the involvement of various organs became recognized as a complication associated with IgG4-related disease [1,19,20]. Table 2 showed each organ involvement in IgG4-related systemic disease. Lacrimal and salivary gland involvement are features of MD and involvement of submandibular gland alone is called Kuttner's tumor. Pancreatic involvement is AIP, and the bile duct involvement is sclerosing cholangitis [21]. Renal involvement is IgG4-associated nephropathy [22]. Retroperitoneal involvement comprises retroperitoneal fibrosis [23]. Involvement of the lung, lymph nodes, prostate and pituitary gland are also reported. Typical imaging findings in pancreatic and renal involvement were demonstrated in Fig. 1C and D. These lesions comprise diffuse infiltration of mononuclear cells with numerous

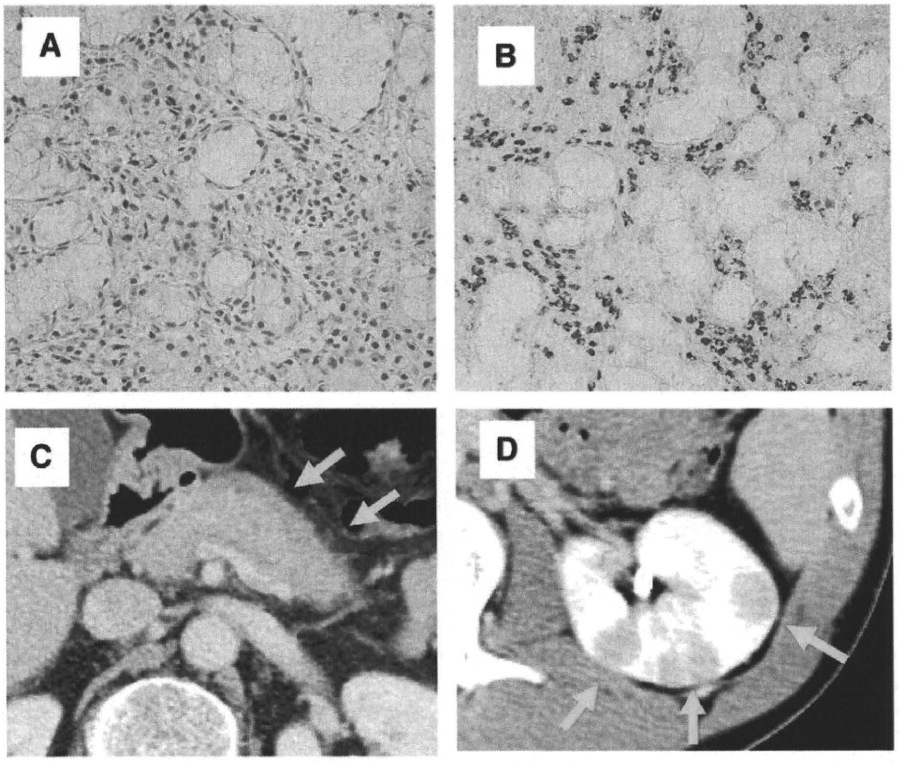

Fig. 1. (A) Specimens of labial salivary glands in Mikulicz's disease showed diffuse infiltration of mononuclear cells (Hematoxylin–Eosin stain). (B) Specimens of labial salivary glands in Mikulicz's disease showed abundant IgG4-positive plasma cells (anti-IgG4 antibody stain). (C) Abdominal CT scan demonstrated swelling of the pancreas with a capsule-like rim (arrow) in autoimmune pancreatitis. (D) Enhanced abdominal CT scan revealed a focal poorly enhanced lesion (arrow) in IgG4 associated nephropathy.

IgG4 positive plasma cells and fibrosis, suggesting a common pathogenesis in IgG4-related disease. In addition, multiple organ involvement in a timely and spatial manner is one of features of IgG4-related systemic diseases. Therefore it is necessary to monitor systemically and continuously to determine when to start treatment.

7. Research activities with regard to IgG4-related diseases in Japan

In 2004, MD study group was established under the leadership of Sugai, who was a previous president of Japanese Society for SS. In 2008, this group was approved as a committee in Japanese Society for SS. Masaki reported the results conducted in the study group in 2009 [19]. Last year new research group has started granted by Japanese Ministry of Health, Labor and Welfare. In 2009, the 10th international symposium on SS was held with Youinou as a president in Brest, France and the author could have an opportunity to introduce IgG4-related disease [24]. We hope that IgG4-related disease will become approved as an independent clinical entity in the world and this paper will become a starting point in order to elucidate several problems and establish the treatment strategies for IgG4-related disease.

Table 2
Disorders included in IgG4-related systemic disease.

Organ system	
Lacrimal and salivary gland	Mikulicz's disease, Kuttner's tumor, dacryoadenitis, ocular IgG4-related disease
Respiratory	IgG4-related pulmonary disease, inflammatory pseudotumor
Digestive	Enterocolitis
Hepatobiliary	Sclerosing cholangitis, igg4 hepatic disease
Pancreas	Autoimmune pancreatitis
Renal urinary	IgG4-associated nephropathy, tubulointerstitial nephropathy, retroperitoneal fibrosis, prostitis
Endocrine	Autoimmune hypophysitis, Riedel's thyroiditis, diabetes mellitus
Nervous	Cranial pachymeningitis
Lymphatic	IgG4-associated lymphadeopathy, Castleman's disease
Musculoskeletal	Arthritis
Cardiovascular	Inflammatory abdominal aneurysm

Take-home messages

- IgG4-related disease is a distinct clinical entity, whose characteristic features are elevated serum IgG4 level, infiltration of IgG4 positive plasma cells, mass-forming lesion with fibrosis, and good response to corticosteroids.
- IgG4-related disease targets multiple organs including pancreas (autoimmune pancreatitis) and lacrimal/salivary glands (Mikulicz's disease) in a timely and spatial manner.
- The etiology of IgG4-related diseases remains to be elucidated and it is necessary to accumulate and analyze larger data from patients with IgG4-related disease worldwide.

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B cell depletion in diffuse progressive systemic sclerosis: safety, skin score modification and IL-6 modulation in an up to thirty-six months follow-up open-label trial.

An over-expression of CD19 has been shown in B cells of systemic sclerosis (SSc) and B cells are thought to contribute to the induction of skin fibrosis in the tight skin mouse model. The aim here, **Bosello S. et al.** (**Arthritis Res Ther 2010; 12: R54**) was to define the outcome on safety and the change in skin score after rituximab therapy in SSc patients and to correlate the clinical characteristics with the levels of interleukin (IL)-6 and with the immune cell infiltrate detected by immunohistochemistry. Nine patients with SSc with mean age 40.9 ± 11.1 years were treated with anti-CD20, Ig at time 0 and after 14 days. Skin biopsy was performed at baseline and during the follow-up. B-cell activating factor (BAFF) and IL-6 levels were also determined at the follow-up times. After six months, patients presented a median decrease of the skin score of 43.3% (range 21.1 – 64.0%), and a decrease in disease activity index and disease severity index. IL-6 levels decreased permanently during the follow up. After treatment, a complete depletion of peripheral blood B cells observed in all but 2 patients. Only 3 patients presented CD20 positive cells in the biopsy of the involved skin at baseline. Thus, anti-CD20 treatment has been well tolerated and SSc patients experienced an improvement of the skin score and of clinical symptoms. The clear fall in IL-6 levels could contribute to the skin fibrosis improvement, while the presence of B cells in the skin seems to be irrelevant with respect to the outcome after B cell depletion.

Treatment with a toll-like receptor inhibitory GpG oligonucleotide delays and attenuates lupus nephritis in NZB/W mice.

Activation of the innate immune system by DNA containing hypomethylated CpG motifs has been implicated in the pathogenesis of systemic lupus erythematosus (SLE). Here, **Graham KL. et al. (Autoimmunity 2010; 43: 140-55)** examined the consequences of immunostimulatory CpG-oligodeoxynucleotide (ODN) and inhibitory GpG-ODN treatment in the NZB x NZW F1 (NZB/W) murine model of SLE. Beginning at 5 months of age, we administered CpG-ODN or GpG-ODN at regular intervals to female NZB/W animals. The authors determined the effects of ODN administration on NZB/W mouse lymphocyte function, and the specificity of ODN binding to Toll-like receptors (TLRs) other than TLR-9. While CpG-ODN treatment did not appear to have a major impact on disease severity, GpG-ODN treatment significantly delayed the onset of proteinuria in NZB/W mice. Interestingly, short-term GpG-ODN treatment promoted Th2-type T and B cell responses, and inhibited B cell proliferation in-vitro. On the other hand, extended GpG-ODN treatment did not result in sustained Th2 responses or significantly reduced renal disease. Moreover, the binding of CpG-ODN and GpG-ODN was not restricted to TLR-9 as both ODNs also interacted with TLR-3, TLR-7, and TLR-8. Taken together, the data indicate that the protective mechanism of GpG-ODN treatment in the NZB/W model of lupus nephritis involves modulating T cell cytokine profiles and B lymphocyte activation through the inhibition of several TLRs including TLR-7 and TLR-9.

B-cell reconstitution and BAFF after Alemtuzumab (Campath-1H) treatment of multiple sclerosis.

Treatment with alemtuzumab is highly effective in relapsing-remitting multiple sclerosis; however, 30% of patients develop autoimmunity. Alemtuzumab (previously called Campath 1-H) induces a prolonged T cell lymphopenia with memory cells dominating the reconstituting T-cell pool for at least 3 months. Here, **Thompson S. et al. (J Clin Immunol 2010; 30: 99-105)** show that B-cell recovery is rapid, returning to baseline by 3 months and rising to 165% of baseline by 12 months after treatment. Immature transitional 1 B cells are the predominant cell type 1 month after treatment. This coincides with a surge in serum B-cell activating factor (BAFF), which remains elevated by 33% for at least 12 months after alemtuzumab. BAFF is critical for transition to the mature naïve B-cell phenotype, which dominates from 3 months after alemtuzumab. Differentiation to memory B cells is slow so there are radical and prolonged alterations to the B-cell pool after alemtuzumab.