2. Historical details of Mikulicz's disease

2.1. First case reported by Mikulicz-Radecki

Johann von Mikulicz-Radecki (Fig. 1) was born in 1850 in Czerniowce, a city in the Bukowina region (currently split between Romania and Ukraine). He was regarded as one of the key figures in the surgical world of Europe, around the turn of the 19th century. His name was memorialized in the fields of surgical antisepsis, and esophageal and gastric surgery. He was also the first to describe the method for surgical treatment of maxillary sinuses, plastic surgery of the nose, esophagoscopy, and lateral pharyngotomy of tonsillar carcinoma [7,8]. As an ardent proponent of antiseptic procedures, he contributed to their perfection. He was the first to introduce abdominal swabs and the abdominal gauze drainage system, and used a gauze mask and gloves during surgery [7,8].

In 1888, Mikulicz-Radecki first reported a case of what was later called Mikulicz's disease [9] (Fig. 2). The patient showed symmetrical bilateral edema and enlargement of the salivary and lacrimal glands, in which lymphocytic infiltration was found on microscopic examination [8]. Subsequent studies described this syndrome as MD; clinical features included benign and chronic dacryoadenitis with bilateral painless swelling of lacrimal and salivary glands and decreased lacrimation associated with dry mouth and dry eyes, but no arthritis or blurred vision.

Fig. 1. Portrait of Mikulicz-Radecki (1850–1905) [cited from reference 7]. He contributed immensely to cancer surgery. Besides the development of operations on digestive organs, he contributed to the area of head and neck surgery. Mikulicz forceps, still the most widely used peritoneal forceps, is one of the surgical instruments devised by Mikulicz.

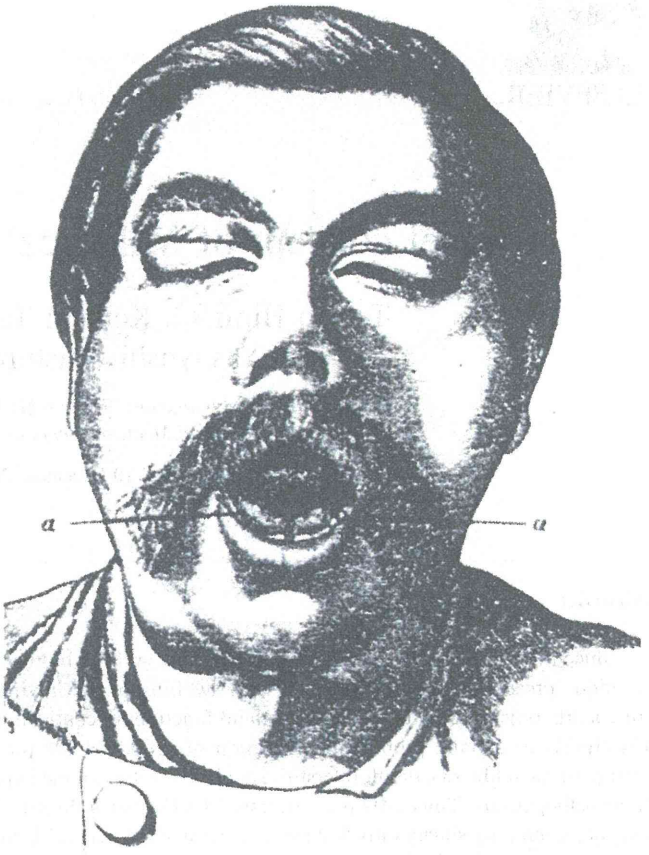

Fig. 2. Illustration of the first reported case of Mikulicz's disease (MD). A 42-year-old male developed bilateral swelling of the lacrimal, parotid, and submandibular glands.

2.2. Controversies regarding Mikulicz's disease and Sjögren's syndrome

In 1927, Schaffer compared the case reported by Mikulicz-Radecki in 1888 with known diseases showing obvious similarities, such as sarcoidosis and lymphoma, and reported that the symptoms in this case constituted Mikulicz syndrome; they then designated Mikulicz syndrome of idiopathic origin as MD [10]. In 1933, Sjögren summarized the findings from 19 cases of keratoconjunctivitis sicca; in 2 of these cases, swelling of the major salivary glands was observed [11]. The concept of SS was established after that report. In 1953, Morgan and Castleman examined specimens obtained from 18 patients diagnosed with MD; they concluded that the histological findings in MD and SS were similar and that most patients diagnosed with MD could be considered to be suffering from SS [6].

Thereafter, MD has been recognized as a subtype of SS, and there was no major disagreement regarding the two illnesses for just over half a century. However, cases were

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frequently reported in Japan. Particularly, in the field of otorhinolaryngology, before the concept of IgG4-related illnesses had been established in 1984, Konno et al., from their analyses of detailed clinical cases, had already proposed that MD is an independent entity and had demonstrated its similarity to KT [12]. In 1989 again, Konno et al. reported on the differences in clinical symptoms of MD and SS. More specifically, they indicated differences in sex, salivary gland angiograms, extent of salivary disorders, antinuclear antibodies, and positive ratios of anti-SS-A and anti-SS-B antibodies [13]. The minor salivary glands of SS are infiltrated by mononuclear cells; this infiltration can be resolved with corticosteroid administration, but salivary function does not recover [14]. The histopathological basis of this phenomenon is the occurrence of extensive apoptosis in the minor salivary glands of patients with SS. Tsubota et al. recently reported that the extent of apoptosis in the salivary glands is significantly lower in MD than in SS [15,16]. Further, patients with MD have been reported to have elevated serum IgG4 levels and infiltration of IgG4-expressing plasmacytes in lacrimal and salivary glands [3]. Thus, MD differs from SS and is now thought to be a systemic "IgG4-related plasmacytic disease".

2.3. Historical details of Küttner's tumor

Küttner's tumor (KT), which was first described as chronic sclerosing sialadenitis by Küttner in 1896 [17], is a rare and chronic inflammatory disorder of the salivary glands and most commonly affects the submandibular glands [15,16]. Patients with KT present with firm swelling of the salivary glands, and clinical differentiation of KT from the neoplasm is difficult [18,19], hence the name Küttner's "tumor" [20]. Although KT is frequently associated with sialoliths, sialolithiasis may be a secondary process in KT [20,21]. Monoclonal and oligoclonal cytotoxic T-cell populations found in the affected salivary gland of KT patients suggest an immune reaction to intraductal agent(s) [22–24]. Secretory dysfunction of the salivary glands may also lead to inspissation of saliva in the ducts and chronic inflammation of the salivary glands in patients with KT [19–21]. KT is occasionally associated with similar sclerosing lesions in extrasalivary glandular tissues, such as those of the bile duct (sclerosing cholangitis) and the retroperitoneum (retroperitoneal fibrosis) [25–27]. The concomitant occurrence of such lesions is referred to as multifocal fibrosclerosis, and KT could be regarded as a manifestation of multifocal fibrosclerosis. In addition, several studies have reported an association between KT and sclerosing pancreatitis [28,29]. Recent studies have shown that sclerosing pancreatitis, which is also called AIP or lymphoplasmacytic sclerosing pancreatitis, is a unique IgG4-related disease [5,15,30].

Table 1
The clinical diagnostic criteria of IgG4-related Mikulicz's disease.

(1)	Persistent (≥3 months), symmetrical swelling of the lacrimal, parotid and submandibular glands involving, at least two pairs.
(2)	Serologically high levels of immunoglobulin (Ig) G4 (≥1.35 g/L).
(3)	Marked IgG4-positive plasmaeytes infiltration (≥50% IgG4-positive/IgG-positive cells in five high power fields) into lacrimal and salivary gland tissues.

In terms of diagnosis, IgG4-related Mikuliez's disease is defined as satisfying Item (1) and either Item (2) and/or (3). This form of systemic IgG4-related disease often accompanies multiple organ lesions. Sarcoidosis, Castleman's disease, Wegener's granulomatosis and malignant lymphoma need to be considered as differential diagnoses.

3. Clinical features of Mikulicz's disease

3.1. Differences between Mikulicz's disease and Sjögren's syndrome

We examined 44 patients with MD (17 men, 27 women). All patients had previously consulted doctors at Sapporo Medical University and its related facilities in since 2001. MD was diagnosed according to the criteria of the Japanese Medical Society for Sjögren's Syndrome (2008) (Table 1).

Background characteristics of the patients with MD are shown in Table 2. The mean age of these patients was 55.2 ± 14.1 years (range, 25–88 years) and the sex ratio was approximately 2:1 in favor of females. In SS, the ratio is about 20:1 (female: male) [15]. Anti-SS-A and anti-SS-B antibodies were absent in all MD patients except one. The enlargement of lacrimal and salivary glands in MD patients was elastic, painless, and persistent (occurring for more than 3 months) (Fig. 3). Half of the MD patients did not exhibit keratoconjunctivitis sicca. With regard to salivary gland function, secretion by these glands in MD patients was normal or slightly decreased, and this improved with steroid treatment. Sialography was also normal, and the "apple-tree sign", which is typical of SS, was not observed in MD patients. In contrast, the lacrimal and salivary swelling in SS patients occurred repeatedly and disappeared without treatment. The sicca symptoms were more severe in SS patients than in MD patients. We prescribed glucocorticoids for SS patients to treat the swelling of the lateral

Table 2
Clinical features of Mikulicz's disease.

	Mikulicz' disease ($n = 44$)
Mean age of disease onset	55.2 ± 1.4.1
Sex ratio (M:F)	1:1.6
Hypergammaglobulinemia	32 (72.7%)
(mean serum IgG mg ± SD)	(2723.1 ± 1693.6)
Anti-SS-A antibody	1
Anti-SS-B antibody	0
Antinuclear antibody	7
MPO-ANCA	0

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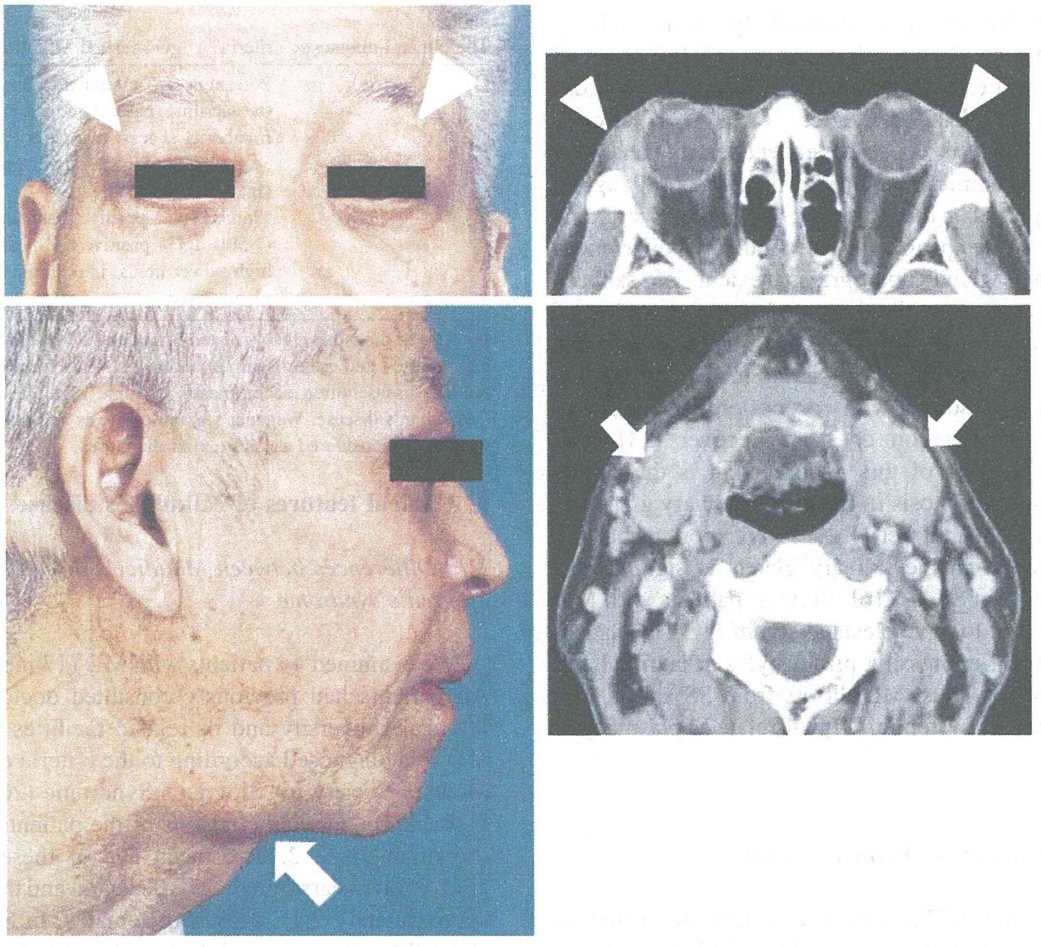

Fig. 3. Facial views and computed tomography images of MD patients. The patients show persistent symmetrical enlargement of the lacrimal (arrow heads) and submandibular glands (arrows).

submandibular gland, but the salivary secretion did not increase. Generally, improvements in glandular secretion are not expected in the advanced stages of SS because SS is an autoimmune disease that irreversibly damages glands [31]. Thus, systemic corticosteroids were usually used for treating only severe extraglandular diseases, i.e., diffuse interstitial pneumonia, glomerulonephritis, vasculitis, and peripheral neuropathy [32,33]. The impact of steroids on the natural course of SS is not well established. Thus, the clinical features of MD are quite different from those of typical SS (Table 3).

3.2. *Mikulicz's disease as an IgG4-related disease*

Serum IgG subclasses in of MD and SS patients were measured using nephelometry. The IgG4 level was 894.1 mg/dl in MD patients and 75.4 mg/dl in SS patients (Fig. 4a). IgG4 levels accounted for 25.9% of the total IgG

Table 3
Differences between Mikulicz's disease and Sjögren's syndrome (modified from reference [60]).

	Mikulicz's disease	Sjögren's syndrome
Age distribution	From 50s to 60s	From 40s to 50s
Sex ration	3:1 in favor of females	20:1 in favor of females
Gland swelling	Persistent	Recurrent
Dysfunction of salivary secretion	None – slight	Mild – severe
Keratoconjunctivitis sicca	None – slight	Mild – severe
Response to steroid	Very good	No change, or sometimes good
Serum IgG	Normal – very high	Normal – high
Antinuclear body	Dominance of negative cases	Dominance of positive cases
Anti-SS-A/SS-B antibodies	Negative	Positive (70%/30%)
Serum IgG4	Severely high	Normal
Glands biopsy	Infiltration of abundant IgG4-positive plasmacytes	No detection of IgG4-positive cells

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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-

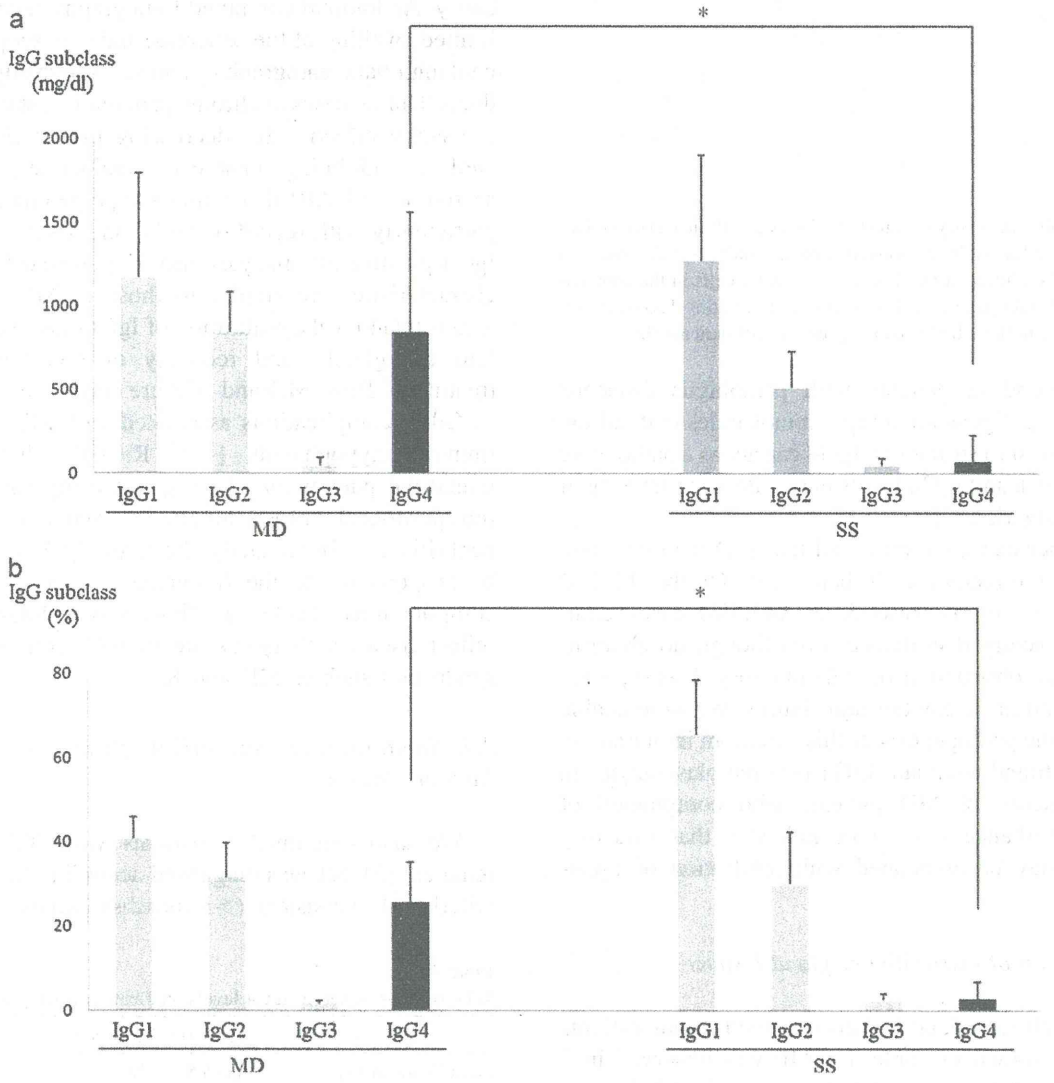

Fig. 4. Comparison of serum levels of IgG subclasses (a) and ratios of each IgG subclass/total IgG (b) between MD and SS. The statistical significance was determined by the Mann–Whitney *U* test. Serum IgG4 levels were significantly higher in MD than in SS for levels (a) as well as ratios (b). *P values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

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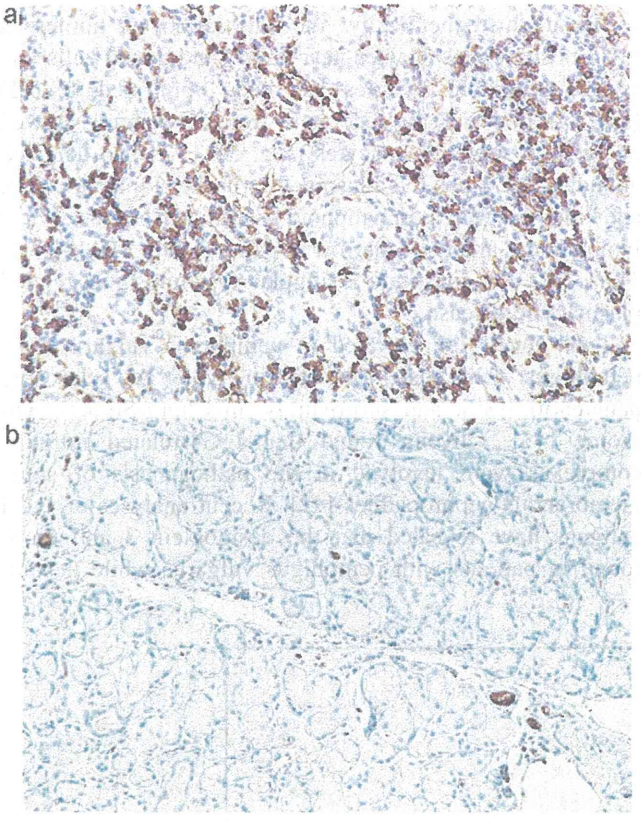

Fig. 5. Immunohistochemistry for IgG4 in salivary glands in MD (a) and SS (b). Immunoperoxidase stain, hematoxylin counterstain, ×200. Abundant IgG4-postive cells infiltrate around acinar and ductal cells in the submandibular glands of MD patients (a), whereas no infiltrating IgG4-positive cells are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

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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.

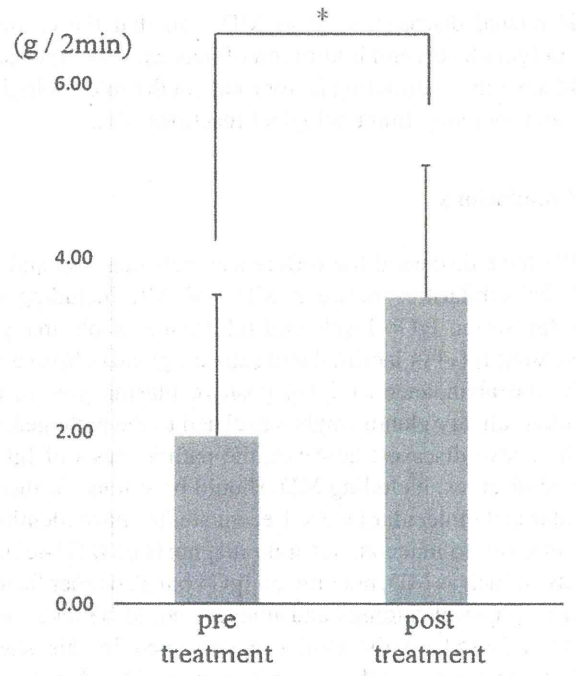

Fig. 6. Changes in salivary secretion by Saxon's test after steroid treatment. Administration of glucocorticoids for 2 months increases salivary secretion from 1.95 g/2 min to 3.55 g/2 min. *P values of <0.01 compared to pre-treatment salivary secretion ($P < 0.01$).

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

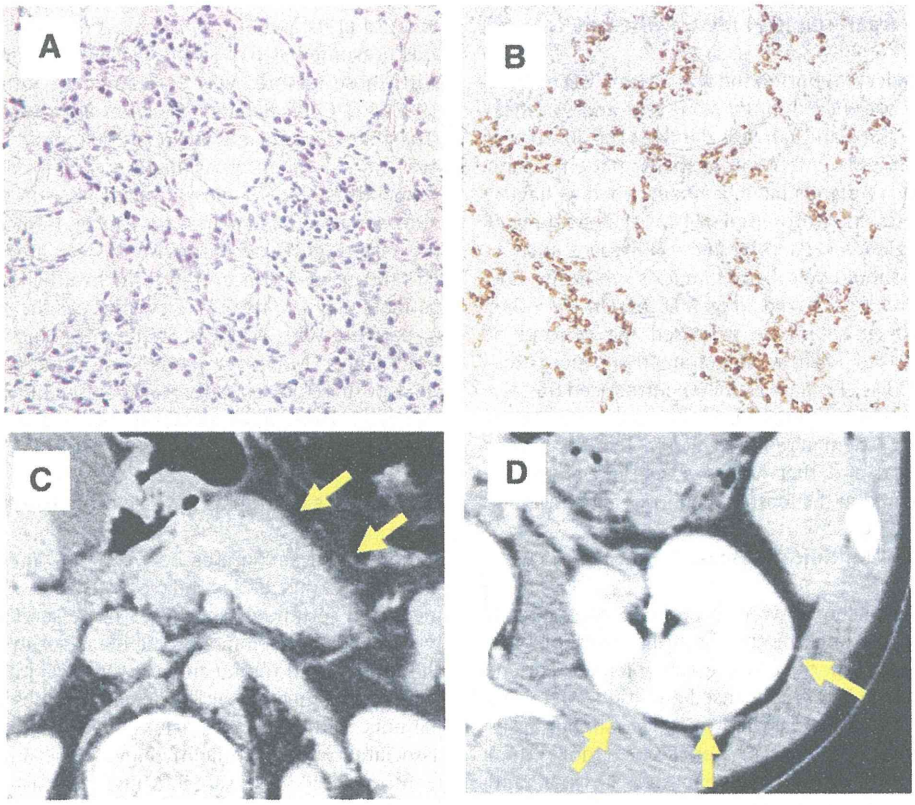

Fig. 1. (A) Specimens of labial salivary glands in Mikulicz's disease showed diffuse infiltration of mononuclear cells (Hematoxylin–Eosin stain). (B) Specimens of labial salivary glands in Mikulicz's disease showed abundant IgG4-positive plasma cells (anti-IgG4 antibody stain). (C) Abdominal CT scan 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.

ミクリッツ病に関する
全国疫学調査

ミクリッツ病に関する疫学の概要

ミクリッツ病およびIgG4関連疾患は、稀発性である（疾患に対する無知にも起因している）ため、その病態生理の解明や治療法の検討には症例の集積が必要である。また行政施策など、さまざまな対策を行う場合、現在のミクリッツ病の診療に関する実態や将来予測が、きわめて重要となる。その中でも、数の捕捉、すなわち罹患率や有病率などの把握は最も基本的な事項である。そのためIgG4関連ミクリッツ病の疫学的検討を全国的に行い、国内に置けるミクリッツ病の有病率の推計を試みた。この全国疫学調査は、患者数推計のための一次調査と、臨床疫学像を把握するための二次調査から構成した。一次調査は病床数200以上のきわめて多数の医療機関に対して行い、回収率を高めるために患者数の報告のみにとどめ、二次調査では個々の患者の人口学的事項、臨床的事項を調査した。患者の性別、発症および診断時の年月日など、ほとんどの疾患に共通な項目と、症状、診断、治療など疾患に固有の項目を設定した。また、二次調査においても返送率を高めるため、調査項目数を限定し、回答しやすい質問形式としておこなった。

方法

日本全国に存在する病院を対象に病床数（大学病院、500床以上、200床以上500床未満）を用い層別化し、それぞれ内科、眼科、耳鼻咽喉科に対し一次調査表を送付した（表 1）。一次調査における質問は以下の通り。

①貴科におきまして、現在、下記の１）～３）のすべての条件を満たす患者さまは何人おられますでしょうか。
両側性、対称性に涙腺と唾液腺（耳下腺または／および顎下腺）　腫脹を持続性に認める。
涙腺または／および唾液腺について、組織学的に著明な炎症細胞浸潤を認める。
典型的なシェーグレン症候群、サルコイドーシスや悪性リンパ腫を除外できる。・・・・・・・・・
（　　）人
②さらに血清学的にIgG4高値（135 mg/dl以上）を示す、または組織を抗IgG4抗体で免疫染色を行い、多数の陽性細胞を認める患者さま（IgG4関連ミクリッツ病と診断された患者さま）は何人おられますでしょうか。（検査されていない場合は未記入で結構です。）
・・・・・・・・・・・・・・・・・・・・・・・・（　　）人
③二次調査に協力します　□はい / □いいえ

一次調査の返答のあったものの内、ミクリッツ病の症例があり、かつ二次調査への協力の承諾が得られたものに対し二次調査票（図 1）を送付した。

ミクリッツ病全国疫学調査票

2011年

貴施設名＿＿＿＿＿＿＿＿病院＿＿＿＿科　記載者ご氏名＿＿＿＿＿＿＿＿

性別 □男性 □女性　診断時年齢＿＿歳

診断名 ミクリッツ病 (その他合併症:　　)

診断の際、IgG4関連ミクリッツ病の診断基準(日本シェーグレン症候群学会)を
□使用した □使用しなかった

血清IgG	mg/dl、	血清IgG4　　mg/dl
抗核抗体	□陽性(＿＿＿倍、染色型＿＿＿＿＿)	□陰性
リウマトイド因子	□陽性	□陰性
他の自己抗体	□陽性(　　)	□陰性

合併症

自己免疫性膵炎	□あり	□なし
腎障害	□あり(□間質性腎炎である □でない)	□なし
肺・気道病変	□あり(□肺病変 □気道病変)	□なし
後腹膜線維症	□あり(□水腎症あり □水腎症なし)	□なし
下垂体炎	□あり	□なし
甲状腺炎	□あり	□なし
前立腺炎	□あり	□なし
その他	□あり(　　)	□なし

治療　□あり　□なし

初期治療　ステロイド＿＿mg/日

現在の治療　ステロイド＿＿mg/日、免疫抑制剤(　　)併用 □あり □なし

現在の状態　□臨床的に寛解 □再燃 □死亡 □不明

ご協力ありがとうございました。

ミクリッツ病およびIgG4関連疾患の診断および治療方法の更なる推進に関する研究班

図1　二次調査票

二次調査における質問事項は以下の通り。

①患者の性別および診断時の年齢

②診断名および合併症

③診断の際、IgG4 関連ミクリッツ病の診断基準の使用の有無

④血清 IgG 値および血清 IgG4 値

⑤抗核抗体の有無、リウマトイド因子の有無および他の自己抗体の有無

⑥合併症について

自己免疫性膵炎の有無

腎障害の有無

肺・気道病変の有無

後腹膜線維症の有無

下垂体炎の有無

甲状腺炎の有無

前立腺炎の有無

その他の有無

⑦治療の有無

⑧初期治療としてのステロイド投与量

⑨現在の治療としてのステロイド投与量および免疫抑制剤併用の有無

⑩現在の状態は寛解か再燃か死亡か不明

二次調査回収後、各項目についてまとめた。

結果

1. 一次調査の対象病院への送付と回収率について（表 1）

全国の 200 床以上を有する病院の内科（リウマチ・膠原病科を含む）を対象に大学病院 108 箇所（100%）、500 床以上の病院の内科 320 箇所（100%）、200 床以上 500 床未満の病院の内科 572 箇所（33%）へ一次調査を送付した（() 内は抽出率）。大学病院からは 58 箇所（53.7%）、500 床以上の病院の内科からは 110 箇所（34.4%）、200 床以上 500 床未満の病院の内科からは 217 箇所（37.9%）から回答を得た（() 内は回収率）。そのうち患者が存在し、かつ二次調査への協力が可能であると答えた大学病院 30 箇所、500 床以上の病院の内科 22 箇所、200 床以上 500 床未満の病院の内科 11 箇所へ二次調査を送付した。

同様に全国の 200 床以上を有する病院の眼科を対象に大学病院 103 箇所（100%）、500 床以上の病院の眼科 260 箇所（100%）、200 床以上 500 床未満の病院の眼科 637 箇所（70%）へ一次調査を送付した（() 内は抽出率）。大学病院からは 44 箇所（42.7%）、500 床以上の病院の眼科からは 94 箇所（36.2%）、200 床以上 500 床未満の病院の眼科からは 224

箇所（35.2%）から回答を得た（() 内は回収率)。そのうち患者が存在し、かつ二次調査への協力が可能であると答えた大学病院の眼科 7 箇所、500 床以上の病院の眼科 7 箇所、200 床以上 500 床未満の病院の眼科 4 箇所へ二次調査を送付した。

また同様に全国の 200 床以上を有する病院の耳鼻咽喉科を対象に大学病院 101 箇所（100%)、500 床以上の病院の耳鼻咽喉科 261 箇所（100%)、200 床以上 500 床未満の病院の耳鼻咽喉科 638 箇所（75%）へ一次調査を送付した（() 内は抽出率)。大学病院からは 49 箇所（48.5%)、500 床以上の病院の耳鼻咽喉科からは 103 箇所（39.5%)、200 床以上 500 床未満の病院の耳鼻咽喉科からは 242 箇所（37.9%）から回答を得た（() 内は回収率)。そのうち患者が存在し、かつ二次調査への協力が可能であると答えた大学病院の耳鼻咽喉科 19 箇所、500 床以上の病院の耳鼻咽喉科 18 箇所、200 床以上 500 床未満の病院の耳鼻咽喉科 16 箇所へ二次調査を送付した。

対象	調査機関数（病院数）	抽出率	一次調査対象機関数	一次調査返答数	回収率
内科	**合計　2174**		**1000**	**384**	**38.4%**
University hospital	108	100%	108	58	53.7%
>500 beds	320	100%	320	110	34.4%
499-200 beds	1746	33%	572	217	37.9%
眼科	**合計　1276**		**1000**	**362**	**36.2%**
University hospital	103	100%	103	44	42.7%
>500 beds	260	100%	260	94	36.2%
499-200 beds	913	70%	637	224	35.2%
耳鼻咽喉科	**合計　1211**		**1000**	**394**	**39.4%**
University hospital	101	100%	101	49	48.5%
>500 beds	261	100%	261	103	39.5%
499-200 beds	849	75%	638	242	37.9%
合計	***4661***		***3000***	***1140***	***38.0%***

表 1　一次調査対象病院数および抽出率と回収率

2.　二次調査対象病院への送付と回収率について（表 2 参照）

二次調査は大学病院の内科 30 箇所、500 床以上の病院の内科 22 箇所、200 床以上 500 床未満の病院の内科 11 箇所に送付し、それぞれ 26 箇所（86.7%)、14 箇所（63.6%)、8 箇所（72.7%）から回答を得た（() 内は回収率)。また大学病院の眼科 7 箇所、500 床以上の病院の眼科 7 箇所、200 床以上 500 床未満の病院の眼科 4 箇所に送付し、それぞれ 6 箇所（85.7%)、5 箇所（71.4%)、3 箇所（75.0%）から回答を得た（() 内は回収率)。さらに大学病院の耳鼻咽喉科 19 箇所、500 床以上の病院の耳鼻咽喉科 18 箇所、

200床以上500床未満の病院の耳鼻咽喉科16箇所に送付し、それぞれ15箇所(78.9%)、12箇所（66.7%)、11箇所（68.8%）から回答を得た（() 内は回収率)。

対象	二次調査 対象機関数	二次調査 回答数	回収率
内科	**63**	**48**	**76.2%**
University hospital	30	26	86.7%
>500 beds	22	14	63.6%
499-200 beds	11	8	72.7%
眼科	**18**	**14**	**77.8%**
University hospital	7	6	85.7%
>500 beds	7	5	71.4%
499-200 beds	4	3	75.0%
耳鼻咽喉科	**53**	**38**	**71.7%**
University hospital	19	15	78.9%
>500 beds	18	12	66.7%
499-200 beds	16	11	68.8%
合計	***134***	***100***	***74.6%***

表2　二次調査対象機関数と回収率

3. 患者推計

全国の病院において診断がなされているミクリッツ病患者数を、一次調査の結果から以下の式により推計した。

$$\text{推計患者数} = \frac{\text{報告患者数}}{\text{回収期間数/対象期間数}}$$

この推計は層毎に行われ、その総和をもって報告患者数とした。また、(1)式により各層の標準誤差sを推定したのち、(2)式によりこれを統合しs,とし、さらに(3)式によって95%信頼区間の推定値とした。N_iは患者数をiと報告した機関数、Nは各層の回収機関数、nは対象機関数、kは層数となっている。結果を表3にまとめた。これらの計算はすべて、全国疫学調査マニュアル第2版を参照し行われた（2006，厚生労働省難治性疾患克服事業　特定疾患の疫学に関する研究班編)。

$$s = \sqrt{\frac{\sum i^2 \cdot N_i/N - (\sum i \cdot N_i/N)^2}{n-1} \cdot n^3(1/N - 1/n)} \quad \cdots (1)$$

$$s. = \sqrt{s_1^2 + s_2^2 + \cdots + s_k^2} \quad \cdots (2)$$

$$(\text{推計患者数} - 1.96 \cdot s., \text{推計患者数} + 1.96 \cdot s.) \quad \cdots (3)$$

対象	一次調査 患者数	推計 患者数	95%信頼区間	
内科	**213**	**495**	**315**	**676**
University honspital	163	304	135	472
>500 beds	41	119	71	168
499–200 beds	9	72	29	116
眼科	**68**	**186**	**96**	**276**
University honspital	29	68	21	115
>500 beds	31	86	13	158
499–200 beds	8	33	9	56
耳鼻咽喉科	**160**	**397**	**314**	**481**
University honspital	87	179	120	239
>500 beds	39	99	64	134
499–200 beds	34	119	72	167
合計	***441 人***	***1079 人***	***861***	***1297***

表 3　ミクリッツ病報告患者数ならびに推計患者数とその信頼区間

。二次調査より詳細な情報が得られた患者数は 256 名であった。その内訳は、大学病院の内科で診断されているものが 127 名、500 床以上の病院の内科では 21 名、200 床以上 500 床未満の病院の内科では 7 名、大学病院の眼科では、17 名、500 床以上の病院の眼科では 9 名、200 床以上 500 床未満の病院の眼科では 2 名、大学病院の耳鼻咽喉科では 40 名、500 床以上の病院の耳鼻咽喉科では 20 名、200 床以上 500 床未満の病院の耳鼻咽喉科では 12 名であった。

報告された患者の分布については図 2 に示すように、北海道に 32.4%にあたる 83 人が存在し、次いで東京都、大阪府が同数であり 8.98%にあたる 23 人が存在していた。

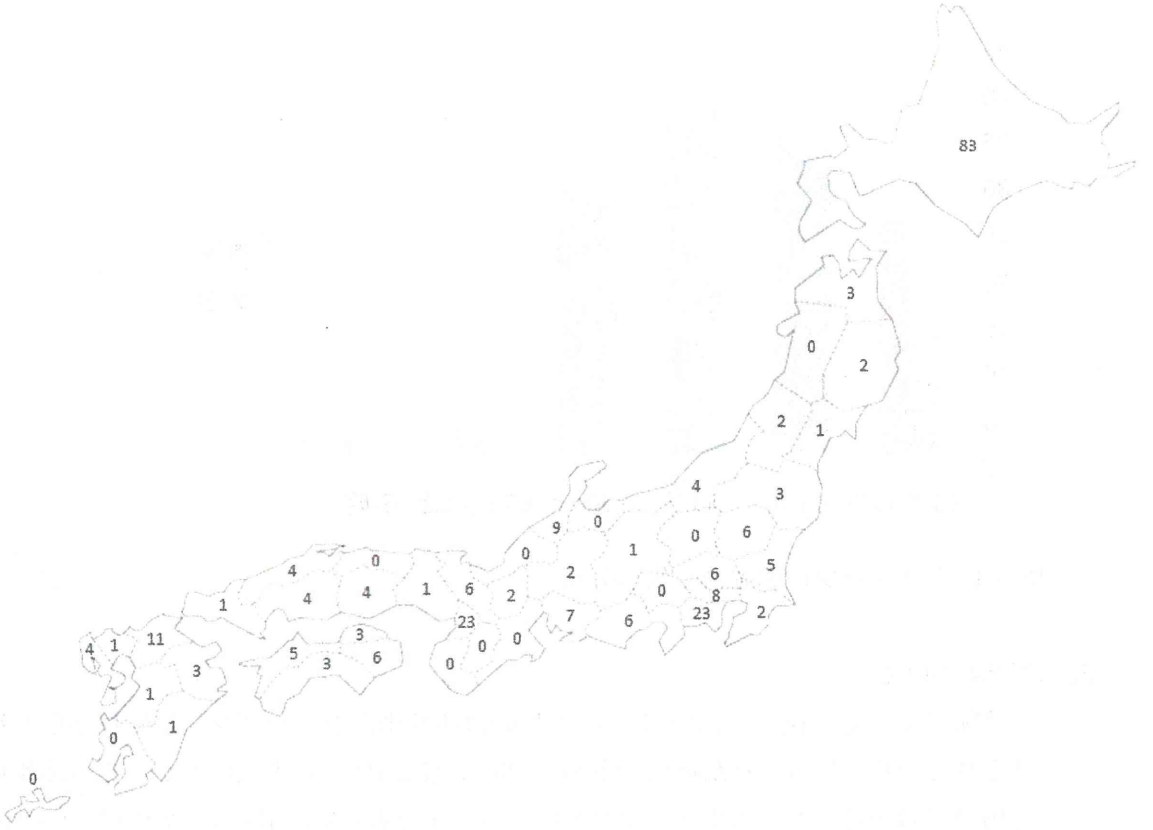

図 2　ミクリッツ病患者の都道府県分布

4. 患者の年齢と性差

報告された患者 256 名の性差（(図 3a)）と年代別における分布（図 3b）を示す。

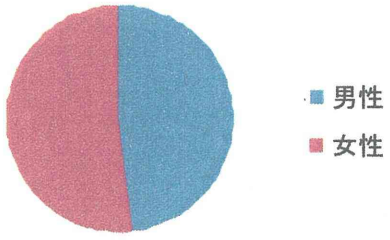

図 3-a ミクリッツ病患者 256 名の性差

性差においては男性 48.0%、女性 52.0%とやや女性に多いものの、ほぼ同程度であり、性差は無いものと考えられる。また年代に関しては男女とも 50 代から 70 代に多く、中年以降に見られる疾患と考えられる。