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

Hiroki Takahashi a,⁎, Motohisa Yamamoto a, Chisako Suzuki a, Yasuyoshi Naishiro a, Yasuhisa Shinomura a, Kohzoh Imai b

a First Department of Internal Medicine, Sapporo Medical University School of Medicine, Japan
b Sapporo Medical University, Japan

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 detection 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.

© 2010 Published by Elsevier B.V.
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 as Tsubota reported the first case of MD in 1888. 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 gamma-globulin 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 assumed 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.

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 plasma 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 interlobular 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]. Retropitoneal 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
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.

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.

References


Table 2

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Disorders included in IgG4-related systemic disease.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacrimal and salivary gland</td>
<td>Mikulicz's disease, Kuttner's tumor, dacryoadenitis, ocular IgG4-related disease</td>
</tr>
<tr>
<td>Respiratory</td>
<td>IgG4-related pulmonary disease, inflammatory pseudotumor</td>
</tr>
<tr>
<td>Digestive</td>
<td>Enterocolitis</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>Sclerosing cholangitis, igg4 hepatic disease</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Autoimmune pancreatitis</td>
</tr>
<tr>
<td>Renal urinary</td>
<td>IgG4-associated nephropathy, tubulointerstitial nephropathy, retroperitoneal fibrosis, prostatitis</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Autoimmune hypophysitis, Riedel's thyroiditis, diabetes mellitus</td>
</tr>
<tr>
<td>Nervous</td>
<td>Cranial pachymeningitis</td>
</tr>
<tr>
<td>Lymphatic</td>
<td>IgG4-associated lymphadeopathy, Castleman's disease</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Arthritis</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Inflammatory abdominal aneurysm</td>
</tr>
</tbody>
</table>
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 interferon (IFN)-γ 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 × 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 have a major impact on disease severity, CpG-ODN treatment significantly delayed the onset of proteinuria in NZB/W mice. Interestingly, short-term CpG-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 CpG-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-1H) 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. Alemtuzumab is highly effective in relapsing-remitting multiple sclerosis; however, 30% of patients develop autoimmunity. Alemtuzumab (previously called Campath-1H) 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. Alemtuzumab is highly effective in relapsing-remitting multiple sclerosis; however, 30% of patients develop autoimmunity. Alemtuzumab (previously called Campath-1H) induces a prolonged T cell lymphopenia with memory cells dominating the reconstituting T-cell pool for at least 3 months.