History: Lacrimal and Salivary Glands

4

Susumu Sugai

4.1 Mikulicz's Disease

Mikulicz's disease [1, 2] and a case later regarded as the first described case of Sjögren's syndrome [3] were reported in the same year, 1888. Mikulicz's disease was presented at a medical meeting [4], while Sjögren's syndrome received first notice in an English journal. After Mikulicz's first report, confusion about the nature of this disease reigned for more than 60 years until the paper of Morgan and Castleman in 1953 [5], which appeared to settle the confusion by proposing that Mikulicz's disease, in fact, was a subset of Sjögren's syndrome. More than half a century later, however, Japanese investigators established Mikulicz's disease as a subset of IgG4-related disease [6].

Jan Mikulicz-Radecki, a Polish surgeon who lived in what was then Prussia, pioneered several surgical interventions and tools that had a lasting impact on his field. He is regarded rightly as one of the fathers of modern surgery. Ironically, this pioneer of gastric resection for cancer who had performed 183 gastrectomies during the course of his career died himself of gastric cancer at the age of 55 [7, 8].

Mikulicz was born in 1850 in Chernovcy (Czernowitz), the capital of a Polish–Austrian province. He was the son of a Polish nobleman. After finishing medical studies in Vienna, he worked by the side of the great professor and surgeon, Theodor Billroth, for 8 years as an assistant. Mikulicz designed the first endoscope for examining the esophagus and stomach and thereby became the first surgeon to observe cancer of the esophagus and stomach endoscopically before operation in a living patient. Mikulicz was appointed head of the surgical department in Wroclaw and was visited by outstanding surgeons from all over the world. He also traveled to Europe, Russia, and the United States, where he performed surgical demonstrations [7, 8].

While working at Königsberg, Mikulicz [4] reported before the *Verein für Wissenschaftliche Heilkunde* ("Association for Scientific Healing") a case of chronic, bilateral, painless enlargement of the lacrimal and salivary glands. He published this case in Billroth's *Festschrift für die Beiträge zur Chirurgie* ("Festschrift for Contributions in Surgery") in 1892 [1, 2]. The patient was a 42-year-old farmer who first experienced swelling of the lacrimal glands and then of the submandibular and parotid glands over a 7-month period (Fig. 4.1). He had difficulty in seeing, eating, and speaking. After obtaining no improvement with the medicine prescribed by his local physician, he consulted Mikulicz. Mikulicz described the findings of his examination as follows. "A small nodulated, firm tumor was palpable under the eyelid skin and the eyeballs were displaced inward and forward. Under each angle of the jaw projected a tumor about the size of a hen's egg covered by normal skin. Inside the mouth swellings of sublingual glands were so remarkable that these occupied the floor of the oral cavity on both sides of the frenulum. The palate on both sides was occupied by a sharply delineated swelling almost the size of a chestnut. Under the buccal mucous membrane there were movable nodules, about the size of a pea on each side of the excretory opening of Stensen's duct. A copious secretion of saliva took place during the examination [1]".

Mikulicz removed two thirds of the patient's lacrimal tumors bilaterally in an attempt to ameliorate the patient's visual impairment. By the time of the first postoperative visit 2 months later, however, the lacrimal gland swelling had reappeared and the submandibular tumors had increased in size. Pilocarpine injections were performed in the hope of promoting secretion as a means of reducing the size of the salivary glands but despite profuse salivation, the result was not satisfactory. These passages are noteworthy not only for their historical interest and insights into the medical thinking of Mikulicz' day, but also because they demonstrate clearly that the patient did not suffer from xerostomia.

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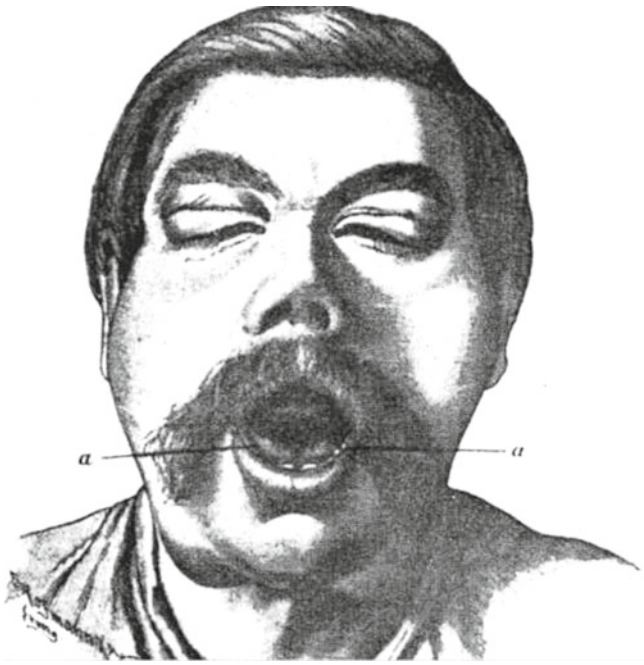

Fig. 4.1 Original patient described by Mikulicz, a 42-year-old male

Further excision of the remaining portions of the lacrimal and submandibular glands resulted in improvement, although swelling of the parotid glands persisted. The patient wrote to Mikulicz after discharge that he did not have trouble in the use of his eyes and was very satisfied with his condition, although the swelling of the parotid glands seemed to have increased. Unfortunately, 14 months after the onset of his glandular enlargement, the patient developed signs of peritonitis of unclear etiology and uncertain relationship (if any) to his glandular disease and died of probable perityphlitis over the period of a week. The swellings in the parotid glands and mouth were reported to have regressed markedly within a few days during the patient's terminal illness and had nearly disappeared before his death.

Descriptions of the resected tumors are instructive. Each was about the size of a child's fist, and the transverse section showed the normal structure of the gland. In places, it had a more homogeneous, pale reddish yellow, amyloid mass of lesser transparency. Microscopic examination of the excised salivary and lacrimal glands disclosed uniformly arranged tissue consisting of small round cells. In some places the cells laid compactly together, and in other places a fine reticulum was seen between them. Imbedded within these small-celled main masses were normal-appearing clusters of salivary gland acini, separated from one another in varying distances by the round cell tissue [1].

Mikulicz scoured the medical literature for similar cases. He noted four cases reported by Fuchs [9], Haltenhoff [10], Reymond [11], and Adler [12]. He also found descriptions of three cases in which enlargement of the lacrimal glands alone was reported by Arnold [13], Korn [14], and Power [15]. Mikulicz found no cases in which only the salivary glands were affected.

Mikulicz summarized this condition as follows: "The disease process exhibits itself clinically as a slowly arising, huge enlargement of all the salivary and lacrimal glands, without inflammatory signs and without demonstrable systemic manifestations. The process remains sharply confined to the region of these glands and involves neither the neighboring structures nor other organs or tissues. The microscopic examination reveals that the true parenchyma of the glands plays an entirely passive role. The increase in size is entirely brought about by a massive small-cell infiltration in the interstitial connective tissue." [1]

Mikulicz considered this disease to be a chronic process, first occurring in the lacrimal glands and under certain circumstances remaining localized but also with the potential for extension to the salivary glands. He strongly denied the possibility of malignancy such as sarcoma, lymphoma, or leukemia, as neither his case nor any of the others have features of cancer. He also rejected the notion of an infectious etiology such as mumps or tuberculosis.

Mikulicz remained stymied at the end of his examination of this disease with regard to the question of etiology. He wrote at the end of his paper, "Hoffentlich gelingt es künftigen Beobachtern, die Rätsel zu lösen, die uns diese merkwürdige Krankheit stellt (I hope that future observers will succeed in solving the riddle that this remarkable disease presents to us)" [1].

4.2 Confusion and Changes of the Concept of Mikulicz's Disease

According to Howard [16], four authors before Mikulicz had reported a total of five cases that were considered to be similar to the case of Mikulicz (Berlin [17]: two cases, Power [15], Haltenhoff [10], and Fuchs [9]). Although Mikulicz found no cases of isolated salivary gland swelling, in 1896 Küttner reported two cases of chronic inflammatory swelling of the submandibular glands [18]. For more than 100 years after Küttner's publication, the term "Küttner's tumor" was used loosely to refer to submandibular gland enlargement of a variety of causes. After the 2009 report of Kitagawa et al. [19], many cases of "Küttner's tumor" are now recognized to be a common manifestation of IgG4-related disease.

Within less than 10 years, despite Mikulicz's published description and concept of the disease, many reports appeared in the literature of patients with bilateral chronic enlargement of the lacrimal and/or salivary glands, classified as Mikulicz's disease. Von Brunn [20] argued in 1905 that the condition described by Mikulicz is a symptom complex,

rather than a disease entity, and that it is closely related to pseudoleukemia and leukemia. In 1907, Napp [21] reported that this condition may be produced by any one of several causes, including leukemia, malignant lymphoma, atypical lymphomatosis, sarcoidosis, and tuberculosis. In 1909, Howard [16] reviewed 81 cases collected from the literature and it became evident that, although all of these patients had the one common feature of symmetrical enlargement of the lacrimal or salivary glands, they differed widely in many other important aspects, leading to substantial confusion in the definition of "Mikulicz's disease." In many patients, the clinical course of this disease was that of a benign, self-limited condition, whereas in others it was rapidly fatal. Moreover, the pathological material obtained at biopsy or autopsy differed widely. It therefore became obvious that "Mikulicz's disease" was not one single pathologic entity but rather a syndrome that had any number of causes. Howard grouped them under three headings: [1] Mikulicz's disease proper, [2] pseudoleukemia, and [3] leukemia.

When referring to Mikulicz's disease proper, some authors looked beyond the diffuse lymphocytic infiltration and fibrosis present and focused attention instead on the unique pathological findings observed in that condition, particularly the lymphoid follicles and "conglutination cells" that originated from gland-epithelial cells [22, 23]. In 1914, Thursfield [24] first attempted to classify the syndrome on an etiologic basis. He divided all patients into eight groups: a congenital, familial, and hereditary condition; Mikulicz's disease proper; Mikulicz's disease with involvement of the lymphatic apparatus; leukemia; tuberculosis; syphilis; gout; and sialodochitis fibrinosa. In 1927, Schaffer and Jacobsen [25] reduced Thursfield's grouping into two groups: Mikulicz's disease proper and Mikulicz's syndrome caused by leukemia, lymphosarcoma, or tuberculosis. This classification was sensible and proper because they stressed the existence of Mikulicz's disease of unknown etiology. However, the basic histopathological features of Mikulicz's disease proper remained undefined.

In 1933, Sjögren [26] published a monograph on 19 patients entitled "Zur Kenntnis der Keratoconjunctivitis sicca" ("On the Identification of Keratoconjunctivitis sicca"). Sjögren correctly described many of the clinical components and histopathological changes, including those of the lacrimal and salivary glands and of the syndrome that later bore his name, Sjögren's syndrome. From the time of that description onwards, Sjögren's syndrome became one of the most important diseases to be differentiated from Mikulicz's disease.

In contrast, attempts to codify an understanding of Mikulicz's disease became even more muddled. Godwin [27] studied 11 cases of parotid tumors that showed unique and common microscopic features. For these patients with a good prognosis, several different pathological diagnoses might have been made based on previous understanding such as adenolymphoma, chronic infiltration, lymphoepithelioma, lymphocytic tumor, or Mikulicz's disease. The lesions microscopically consisted of a mass of lymphoid tissue consisting of either scattered foci of metaplastic epithelial cells or solid foci of closely packed cells. Some of those cases had findings closely resembling the epimyoepithelial islands reported by Morgan and Castleman 1 year later. To resolve the widespread confusion about Mikulicz's disease due to the impossibility of determining its characteristics from the unclear histological drawings in Mikulicz's paper, Godwin proposed in 1952 that the terms "Mikulicz's disease" and "Mikulicz's syndrome" be deleted and replaced by the term, "benign lymphoepithelial lesion."

Based on the understanding that an adequate histopathologic study of Mikulicz's disease was not available and that it was necessary to differentiate Mikulicz's disease from similar diseases on a histological basis, Morgan and Castleman in 1953 [5] studied 18 patients with clinically and pathologically defined Mikulicz's disease. The authors had had experience with the uncertainty of differentiating Mikulicz's disease from malignant lymphomas arising in the lacrimal or salivary glands. Despite the fact that six of their patients had been diagnosed as having malignant lymphoma, all had remained free of disease recurrences 9–16 years after surgical removal of their tumors. Histological examination of these six patients disclosed a characteristic alteration in the duct epithelium, in addition to diffuse lymphoid infiltration in the gland substance. Twelve additional patients were collected from either their own files (eight cases) or affiliated hospitals (four cases). The clinical and pathological aspects of these 18 patients were regarded as best fitting the original description of Mikulicz [28]. These patients had had diagnoses of chronic inflammation, Mikulicz's disease, metastatic carcinoma, atypical adenocystoma lymphomatosum, mixed tumor, lymphocytic leukemia, and malignant lymphoma, with many of them thought to have malignant diseases.

The data on 18 patients in these two papers [5, 28] are summarized in Table 4.1. Clinical review revealed that most of these patients had a history of a non-tender, progressively enlarging mass in the region of one or more salivary or lacrimal glands. In nine of them, swellings were confined to one parotid gland; in one patient, swelling was in a single submandibular gland; and in two patients, ipsilateral parotid and submandibular glands. Bilateral swelling was observed in three patients in parotid and submandibular glands; in two patients, parotid glands. Only one patient showed lacrimal gland swelling. Three patients died of apparently unrelated diseases. Autopsies done in these patients showed no evidence of malignant lymphoma. The age of the 18 patients ranged from 15 to 70 years. Fifteen patients were female, 12 of whom were between 37 and 59 years of age. The ages of the males were 15, 39, and 70 years. Two patients had

Table 4.1 Date in 18 patients (formed from papers 5 and 28)

Pt. no.	Sex	Age (years)	Affected glands	Clinical history	Follow-up (years)
1	F	35	P, P, SM, SM	Conjunctivitis	7
2	F	61	P, P, SM, SM	Dry M	7
3	F	62	P, P, SM, SM	Dry M, degenerative arthritis	7
4	F	39	L, L	KCS	3.7
5	F	47	P, P	KCS, Dry M, disseminated LE	Autopsy
6	F	55	P, P	Dry M, rheumatoid arthritis	Autopsy (Inf Hp)
7	M	70	P, SM	Arthritis	7
8	F	59	P, SM	–	Autopsy (post-op)
9	F	37	P	–	0.1
10	M	39	P	–	18
11	F	48	P	–	20
12	F	47	P	–	5.7
13	F	50	P	–	4
14	F	56	P	Dry M	18
15	F	37	P	Dry M, rheumatoid arthritis	15
16	F	40	P	Retinal arteritis	17
17	F	69	P	Dry M, degenerative arthritis	10
18	M	15	SM	Rheumatic fever	5.3
	F 15, M 3 (number)	F 48.4, M 41.3 (average age)			

P parotid gland, *Dry M* dry mouth, *Inf Hp* infectious hepatitis, *SM* submaxillary gland, *KCS* keratoconjunctivitis sicca, *Post-op* postoperation, *L* lacrimal gland, *LE* lupus erythematosus

keratoconjunctivitis sicca, one had diminished tear production (cheesy eye discharge), and one had recurrent bilateral conjunctivitis. Five patients had arthritis, including three with rheumatoid arthritis. One patient died of disseminated lupus erythematosus, and the 15-year-old boy had rheumatic fever.

On pathological examination, the cut surface of the tumor showed preservation of the lobular architecture and marked enlargement of the individual lobules. There were two fundamental changes in their findings: [1] a gradual lymphoid infiltration and proliferation within the lobule, with subsequent atrophy and loss of acinar tissue, and [2] an alteration of the ducts, characterized by a typical intraductal cellular proliferation and gradual narrowing of the ductal lumen leading to the formation of a compact cellular island lying in a stroma of lymphoid tissue. Morgan and Castleman thought that the microscopic features of these cases were so similar as to leave no room for doubt that a single disease process was common to all.

The tissue was characterized by lymphocytic infiltration, which replaced the glandular parenchyma concomitantly with intraductal proliferation of epithelial and myoepithelial cells. The latter change resulted in the obliteration of the ductal lumens and the formation of solid cell masses, which they called "epimyoepithelial islands" (Figs. 4.2 and 4.3) scattered throughout the lymphomatoid stroma (Fig. 4.4).

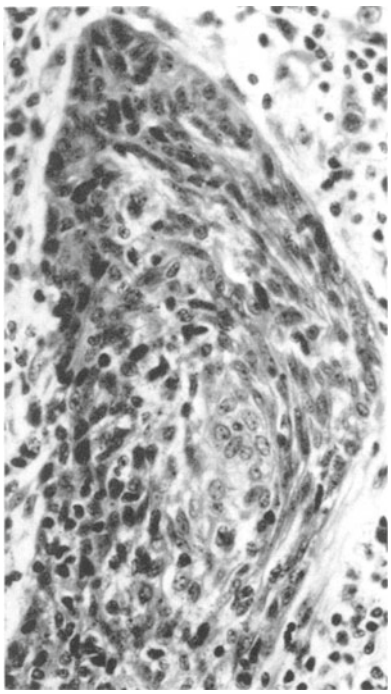

Fig. 4.2 An epimyoepithelial island named by Morgan and Castleman, the formation of a compact cellular island in a stroma of lymphoid tissue

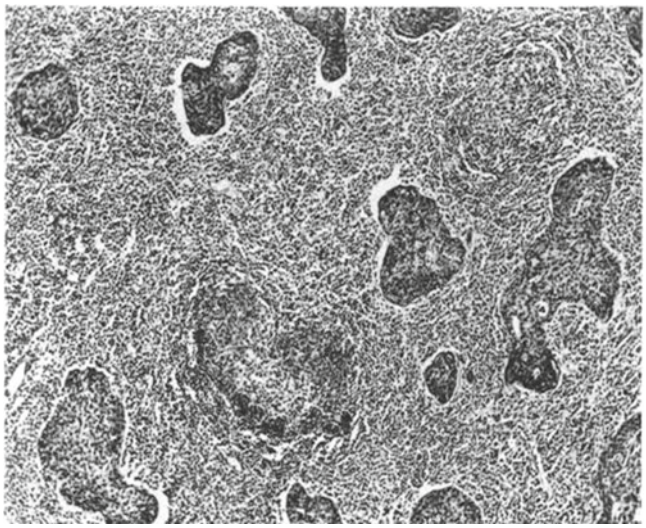

Fig. 4.3 Epimyoepithelial islands in a lymphoid stroma shown by Morgan and Castleman

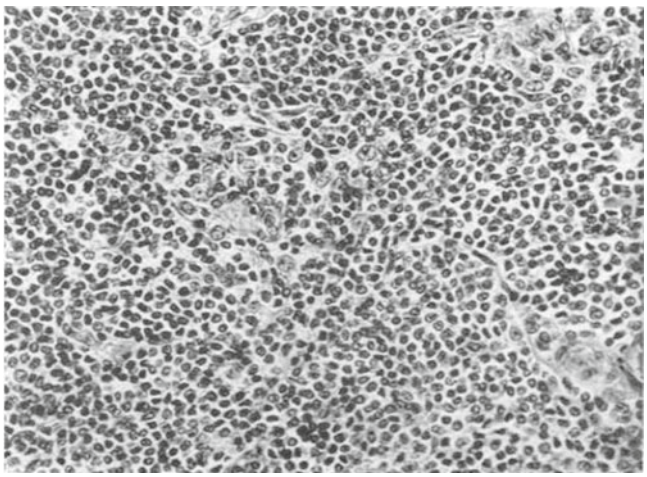

Fig. 4.4 Massive lymphocytic infiltration shown by Morgan and Castleman

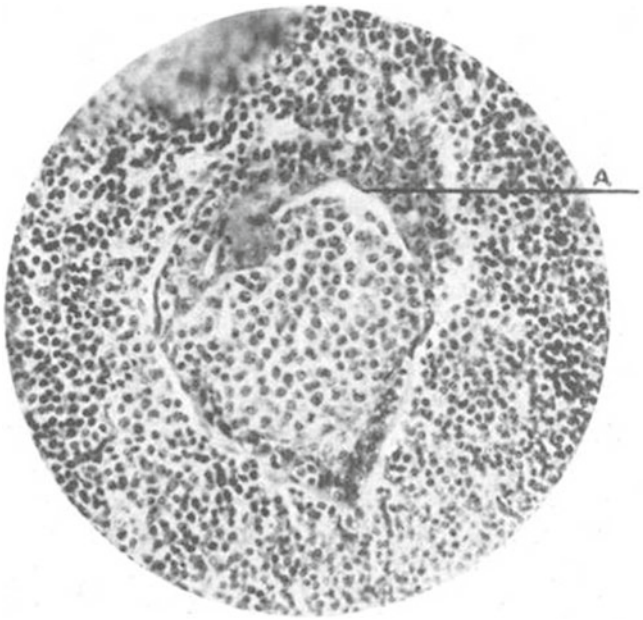

Fig. 4.5 A patient reported by Smith, a 62-year-old female. Microscopic findings of lymphocyte infiltration with proliferation of ductal cells

Figure 4.4 appears to me to show mucosa-associated lymphoid tissue (MALT) lymphoma judging from the modern understanding of lymphoma. In differentiating Mikulicz's disease from malignant lymphoma, Morgan and Castleman stressed that the presence of these epimyoepithelial islands was the most dependable diagnostic feature, with the formation of these epimyoepithelial islands probably being pathognomonic of Mikulicz's disease. They understood that the primary lesion in Mikulicz's disease was in the duct system, with involvement of lymphoid tissue being a secondary response. In a search of the literature they found a case reported previously by Smith and Bump [29], who drew attention to the unique microscopic finding, an island of cells composed of metaplastic ductal cells. Their pictures were similar to the epimyoepithelial islands named by Morgan and Castleman (Fig. 4.5). This picture, too, might be that of MALT lymphoma. They did not mention the important paper published 1 year before them by Godwin [27].

Morgan and Castleman finally concluded that "on the basis of certain clinical and pathologic similarities to Sjögren's syndrome, it seems likely that Mikulicz's disease is not a distinct clinical and pathologic disease entity as previously believed, but merely one manifestation of a more generalized symptom complex known as Sjögren's syndrome."

In another paper, Morgan [28] reported that Sjögren's original microscopic slides of salivary glands showed all the features previously reported in the 18 patients with Mikulicz's disease described by Morgan and Castleman. He described that Mikulicz's disease and Sjögren's syndrome were similar in their clinical nature and course; their tendency to occur in middle age; their preponderance in women; their identical histological findings in the salivary and lacrimal glands; and the coexistence in both groups of similar associated lesions, in addition to disease in the salivary glands, such as keratoconjunctivitis sicca, xerostomia, and rheumatoid arthritis. Of these 18 patients, nine had one or more of the features of Sjögren's syndrome in addition to the diseases of the salivary glands (Table 4.1). He thought that this degree of similarity suggests that the two conditions are related, if not actually the same pathologic process. Morgan argued that, in contrast to Mikulicz's contention that the disease always involved the lacrimal glands, the disorder described in his own cases was

more commonly confined to the salivary glands. At variance with the long-held belief that the glandular involvement in Mikulicz's disease is always bilateral, 12 of their 18 patients had only unilateral enlargement.

As only one of the 18 patients had enlarged lacrimal glands, Morgan described that lacrimal glands were less frequently enlarged in Mikulicz's disease than previous authors had believed and the presence or absence of one physical finding, such as enlargement of lacrimal glands, should not be used as a basis for dividing such cases into two entities. Then, he concluded that the condition characterized by chronic enlargement of the salivary or lacrimal glands, which in the past had been called Mikulicz's disease, may be a less highly developed variant of a larger symptom complex, Sjögren's syndrome.

The conclusion drawn by Morgan and Castleman that Mikulicz's disease is a subset of Sjögren's syndrome was so rapidly and widely accepted among researchers at that time in the USA and Europe that subsequently the number of English-language reports on Mikulicz's disease decreased significantly.

In retrospect, however, it is appreciated that these papers obfuscated rather than clarified the concept of Mikulicz's disease. By focusing on 18 patients, many of whom were very different from the original patient described by Mikulicz, Morgan and Castleman derived a different disease picture from that originally proposed, namely one manifestation of Sjögren's syndrome. In contrast to Mikulicz's contention that the disease is bilateral and involves the lacrimal glands, the authors reported bilateral involvement in only six of 18 patients. Ten patients had swelling of a single parotid or submandibular gland and only one involvement of both lacrimal glands. Most of their patients were women, in the fifth and sixth decades, and nine of these 18 patients had one or more of the features of Sjögren's syndrome. It is important to note that Mikulicz's original patient showed copious salivation.

The most problematic issue in their paper was that the selection criteria that Morgan and Castleman used for recruiting patients were not fully described, except for one: "a characteristic alteration in the duct epithelium in addition to diffuse lymphoid infiltration of the gland substance." The important histological finding described as "epimyoepithelial islands," which was thought to differentiate Mikulicz's disease from other diseases, is now called lymphoepithelial lesions or lymphoepithelial sialadenitis and is considered to be a typical feature of the active and more advanced cases of Sjögren's syndrome.

I paid attention to the presence of the lymphoepithelial lesion in Sjögren's syndrome because intraductal infiltration of lymphocytes and proliferation of ductal cells leading to the lymphoepithelial lesion are distinctive microscopic features of Sjögren's syndrome, but not of Mikulicz's disease. Our group think that the lymphoepithelial lesion might be a locus of lymphoma development in Sjögren's syndrome [30] and that the mucosal epithelial cell presents antigens to lymphocytes in Sjögren's syndrome. In relation to this, Moutsopoulos had proposed autoimmune epithelitis as a key feature of Sjögren's syndrome [31]. Accordingly, we regard the lack of the lymphoepithelial lesion as one of the microscopic features of Mikulicz's disease in addition to the presence of lymphocytes, IgG4-bearing plasma cells, lymph follicles, and fibrosis in affected tissues.

4.3 Mikulicz's Disease and IgG4-Related Disease in Japan

Since the appearance of the papers by Morgan and Castleman, more than 20 patients with Mikulicz's disease have been reported in Japan mainly in Japanese, and discussion has continued on the similarities and differences between Mikulicz's disease and Sjögren's syndrome. Konno [32] reported that Mikulicz's disease differs from Sjögren's syndrome in three aspects: (1) no gender difference is evident in Mikulicz's disease, (2) the function of the salivary and lacrimal glands in Mikulicz's disease recovers to normal after disappearance of gland swelling, and (3) sialography in patients with Mikulicz's disease shows only mild damage and is quite different from that of Sjögren's syndrome.

Konno argued that the pathological findings described by Morgan and Castleman, including epimyoepithelial islands, were not confined to Mikulicz's disease or Sjögren's syndrome, but could be observed in other conditions, such as chronic inflammation, in circumstances in which the salivary glands were severely damaged. In 1993, Suzuki et al [33] described a 73-year-old man with Sjögren's syndrome who showed huge swelling of the bilateral lacrimal and submandibular glands and a serum IgG4 concentration of 5,800 mg/dL. After treatment with 30 mg prednisolone for 1 month, the swelling of the glands and serum abnormality disappeared almost completely. This case is no doubt considered to be the first report of a high level of IgG4 in a patient with Mikulicz's disease. Tsubota et al. [34] reported in 2000 that, compared to patients with Sjögren's syndrome, patients with Mikulicz's disease showed an almost normal state of the corneal surface with rose bengal and fluorescent staining. They had microscopically fewer APO2.7-positive apoptotic acinar cells in the lacrimal glands and lower expression of Fas and Fas-ligand in lymphocytes. They understood that this was the reason why the function of the lacrimal glands was only slightly, if at all, impaired in patients with Mikulicz's disease despite massive lymphocytic infiltration into the affected

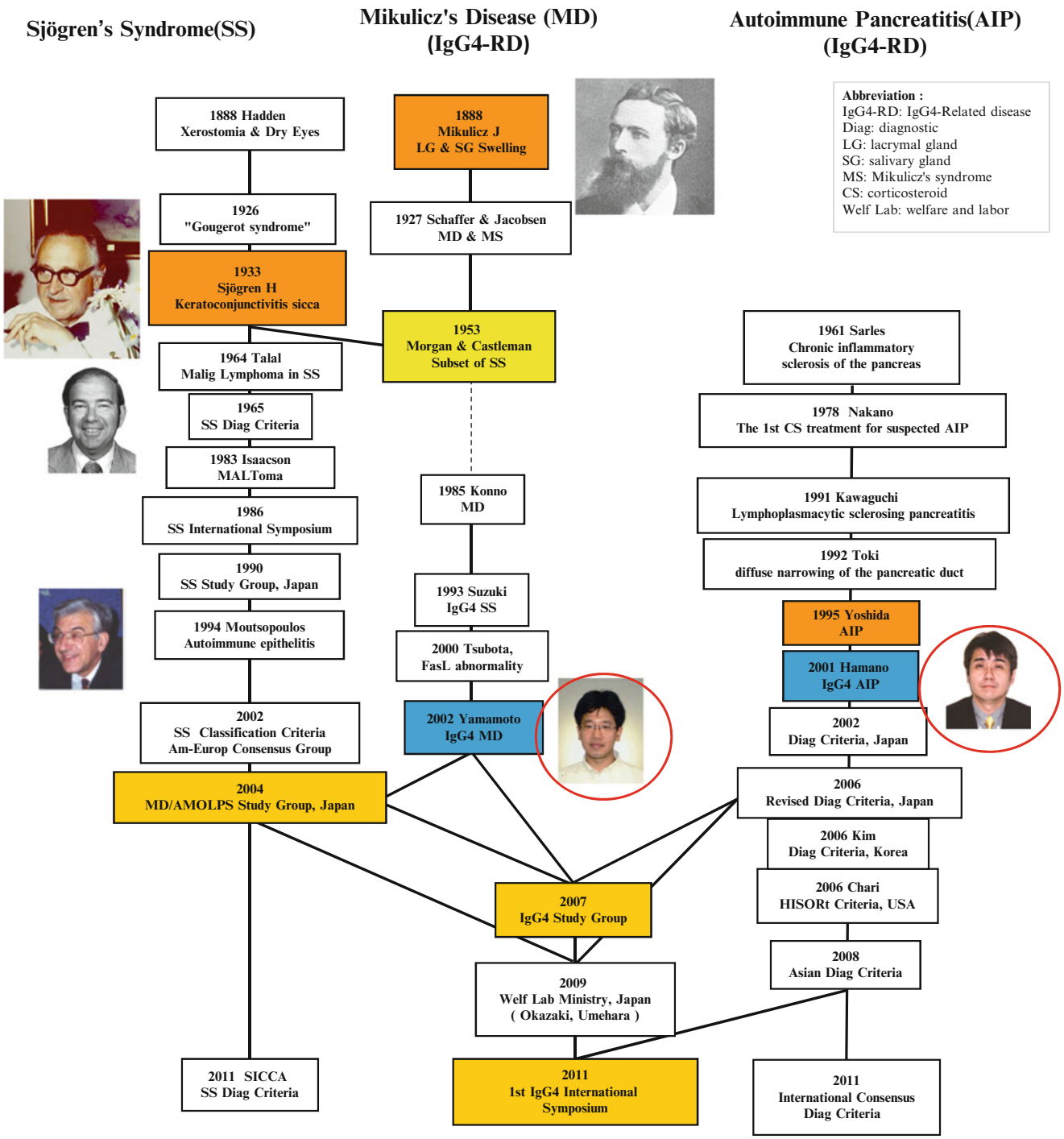

Fig. 4.6 Historic events in Sjögren's syndrome (SS), Mikulicz's disease (MD), and autoimmune pancreatitis (AIP) (Sugai S & Kawa S)

glands. They [35] later found a point mutation in the promoter region of the Fas-ligand gene in one patient with Mikulicz's disease.

Yamamoto et al. [36] reported in 2002 that Mikulicz's disease differed from Sjögren's syndrome in that six patients with Mikulicz's disease showed high serum concentrations of IgG4 and low numbers of Fas-positive cells and apoptotic cells in the salivary glands. This report was the first to convincingly show elevated serum IgG4 values in Mikulicz's disease and appeared only 1 year after the report of Hamano et al. [37], who first showed a high serum IgG4 concentration in patients with sclerosing pancreatitis, which is now

known as type 1 (IgG4-related) autoimmune pancreatitis disease is different from SS. Yamamoto et al. [40, 41] described comprehensively the clinical and laboratory features of Mikulicz's disease. In 2004, the Japanese Medical Society for Sjögren's Syndrome established a study group of Mikulicz's disease/IgG4 + AMOPLS and began to collect records of patients with Mikulicz's disease. Analyses of 64 patients with Mikulicz's disease resulted in the elaboration of a new clinical entity, IgG4-positive multi-organ lymphoproliferative syndrome (IgG4 + MOLPS), by Masaki et al. [42].

The new disease concept, autoimmune pancreatitis with elevated IgG4, originated from Japan and has been accepted globally, especially after the finding of the high concentration of IgG4 in sera and plasma cells in affected tissues by Hamano et al. [37]. Great efforts have been made to establish and revise the diagnostic criteria for autoimmune pancreatitis in Japan, in other parts of Asia and in the USA. During this process, it became understood that some patients with autoimmune pancreatitis have features of Sjögren's syndrome as an extra-pancreatic manifestation, while in some cases Mikulicz's disease also complicates autoimmune pancreatitis. Then, in 2007 clinicians in the field of gastrointestinal and autoimmune disease and pathologists cooperated to establish an IgG4 study group in Japan. Since then, they have accelerated their research activity to better define the whole picture of this disease. In 2009 the Japanese Welfare and Labor Ministry launched three groups, namely IgG4-related systemic sclerosing disease (Okazaki group), IgG4-related multi-organ lymphoproliferative disease (Umehara group), and Mikulicz's disease and IgG4-related disease (Naeshiro group). By thoroughly discussing the clinical and pathological features of this disease, they were able to settle on an appropriate name for it, namely IgG4-related disease, and in establishing clinically useful diagnostic criteria [6]. Comprehensive reviews by outstanding researchers in each field of IgG4-related disease were published in 2011 [43]. Finally, the 1st international symposium on IgG4-related disease was held in Boston, in 2011, organized by Dr. John Stone, the results of which have already been published [44] (Fig. 4.6).

The riddle left by Mikulicz in 1892 is now, 120 years later, being finally solved aided by the recognition of this disease as an IgG4-related disease. We Japanese researchers are proud to have been able to make a significant contribution to this process of scientific discovery. However, neither the pathologic role of IgG4 nor the etiopathogenesis of this disease is yet well understood, and thus, much more work will be required to define and untangle the many riddles remaining and more importantly to use the new knowledge gained to help the patients inflicted with IgG4-related disease in all its manifestations.

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