16 Sialadenitis and Dacryoadenitiss: IgG4-Related Mikulicz's Disease Would Precede Autoimmune Pancreatitis and Be Likely to Relapse

Kensuke Kubota, Kunihiro Hosono, and Atsushi Nakajima

Introduction

Mikulicz's disease (MD) was confirmed as an IgG4-related disease (IgG4-RD) in 2011 and in view of its characteristic clinical features of bilateral and symmetrical swelling of the lacrimal and salivary glands, it may be appropriate to revise the disease's name as IgG4-related dacryoadenitis and sialadenitis (IgG4-DS) [1]. IgG4-DS was the same concept as IgG4-related Mikulicz's disease [1]. IgG4-DS could be diagnosed according to the Japanese consensus criteria established in 2008 [2]. Until recently, IgG4-DS was regarded as a subtype of Sjögren's syndrome (SS); however, now, we consider IgG4-DS, which is responsive to corticosteroid treatment (CST) as quite a different disease entity from SS (Fig. 16.1).

To understand the concept of IgG4-DS, it may be important to know its histological background. First, in 1888, Dr. Johann von Mikulicz published a paper about a patient with symmetrical swelling of the lacrimal, parotid, and submandibular glands, characterized pathologically by mononuclear cell infiltration, the so-called MD [3]. Then in 1933, Dr. Henrik Sjögren published a case series of patients with rheumatoid arthritis associated with keratoconjunctivitis sicca and severe swelling of the parotid glands, the so-called SS [4]. Subsequently, in 1953, Morgan and Castleman classified IgG4-DS as a subtype of SS [5]. Since then, little attention has been paid to IgG4-DS for over 50 years. In 2004, Yamamoto unearthed the definitive differences between IgG4-DS and SS based on clinical data [6]. They revealed that IgG4-DS responded well to CST therapy and that was a reversible condition, unlike SS. In 2012, Umehara proposed the novel clinical entity IgG4-RD, encompassing autoimmune pancreatitis (AIP) and IgG4-DS. Thereafter, IgG4-DS has been regarded as one manifestation of IgG4-RD [7]. It has been suggested that lacrimal gland involvement in IgG4-RD should be referred to as IgG4-related dacryoadenitis, and submandibular gland involvement in IgG4-RD should be referred to as IgG4-related Küttner tumor (IgG4-KT) [1] (Fig. 16.2).

AIP, a major component of IgG4-RD, mainly manifesting as obstructive jaundice and/or deterioration of diabetes mellitus, was first reported by Sarles in 1961 [8] and proposed as a clinical entity by Yoshida et al. in 1995 [9]. Hamano revealed serum IgG4 elevation as a useful finding in the diagnosis for AIP [10]. Although the etiology and mechanism of AIP are still unknown, overproduction of Th2 and regulatory cytokines may play an important role [11, 12]. The characteristic findings of AIP such as elevation of the serum IgG4, infiltration of the affected organs such as the pancreas, bile duct, and gallbladder by IgG4-bearing plasma cells, and its reversibility with CST therapy are similar to those of IgG4-DS. However, AIP is associated with IgG4-DS only in a minority of patients. We describe some patients with AIP associated with IgG4-DS, preceded by dacryoadenitis and sialadenitis [13].

In this section, we summarize the features of IgG4-DS and IgG4-KT from the perspective of AIP because of the paucity of data on the clinical relationship between IgG4-DS/KT and AIP.

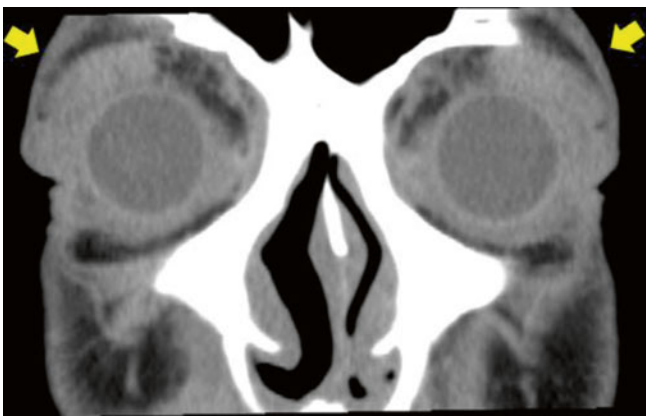

Fig. 16.1 MRI showed IgG4-related dacryoadenitis

K. Kubota, MD, PhD (✉) • K. Hosono, MD, PhD
A. Nakajima, MD, PhD
Division of Hepatogastroenterology,
Yokohama City University Graduate School of Medicine,
Fukuura 3-9, kanazawa, Yokohama 236-0004, Japan
e-mail: kubotak@yokohama-cu.ac.jp

T. Kamisawa, J.B. Chung (eds.), *Autoimmune Pancreatitis*,
DOI 10.1007/978-3-642-55086-7_16, © Springer-Verlag Berlin Heidelberg 2015

Discrimination Between IgG4-Related Mikulicz's Disease and Sjögren's Syndrome

Table 16.1 shows the consensus criteria for the diagnosis of IgG4-related Mikulicz's disease (IgG4-DS) approved by the Japanese society for Sjögren's syndrome (SS) in 2008 [2]. IgG4-DS is regarded as a component of IgG4-RD characterized by lacrimal gland and/or salivary gland involvement. IgG4-DS must be distinguished from disorders such as sarcoidosis, Castleman's disease, Wegener's granulomatosis, lymphoma, and cancer [2] (Table 16.2).

There are several marked symptomatic differences between IgG4-DS and SS, such as IgG4-DS being characterized by bilateral salivary gland/lacrimal gland swelling without tenderness, while SS tends to show unilateral involvement. Sicca is modest in IgG4-DS. In regard to the sex distribution, SS tends to occur predominantly in females, whereas no gender difference in incidence has been reported in patients with IgG4-DS [15].

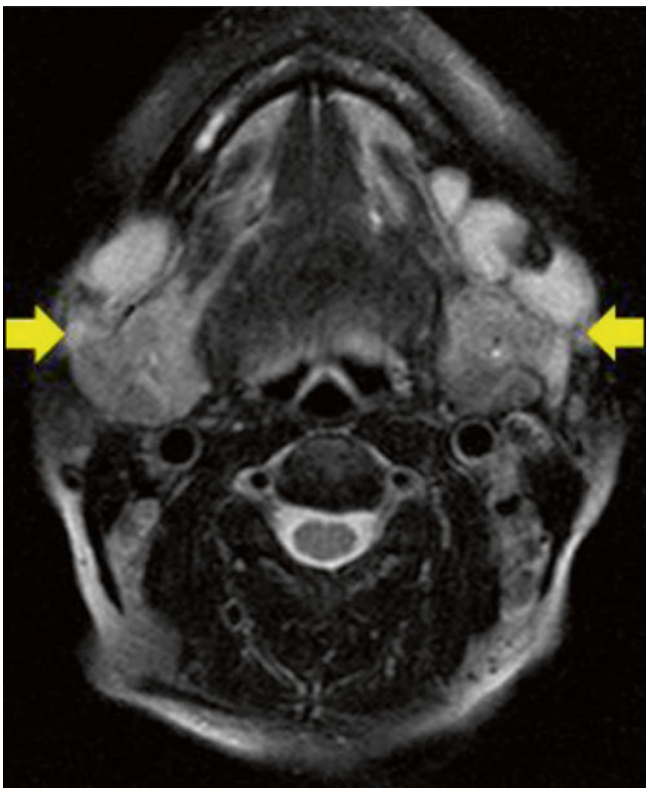

Fig. 16.2 MRI depicted IgG4-related Küttner tumor

Table 16.1 Diagnostic criteria of IgG4-related Mikulicz's disease

1. Symmetrical swelling of at least 2 pairs of lacrimal, parotid, or submandibular glands for at least 3 months
AND
2. Elevated serum IgG4 (>135 mg/dl)
OR
3. Histopathological features including lymphocyte and IgG4 + plasma cell infiltration (IgG4 + plasma cells/IgG + plasma cells >50 %) with typical tissue fibrosis or sclerosis

Masaki et al. [2]
Approved by the Japanese Society for Sjögren's syndrome 2008

Histopathologically, IgG4-DS had been believed to be a subgroup of SS based on histopathologic similarities between the two entities, such as degeneration and disappearance of the glandular acini due to severe mononuclear cell infiltration, proliferation of the ductal epithelial cells and duct stenosis, formation of myoepithelial islands, and cystic dilatation of the peripheral ducts [5]. However, it has been confirmed that these histopathological features can only be detected in SS, and not in IgG4-DS [15]. The most remarkable difference between IgG4-DS and SS is the marked infiltration of the affected organs by IgG4-bearing plasma cells, with the percentage of IgG4-positive cells relative to the total IgG cell population being characteristically more than 40 % in IgG4-DS [2, 15]. On the other hand, infiltration of the salivary glands by IgG4-bearing plasma cells is almost not noted in SS. In the diagnosis of IgG4-DS, the IgG4+/IgG + plasma cell ratio, whose cutoff value is organ-dependent, is reported as a more powerful tool than the total IgG4+ plasma cell count, which is useful for establishing the diagnosis of IgG4-RD [16]. In addition, apoptosis of the acinar and/or duct cells is reported to be frequent and extensive in SS, but not in IgG4-DS [17]. It might be said that the inflammatory reaction is more potent and irreversible in SS than in IgG4-DS.

In regard to the clinical features, symmetric and persistent swelling of more than two of the lacrimal and major salivary glands is seen in IgG4-DS. Most importantly, parotid gland is the major organ affected in SS, while lacrimal and submandibular glands tend to be mainly involved in IgG4-DS. The swelling is short-lived, usually resolving in about a week in IgG4-DS [14].

In regard to the gland function, salivary secretion is severely impaired in SS, while salivary gland function is either normal or only slightly disturbed in IgG4-DS, and the function can usually be improved by CST therapy [15]. Serologically, strongly positive results for anti-SSA/Ro and anti-SSB/La antibodies are obtained in patients with SS, but not in those with IgG4-DS [2]. Not only serum IgG4 but also serum total IgG, IgG2, and IgE concentrations are significantly elevated in IgG4 + MOLPS (multiorgan lymphoproliferative syndrome), now accepted as being equivalent to IgG4-RD which includes IgG4-DS, as compared to SS [2].

Regarding therapy, IgG4-DS is mainly treated with CST and resolution of the gland manifestations is immediately obtained; however, CST therapy is not as effective in most patients of SS as in those with IgG4-DS. However, the relapse rate of IgG4-DS is high as also well-recognized in cases of IgG4-RD.

Table 16.2 Differential diagnosis between IgG4-related Mikulicz's disease (IgG4-DS) and Sjögren's syndrome (SS)

	IgG4-related Mikulicz's disease	Sjögren's syndrome
Age	50–70	40–50
Sex	Male = Female?	Female ≫ Male
Gland swelling	Lacrimal/submandibular/parotid	Parotid
	Lower frequency of apoptosis	Apoptosis of acinar/ductal
Keratoconjunctivitis sicca	Reversible	Mild-severely impaired
Salivary secretion	Reversible	Mild-severely impaired
Sclerosing pancreatitis	7–10 %	No
Retroperitoneal fibrosis	20 %	No
Serum IgG4 (>135 mg/dl)	>80 %	Negative
Anti-SSA/SSB antibodies	Negative	Positive 70 %
Corticosteroid response	Prompt	Almost ineffective

Modified from Yamamoto et al. [14]

Differences Between IgG4-Mikulicz's Disease and IgG4-Küttner Tumor Based on Our Case Series

IgG4-related sialadenitis is observed in IgG4-DS and IgG4-related Küttner tumor (IgG4-KT; gland swelling is noted only in the submandibular glands; IgG4-related submandibular disease) [1]. Because sialadenitis is a common manifestation in both IgG4-MD and IgG4-KT, as in IgG4-RD, it is said to be difficult to set a strict boundary between IgG4-MD and IgG4-KT [7]. Histological evidence is needed to differentiate between these two clinical entities. Küttner tumor was first described in 1896 as a rarely occurring chronic inflammatory disorder of the salivary glands, most commonly the submandibular glands, manifesting as a palpable hard tumor; this condition is also referred to as unilateral sclerosing sialadenitis [18]. As the differential diagnosis between IgG4-KT and neoplasm is difficult, the entity came to be referred to as KT. Prior to proposition of the concept of IgG4-RD, a significant proportion of cases may have been diagnosed as KT [1]. As KT has also been recognized to result from stones in the Wharton duct [18], it has been classified into classical KT and IgG4-KT. Geyer JT clarified the histopathologic differences between classical KT and IgG4-KT [19]. Tiemann et al. revealed a monoclonal cytotoxic T-cell population in the affected salivary glands [20], which suggested that in such cases, KT is IgG4-RD. Takano revealed serologic and histopathologic differences between IgG4-DS and IgG4-KT, such as the mean IgG4 concentration was significantly higher in IgG4-DS than in IgG4-KT [21]. It may be said that the disease activity in IgG4-KT is less than that in IgG4-DS. We diagnosed IgG4-KT based on findings such as persistent bilateral swelling of only the submandibular glands detectable by computed tomography and/or FDG-PET, abundant IgG4-bearing plasma cell infiltration with fibrosis in the submandibular glands on histopathologic examination, and elevated serum IgG4 concentrations (>135 mg/dl) on serological testing (Figs. 16.3 and 16.4).

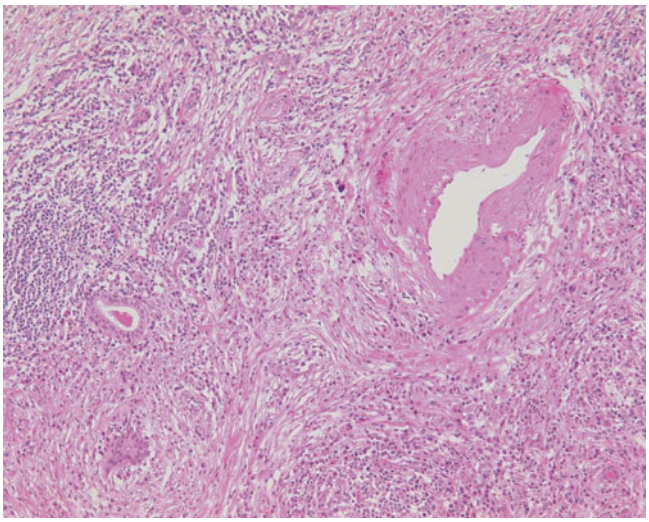

Fig. 16.3 Submandibular gland biopsy specimen showed dense lymphoplasmacytic infiltration with fibrosis

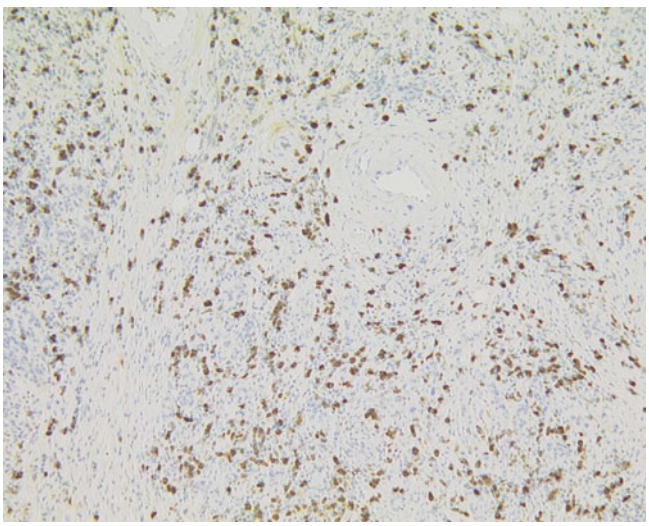

Fig. 16.4 IgG4-bearing plasma cell infiltrations were noted in biopsy specimen of the submandibular gland

Table 16.3 IgG4-related Mikulicz's disease (IgG4-DS) and IgG4-related Küttner disease (IgG4-KT)

Differences between AIP with IgG4-DS and IgG4-KT			
	IgG4-DS ($n=10$)	IgG4-KT ($n=13$)	p
Mean age at onset	63 (52–72)	68 (51–77)	N.S.
Gender ratio (M/F)	6/4 (60 %)	9/4 (69.2 %)	N.S.
Serum IgG (mg/dl)	2,839	2,923	N.S.
Serum IgG4 (mg/dl)	976	888	N.S.
DS/KT precede	*10/2 (83 %)*	*3/10 (23 %)*	*0.005*
Jaundice	5/5 (50 %)	10/3 (76.9 %)	N.S.
Diffuse pancreas swelling	1/9 (90 %)	9/4 (69.2 %)	N.S.
OOI (other than DS/KT)	5/5 (50 %)	11/2 (84.6 %)	N.S.
Relapse	5/5 (50 %)	4/9 (30.8 %)	N.S.
Cancer development	0/10 (0 %)	3/10 (23.1 %)	N.S.

N.S. not significant, *AIP* autoimmune pancreatitis, *IgG4-DS* IgG4-related dacryoadenitis and sialadenitis, *IgG4-KT* IgG4-related Küttner tumor, *M F* male female, *DS/KT precede* IgG4-related dacryoadenitis and sialadenitis/IgG4-related Küttner tumor precede, *OOI* other organ involvement (sclerosing cholangitis, retroperitoneal fibrosis, idiopathic intestinal pneumonitis)

In order to clarify the differences, we retrospectively studied 13 patients with IgG4-KT and 10 patients with IgG4-DS, the patient characteristics illustrated in Table 16.3. All of the patients had been admitted to the Department of Gastroenterology of our hospital; therefore, we could not include IgG4-KT cases without associated AIP, which was a limitation of our study. There were no differences between the two conditions in the mean age at onset, gender ratio, serum IgG level, serum IgG4 level, presence/absence of jaundice, presence/absence of diffuse pancreatic swelling, other organ involvement, relapse, and cancer development. However, IgG4-DS tended to precede the AIP, and in many cases, IgG4-KT was accidentally detected on PET-CT performed during the course of AIP. Diffuse pancreatic swelling tended to be recognized more frequently in patients with IgG4-DS than in patients with IgG4-KT. However, other organ involvement was detected more frequently in IgG4-KT than in IgG4-DS. It could also be said that the inflammation is more aggressive in IgG4-MD than in IgG4-KT. Regarding treatment, IgG4-KT is also treated with CST.

IgG4-Mikulicz's Disease and Autoimmune Pancreatitis Based on Our Case Series

IgG4-DS has been regarded as a component of other organ involvement (OOI) in cases with type 1 AIP. AIP is sometimes associated with Mikulicz's disease (MD; IgG4-DS); however, the significance of IgG4-DS appearing during the clinical course of AIP remains uncertain. We reported that AIP patients with IgG4-DS occurring during the clinical course might show a more hyperactive disease state as compared to AIP patients without IgG4-DS [13]. Although this study was small and retrospective in nature, we clarified that AIP patients presenting with IgG4-DS ($n=5$) tended to manifest different clinical features as compared to AIP patients without IgG4-DS ($n=23$), such as earlier onset, predilection for females, diffuse pancreatic swelling, and high serum titers of IgG4. In addition, in AIP patients with IgG4-DS, the latter tends to precede the gastroenterological event, suggesting that IgG4-DS may serve as a warning sign of subsequent AIP development [13].

Recently, Kuruma et al. compared patients with AIP associated with IgG4-DS, with AIP not associated with IgG4-DS, and IgG4-DS not associated with AIP. They concluded that the relapse rate in the patients with AIP plus IgG4-DS was significantly higher than that in the AIP patients without IgG4-DS; therefore, maintenance CST therapy might be indicated in the former group to reduce the likelihood of relapse [22]. Based on the results of this study, we might say that AIP associated with IgG4-DS is a potentially hyperactive disease state, showing a strong tendency toward relapse [13, 23].

What is the incidence of AIP occurring in association with IgG4-DS? A multicenter long-term outcome study of AIP was published, which showed that IgG4-DS and/or IgG4-KT occurred at a frequency of only 7 % in patients with AIP [23]. Until now, we have encountered 126 type 1 AIP patients, of which 10 (10/126; 7.9 %) had IgG4-DS and 13 (13/126; 10.3 %) had IgG4-KT (Table 16.4). On the other hand, Yamamoto reported that IgG4-DS was associated with AIP in 20 % of cases [17]. This represented a discrepancy of about 10 % in the incidence; however, the patients who initially developed AIP showed a tendency towards subsequently development of IgG4-DS. IgG4-DS preceded AIP in 80 % (8/10) of the cases. This could be a reflection of the author's subspecialty.

We investigated the differences in the features between AIP patients with/without IgG4-DS. There were no significant differences in the mean age of onset, gender ratio, presence/absence of jaundice, extent of pancreatic swelling detected on computed tomography, presence/absence of

Table 16.4 Differences between autoimmune pancreatitis (AIP) with/without IgG4-DS.

Differences between AIP with/without IgG4-DS			
	AIP + IgG4-DS ($n = 10$)	AIP ($n = 100$)	*p*
Mean age at onset	63 (52–72)	64 (25–93)	N.S.
Gender ratio (M/F)	6/4 (60 %)	76/24 (76 %)	N.S.
Serum IgG (mg/dl)	*2,733*	*1,936*	*0.021*
Serum IgG4 (mg/dl)	*976*	*384*	*0.0004*
Jaundice	5/5 (50 %)	50/50 (50 %)	N.S.
Duodenal papillitis	*9/9 (100 %)*	*36/60 (60 %)*	*0.0198*
Diffuse pancreas swelling	9/1 (90 %)	64/31 (67.3 %)	N.S.
OOI (SC, RPF, IIP)	5/5 (50 %)	45/55 (45 %)	N.S.
Relapse	5/5 (50 %)	34/66 (34 %)	N.S.
Cancer development	0/10 (0 %)	22/78 (22 %)	N.S.

N.S. not significant, *AIP* autoimmune pancreatitis, *IgG4-DS* IgG4-related dacryoadenitis and sialadenitis, *M/F* male/female, *OOI* other organ involvement (*SC* sclerosing cholangitis, *RPF* retroperitoneal fibrosis, *IIP* idiopathic intestinal pneumonitis)

other organ involvements, such as sclerosing cholangitis at the hilar part of the bile duct, relapse rate, or incidence of cancer between the two groups. The serum IgG and IgG4 levels were significantly higher in the AIP patients with IgG4-DS than in those without IgG4-DS. In addition, duodenal papillitis, a suggested risk factor for relapse [24], was recognized significantly more frequently in AIP patients with IgG4-DS than in those without IgG4-DS. These results suggest that AIP-associated IgG4-DS is a hyperactive disease state with a propensity to relapse. Therefore, we agree that CST therapy, including maintenance CST therapy, is required in such patients [22].

Prognosis and Prospects of IgG4-Mikulicz's Disease

IgG4-DS is a benign disease that is not fatal and can be controlled by CST; however, relapses are common [25]. Our data showed that AIP with IgG4-DS was a more hyperactive disease state than AIP without IgG4-DS. The reported relapse rate of AIP is 30–40 %, and relapse usually occurs within 3 years of initiation of CST therapy [26]. Therefore, maintenance CST treatment for a sufficient duration is of value, and low-dose CST therapy for more than 3 years is recommended to reduce the relapse rate [26]. We believe that CST is the standard treatment for IgG4-DS, while spontaneous remission (SR) can occur of AIP [24]; there are no case reports of IgG4-DS showing SR.

What should we do in cases of IgG4-DS showing relapse? Readministration of CST may be effective; however, refractory cases might be encountered among AIP patients with IgG4-DS. The mechanism underlying the onset of IgG4-RD, including IgG-DS, remains unknown, Th2-dominant disease has been suggested as one of the aspects of IgG4-RD. Zen et al. described that AIP was characterized by infiltration of helper 2 and regulatory T (Treg) cells, which secrete various cytokines, such as interleukin 10 (IL-10) and tumor growth factor-β (TGF-β). Furthermore, the expression level of FOXP-3 messenger RNA (mRNA) was significantly increased in patients with AIP, and immunohistochemical staining revealed increases in the number of CD4+ CD25+ FOXP3+ cells. Treg may be involved in in situ production of IL-10 and TGF-β, which could be followed by IgG4 class switching and fibroplasia [11].

Recently, the efficacy of immunomodulators or rituximab for the treatment of refractory AIP was studied. B-cell deletion therapy using rituximab, a monoclonal antibody directed against the CD20 antigen on the B cells, has been tried and appears promising [25]. Therefore, although standard treatment for IgG4-DS has been CST, immunomodulator or rituximab therapy should also be evaluated for refractory cases of IgG4-DS.

Is IgG4-DS a risk factor for cancer? There have been only a few papers on the risk of cancer associated with IgG4-DS. Regarding cancer development, there are two reports of an association [27, 28]. Shiokawa mentioned that AIP might develop as a paraneoplastic syndrome in some patients based on a study of the standardized incidence ratio for cancer development, the risk during the first year after AIP diagnosis [27]. Yamamoto also stressed that recognition of the possible risk of cancer development in patients with IgG4-RD is essential and that these patients need to be carefully followed up [28]. In our series of 126 patients, 22 developed cancer (22/126; 17 %; data not published). Out of these, four patients developed pancreatic cancer within 5 years of the onset of AIP, which was not associated with IgG4-DS. We believe that cancer could develop by chance in patients with IgG4-RD, because the latter is usually diagnosed in elderly patients who are already predisposed to cancer. However, due to the tendency for cancer development in these patients, irrespective of the nature of the association, close surveillance for cancer is recommended [28].

References

1. Stone JH, Khosrroshahi A, Desphande V, et al. IgG4-related disease: recommendations for the nomenclature of this condition and its individual organ system manifestations. Arthjritis Rheum. 2012;64:3061–7.
2. Masaki Z, Sugai S, Umemura H. IgG4-related diseases including Mikulicz's disease and sclerosing Pancreatitis: diagnostic insight. J Rheum. 2010;37:1380–5.
3. Mikulicz J.Über eine eigenartige symmetrishe Erkrankung der Tranen und Mundspeicheldrusen. Stuttgart: Beitr.z. Chir. Fesrschr. F. Theodor Billroth;1892. pp. 610–30.
4. Sjögren H. Zur Kenntnis der Keratocojunctivitis Sicca (Keratitis filiformis bei Hypofunktion der Tranendrusen). Acta Ophthalmol. 1933;11(suppl II):1–151.
5. Morgan WS, Castleman B. A clinicopathologic study of "Mikulicz's disease". Am J Pathol. 1953;29:471–503.
6. Yamamoto M, Ohara M, Suzuki C, et al. Elavated IgG4 concentrations in serum of patients with Mikulicz's disease. Scand J Rheumatol. 2004;33:432.
7. Umehara H, Okazaki K, Masaki Y, et al. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. Mod Rheumatol. 2012;22:1–14.
8. Yoshida K, Toki F, Takeuti T, et al. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. Dig Dis Sci. 1995;40:1561–8.
9. Sarles H, Sarles JC, Muratore R, Guien C. Chronic inflammatory sclerosis of the pancreas-an autonomous pancreatic disease? Am J Dig Dis. 1961;6:688–98.
10. Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med. 2001;344:732–8.
11. Zen Y, Fujii T, Harada K, et al. Th2 and regulatory immune reactions are increased in immunoglobin G4-related sclerosing pancreatitis and cholangitis. Hepatology. 2007;45:1538–46.
12. Tanaka A, Moriyama M, Nakashima H, et al. Th2 and regulatory immune reactions contribute to IgG4 production and the initiation of Mikulicz's disease. Arthritis Rheum. 2012;64(1): 254–63.
13. Kubota K, Wada T, Kato S, et al. Highly active state of autoimmune pancreatitis with Mikulicz's disease. Pancreas. 2010;39: e6–10.
14. Yamamoto M, Takahashi H, Ohara M, et al. A new conceptualization for Mikulicz's disease as an IgG4-related plasmacytic disease. Mod Rheumatol. 2006;16:335–40.
15. Yamamoto M, Takahashi H, Sugai S, et al. Clinical and pathological differences between Mikulicz's disease and Sjogren's syndrome. (IgG4-related plasmacytic exocrinopathy). Autoimmunity Rev. 2005;4:195–200.
16. Zen Y, Nakamura Y. IgG4-related disease: cross sectional study of 114 cases. Am Surg Pathol. 2010;34:1812–9.
17. Tubota K, Fujita H, Tadano K. Abnormal expression and function Fas ligand of lacrimal glands and peripheral blood in Sjogren's syndrome patients with enlarged exocrine glands. Clin Exp Immunol. 2002;129:177–82.
18. Küttner H. Ueber entzundliche tumoren der submaxillarspeicheldruse. Beitr Klin Chir. 1896;15:815–34.
19. Geyer JT, Ferry JA, Harris NL, et al. Chronic sclerosing sialadenitis (Kuttner) is an IgG4-associated disease. Am J Surg Pathol. 2010;34:202–10.
20. Tiemann M, Teymoortash A, Schrader C, et al. Chronic sclerosing sialadenitis of the submandibular gland is mainly due to a T lymphocytic immune reaction. Mod Pathol. 2002;15:845–52.
21. Takano K, Yamamoto M, Takahashi H, et al. clinicopathologic similarities between Mikulicz disease and Kuttner tumor. Am J Otolaryngology. 2010;31:429–34.
22. Kuruma S, Kamisawa T, Tabata T, et al. Clinical characteristics of patients with autoimmune pancreatitis with or without Mikulicz's disease and Mikulicz's disease alone. Gut Liver. 2013;7:96–9.
23. Hart PA, Kamisawa T, Witzig TE, Clain JE, Gleeson FC, Klebig RR, et al. Long term outcomes of autoimmune pancreatitis :multicenter, international analysis. Gut. 2013;62:1771–6.
24. Kubota K, Iida H, Fujusawa T, et al. Clinical factors predictive of spontaneous remission or relapse of autoimmune pancreatitis. GIE. 2007;66:1142–51.
25. Hart PA, Topazian MD, Witzig TE, et al. Treatment of relapsing autoimmune pancreatitis with immunomodulators and rituximab: the Mayo Clinic experience. Gut. 2013;62:1607–15.
26. Kamisawa T, Shimosegawa T, Okazaki W, et al. Standard steroid treatment for autoimmune pancreatitis. Gut. 2009;58:1504–7.
27. Shiokawa M, Kodama Y, Yoshimura K, et al. Risk of cancer in patients with autoimmune pancreatitis. Am J Gastroenterol. 2013;108:610–7.
28. Yamamoto M, Takahashi H, Tabeya T, et al. Risk of malignancies in IgG4-related disease. Mod Rheumatol. 2012;22:414–8.