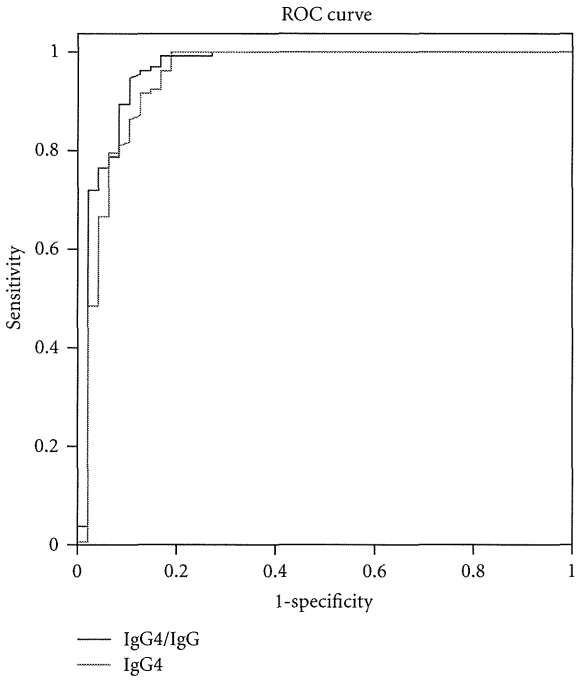

FIGURE 1: ROC curves of absolute serum IgG4 concentration (green) and serum IgG4/IgG ratio (blue). The two curves were almost identical.

histopathology and clinical course compatible with IgG4-RD (Table 2). All 4 patients were diagnosed with IgG4-RD based on a serum IgG4/IgG ratio >8%.

In contrast, neither a serum IgG4 cutoff of >135 mg/dL nor a serum IgG4/IgG ratio >8% was adequate for the diagnosis of four patients with MCD and one each with B-cell lymphoma, scleritis, and Sjögren's syndrome, because all of these patients had hyper-IgG4-globulinemia associated with polyclonal gammopathy. We therefore estimated the sensitivity and specificity of various IgG4/IgG ratios (Table 3). We found that the ROC curves for absolute serum IgG4 concentration and serum IgG4/IgG ratio were almost identical (Figure 1).

3.2. Analysis of IgG4+ Cells in Tissue Samples. We also assessed the ability of the ratio of IgG4+/IgG+ plasma cell ratios in 5 HPFs of tissue samples to diagnose IgG4-RD. We found that a ratio >40% had a sensitivity of 94.4% and a specificity of 85.7% (Table 4). Although >10 IgG4+ cells per HPF had a sensitivity of 100%, They had specificities of only 38.1%.

In tissues containing both fibrotic and nonfibrotic areas, we counting the number cells in each part showed that fibrotic areas contained fewer IgG4+ cells (Table 5).

We also assessed the ability of obliterative phlebitis and storiform fibrosis to diagnose IgG4-RD. Although both had specificities of 100%, their sensitivities were not very high (Table 4).

TABLE 2: Serum IgG and IgG4 concentrations and IgG4/IgG4 ratio of patients with false-positive and false-negative diagnoses of IgG4-RD.

False positives			
Diagnosis	IgG (mg/dL)	IgG4 (mg/dL)	IgG4/IgG
(1) MCD	7,080	4,560	64.4%
(2) MCD	4,420	690	15.6%
(3) B-cell lymphoma	2,510	456	18.2%
(4) MCD	2,960	295	10.0%
(5) MCD	2,476	295	11.9%
(6) B-cell lymphoma	4,010	271	6.8%
(7) Scleritis	2,900	232	8.0%
(8) Sarcoidosis	1,380	189	13.7%
(9) Sjögren's syndrome	3,920	171	4.4%
(10) Malignant lymphoma	1,930	141	7.3%
False negatives			
Diagnosis	IgG(mg/dL)	IgG4(mg/dL)	IgG4/IgG
(1) IgG4-RD	1,149	125	10.9%
(2) IgG4-RD	1,210	123	10.2%
(3) IgG4-RD	1,228	111	9.0%
(4) IgG4-RD	1,260	106	8.4%

IgG4-RD: IgG4-related disease; MCD: multicentric Castleman's disease.

TABLE 3: Sensitivity and specificity of serum cutoff values in the diagnosis of IgG4-RD.

	Sensitivity	Specificity
IgG4 > 135 mg/dL	97.0%	79.6%
IgG4/IgG > 5%	99.2%	83.3%
IgG4/IgG > 6%	97.0%	83.3%
IgG4/IgG > 7%	97.0%	85.4%
IgG4/IgG > 8%	95.5%	87.5%
IgG4/IgG > 9%	92.4%	89.6%
IgG4/IgG > 10%	89.4%	91.7%

4. Discussion

Serum IgG4 >135 mg/dL has been widely accepted as a cutoff value for diagnosis of IgG4-RD. Although this concentration was determined by comparing patients with IgG4-related sclerosing pancreatitis and those with pancreatic cancer [1], it has also been used to diagnose IgG4-RD involving other organs. For example, we have utilized this cutoff value as a diagnostic criterion for IgG4-related Mikulicz's disease [5] and IgG4-related kidney disease [12], and, in 2011, it was adopted in the comprehensive clinical diagnostic criteria of IgG4-related diseases [11]. Most patients with IgG4-RD show multiple organ involvement at diagnosis, with both high absolute serum IgG4 concentrations and serum IgG4/IgG ratios. However, some patients with early and/or limited stage IgG4-RD do not present with high IgG4-globulinemia (Figure 2), with some not having IgG4 concentrations >135 mg/dL. We have therefore tested the

Table 4: Sensitivity and specificity of pathological findings for the diagnosis of IgG4-RD.

	Sensitivity	Specificity
IgG4+/IgG+ > 10%	100.0%	33.3%
IgG4+/IgG+ > 20%	100.0%	47.6%
IgG4+/IgG+ > 30%	100.0%	71.4%
IgG4+/IgG+ > 40%	94.4%	85.7%
IgG4+/IgG+ > 50%	94.4%	95.2%
IgG4+cells/HPF > 10	100.0%	38.1%
IgG4+cells/HPF > 20	97.2%	42.9%
IgG4+cells/HPF > 30	97.2%	61.9%
IgG4+cells/HPF > 40	91.7%	66.7%
IgG4+cells/HPF > 50	86.1%	71.4%
Obliterative phlebitis	54.5%	100.0%
Storiform fibrosis	31.4%	100.0%
Eosinophilia	42.9%	100.0%
Fibrosis	91.4%	82.4%
Lymphocytic infiltration	100.0%	16.7%

Table 5: Recounting in each areas of 17 samples containing both fibrotic and nonfibrotic parts. All patients were diagnosed with IgG4-RD but had biopsy specimens that were too small (samples 1–14) or with relatively large fibrotic areas inadequate to diagnose IgG4-RD (samples 15–17). All samples had >10 IgG4+ cells per HPF.

Tissue	Fibrosis+	Fibrosis−
(1) Pancreas	76.6%	94.0%
(2) Submandibular gland	75.4%	89.2%
(3) Submandibular gland	72.1%	73.0%
(4) Submandibular gland	72.1%	97.3%
(5) Submandibular gland	71.8%	99.1%
(6) Pancreas	67.7%	95.0%
(7) Labial salivary glands	65.0%	70.8%
(8) Lung	58.9%	94.4%
(9) Submandibular gland	49.2%	68.9%
(10) Gall bladder	48.6%	94.0%
(11) Bile duct	46.8%	95.0%
(12) Submandibular gland	46.2%	74.1%
(13) Orbit	44.2%	94.4%
(14) Submandibular gland	43.6%	95.0%
(15) Submandibular gland	33.3%	95.0%
(16) Submandibular gland	25.9%	51.5%
(17) Labial salivary glands	8.0%	76.2%

ability of alternative criteria to diagnose for IgG4-RD. Although we found that a serum IgG4/IgG ratio >5% had the highest sensitivity, the normal ratio is about 5-6%, making this cut off value misleading. An IgG4/IgG ratio >8% had a sensitivity similar to that of absolute IgG4 >135 mg/dL, but a greater specificity, enabling us to diagnose 4 patients with lower absolute IgG4 concentrations as having

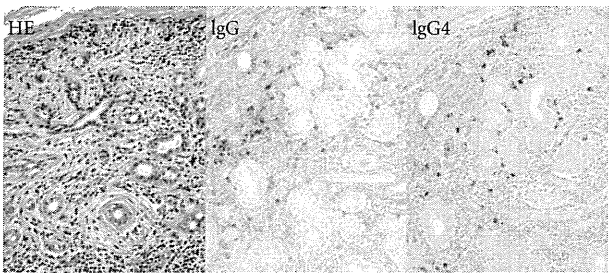

Figure 2: Histopathology of a patient with limited stage IgG4-related dacryoadenitis. A 35-year-old woman presented with swelling of her bilateral lacrimal glands. Her serum IgG and IgG4 concentrations were 1,149 mg/dL and 125 mg/dL, respectively, and her serum IgG4/IgG ratio was 10.88%. Histopathological examination of a lacrimal gland biopsy revealed IgG4+ plasma cell infiltration, with an IgG4+/IgG+ cell ratio of 74.7%, and 53 IgG4+ cells per HPF, although sclerotic changes were not severe. Treatment with prednisolone 20 mg/day resulted in a rapid and dramatic improvement in symptoms. Although using an absolute serum IgG4 cutoff concentration of >135 mg did not result in diagnosis of IgG4-RD, her clinical course and histopathology were typical of IgG4-RD. However, using a serum IgG4/IgG ratio >8% as a cutoff value resulted in a diagnosis of IgG4-RD.

IgG4-RD (Table 2). Since the standard cut off of absolute IgG4 >135 mg/dL demonstrated excellent sensitivity and specificity, it should be utilized, except for patients with early and/or limited IgG4-RD, for whom we propose using an IgG4/IgG ratio >8%.

Careful diagnosis is required in patients with lower IgG4 concentrations, since those patients may have other distinct disorders with different clinical features than IgG4-RD. Patients with untypical clinical courses, including glucocorticoid refractoriness, should be reassessed.

IgG4+/IgG+ plasma cell ratios in tissue >40% and >50%, and >10 IgG4+ cells per HPF have been used for the diagnosis of IgG4-RD. We found that an IgG4+/IgG+ cell ratio >40% in tissue had a sensitivity of 94.4% and a specificity of 85.7% in the diagnosis of IgG4-RD. We also found that IgG4+ plasma cell concentrations in tissue were diminished in fibrotic tissue areas, suggesting that a ratio >40% is a better histopathologic cutoff value. The presence of obliterative phlebitis and storiform fibrosis demonstrated specificities of 100%, but their sensitivities were much lower, indicating that these findings would be useful when added to, but not in place of, other results.

Since patients with disorders such as MCD and lymphoma may demonstrate hyper-IgG4-gammaglobulinemia and massive IgG4+ plasma cell infiltration in tissue, serum IgG4 concentration and IgG4+ cells in tissue are not specific indicators of IgG4-RD. Rather, a diagnosis of IgG4-RD should be based on the overall balance of clinical features, such as disease distribution throughout the body, clinical course, serum concentrations, and histopathology.

The pathologic consensus statement of the first international Symposium on IgG4-RD in Boston did not adopt IgG4+/IgG+ cell ratio in tissue as diagnostic, although it

did suggest cutoffs for numbers of IgG4+ cells in HPFs of various organs. This, however, may be confusing for many pathologists and physicians. Although pathologic findings are very important in the diagnosis for IgG4-RD, clinical features and serological findings should be included.

Recently, some patients with IgG4-RD were found to have lymphoma [13, 14] and other types of cancer [15, 16]. Thus IgG4-RD may not always be a benign disease with good prognosis. Many patients referred to our centers with glucocorticoid refractory IgG4-RD were diagnosed incorrectly, suggesting the need for more accurate diagnostic criteria for these diseases.

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ORIGINAL ARTICLE

Risk of malignancies in IgG4-related disease

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Abstract IgG4-related disease (IgG4-RD) is considered a systemic, chronic, and inflammatory disorder that is characterized by the enlargement of involved organs, elevated levels of IgG4, and abundant infiltration of plasmacytes with IgG4 and fibrosis in involved organs. It is necessary to differentiate IgG4-RD from malignant tumors. Recently we have looked at case reports of IgG4-RD with malignancy that was discovered at systemic screening. In this study, we analyzed the relationship between IgG4-RD and malignancies. The study subjects were 106 patients with IgG4-RD who had been referred to our hospital since April 1997. We analyzed the clinical characteristics of IgG4-RD patients who had cancer that was observed upon the initial diagnosis of IgG4-RD or that occurred during an average follow-up period of 3.1 years. Using data from national cancer registries that monitor cancer incidence in Japan, we evaluated the standardized incidence ratio (SIR) for malignancies in IgG4-RD. Malignancies were observed in 11 of the IgG4-RD patients (10.4%). The malignancies were all different and included lung cancer, colon cancer, and lymphoma. With the exception of the age at which the IgG4-RD diagnosis was made, there were no common features in patients with cancer and those without. The SIR for these malignancies in IgG4-RD was 383.0, which was higher than that for the general population. We should be cognizant of the possible existence of malignancies in patients with IgG4-RD at the time of diagnosis and during follow-up care.

Keywords Cancer · IgG4 · Lymphoma

Introduction

IgG4-related disease (IgG4-RD) is characterized by enlargement of the affected organs along with elevated levels of serum IgG4, and abundant infiltration of IgG4-bearing plasma cells and fibrosis. IgG4-RD is a new concept of systemic and chronic inflammation [1], and usually includes Mikulicz's disease (MD) and autoimmune pancreatitis (AIP) [2, 3]. IgG4-RD is an important disease for rheumatologists, as it often presents as positive for rheumatoid factor, and patients have hypocomplementemia and elevated levels of circulating immune complexes [4].

Previously, we have often diagnosed IgG4-RD simply by the elevation of serum IgG4, but it has since been shown that differential diagnosis is important so as to exclude the possibility of malignant tumors. IgG4-RD with pancreatic cancer has often been reported in patients with AIP [5, 6]. We extracted IgG4-RD cases complicated by malignancies at diagnosis or during the follow-up of patients who were registered in the SMART database (Sapporo Medical University and Related institutes database for investigation and best Treatments of IgG4-RD), and analyzed their clinical characteristics. We examined whether the cancer incidence in these patients was higher than that in the general population.

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Patients, materials, and methods

The subjects were 106 patients with IgG4-RD, who had visited Sapporo Medical University Hospital beginning in April 1997 and were registered in the SMART database. The patients comprised 50 males and 56 females, with a mean age of 59.02 years at the onset of IgG4-RD, and 60.85 years at the time of diagnosis. Of the 106 patients, 67 were diagnosed with MD, 17 with Küttner's tumor (chronic sclerosing sialadenitis), 12 with IgG4-related dacryoadenitis, and 10 with AIP.

These patients satisfied the tentative criteria for IgG4-RD that consisted of: (1) enlargement of the affected organs; (2) elevated levels of serum IgG4 (>1.35 g/L); and (3) abundant infiltration of IgG4-positive plasmacytes and fibrosis. We separated the patients with diagnoses of IgG4-RD complicated by malignancies and those who developed complications during follow-up (average 3.1 years, maximum 14.3 years) and analyzed their clinical features. We calculated the standardized incidence ratio (SIR) for malignant neoplasms in IgG4-RD using the aforementioned database employed in the monitoring of cancer incidence in Japan [7].

Results

Two patients with malignant neoplasms

Case 1

A 30-year-old woman noticed a mass in her left breast in the winter of 1999. A nipple-areola-sparing mastectomy was performed and revealed a pathologic, inflammatory pseudotumor. Later that same year, the patient was admitted to our hospital; a biopsy taken from her right eyelid disclosed mucosa-associated lymphoid tissue (MALT) lymphoma of the lacrimal gland. Southern blotting IgH gene rearrangement was detected. There were additional complications due to mediastinal lymphoma lesions, and radiation therapy and chemotherapy were administered. The patient was then in remission until 2008, when the enlargement of bilateral submandibular glands was observed. The serological data showed no antinuclear antibody or anti-SS-A antibody. She did not suffer from sicca symptoms. The Saxon's test result was 3.55 g/2 min and the Schirmer's test results were 12 mm/5 min for the right eye, and 14 mm/5 min for the left eye. We noticed an elevation of serum IgG4 (13.50 g/L) and performed a submandibular gland biopsy, which revealed prominent infiltration of IgG4-bearing plasmacytes and fibrosis. There was no IgH rearrangement in the submandibular gland. We retrospectively analyzed the breast and lacrimal gland specimens taken in 1999; both showed remarkably high IgG4-positive plasma cell infiltration. The patient was diagnosed with MALT lymphoma, which subsequently led to MD.

Case 2

A 77-year-old woman became aware of bilateral submandibular enlargements in June 2009. Otolaryngologists suspected Sjögren's syndrome (SS), and the patient was admitted to our hospital. There was no evidence of sicca syndrome. Serological analysis revealed negativity for anti-SS-A antibody, but did show elevated levels of serum IgG4 (4.48 g/L). The submandibular gland biopsy revealed prominent infiltration of plasmacytes with IgG4. IgH rearrangement was not found. We diagnosed Küttner's tumor (chronic sclerosing sialadenitis). Positron emission tomography (PET) revealed no other accumulation of FDG except in the submandibular glands. Administration of glucocorticoid led to remission; however, 1 year after the glucocorticoid was begun, a small ulcer appeared at the right edge of her tongue. The patient underwent oral surgery, and a biopsy of the ulcer disclosed squamous cell carcinoma.

The SMART database registry, which included our 106 patients, showed 11 patients (10.4%) with IgG4-RD with either a concurrent diagnosis of malignancy, or the development of malignancies during follow-up. These patients consisted of three with MD (n = 69, 4.5%), five with Küttner's tumor (chronic sclerosing sialadenitis) (n = 17, 29.4%), one with IgG4-related dacryoadenitis (n = 12, 8.3%), and two with AIP (n = 10, 20.0%). Breast, colorectal, lung, ovarian, lingual, renal, prostate cancer, and hematological malignancies such as malignant lymphoma were apparent (Table 1).

Table 1 Profile of patients with IgG4-related disease complicated by malignancy

IgG4-related disease (n = x)	No. of Pts with Ca.	Malignancy and frequency
Mikulicz's disease (n = 69)	3	4.5% breast, ovary, MALT
Küttner's tumor (n = 17)	5	29.4% colon (2), lung, lingual, NHL
IgG4-related dacryoadenitis (n = 12)	1	8.3% lung
Autoimmune pancreatitis (n = 10)	2	20.0% renal, prostate
Total (n = 106)	11	10.40%

No. number, *Pts* patients, *Ca.* cancer, *MALT* mucosa-associated lymphoid tissue lymphoma, *NHL* non-Hodgkin's lymphoma

Temporal relationship between diagnosis of IgG4-RD and malignancies

A simultaneous diagnosis of IgG4-RD and malignancies was confirmed in 2 of the 11 patients. It was a tendency that the discovery of malignancies was often observed in the first 2 years of follow-up. There were four patients in whom IgG4-RD had developed first (of whom two showed malignant lymphoma) and five patients in whom malignancies had developed first.

Clinical characteristics of the patients with malignancies

Comparing the malignancy and non-malignancy groups of IgG4-RD patients, the average ages at IgG4-RD onset were 67.64 and 58.02 years, respectively, and the mean ages at IgG4-RD diagnosis were 70.27 and 59.76 years, respectively. In the malignancy group, age at onset and age at diagnosis were both significantly higher than these ages in the group without malignancies (both $P < 0.05$). The sex ratio was 6:5 in favor of males in the malignancy group, and 44:51 in favor of females in the non-malignancy group. There was no significant difference in sex ratios between the groups. Serological data showed that IgG and IgG4 levels were 22.11 and 5.82 g/L, respectively, in the malignancy group, and 23.61 and 7.55 g/L, respectively, in the non-malignancy group. There was a tendency towards higher serum IgG and IgG4 concentrations in the non-malignancy group, but this was not statistically significant. As for levels of complement and circulating immune complexes, the malignancy group presented with levels of 42.4 U/mL and 4.4 μg/mL, respectively, and the non-malignancy group presented with levels of 39.8 U/mL and 7.3 μg/mL, respectively. The levels of rheumatoid factor were 16.6 U/mL in the malignancy group and 35.2 U/mL in the non-malignancy group. There were no significant differences in these data between the two groups.

Standardized incidence ratio for cancers in IgG4-related disease

We evaluated the SIR for cancers in IgG4-RD, using the database of national cancer registries in the monitoring of cancer incidence in Japan (2005) [7]. We found from this registry that the SIR for malignancies in male patients with IgG4-RD was 331.1, and that in female patients with IgG4-RD was 471.6. The total was 383.0, which was very high (Table 2).

Discussion

IgG4-RD is a new disease concept defined as a systemic, chronic, and inflammatory disorder. Differentiation from malignant tumors in this disease is clinically very important, as it is characterized by enlargement of the involved

Table 2 Standardized incidence ratio for malignancies in IgG4-related disease

Standard population					IgG4-related disease				
Population aged more than 20 years in Japan, 2005					SMART, 2011				
Sex	Age (years)	Population	No. of Pts with Ca.	Incidence of Ca.[a]	No. of Pts with IgG4-RD	Expected No./1 year	Expected No./3.1 years	Observed No. (average 3.1 years)	Standardized incidence ratio[b]
Male	20–39	17,289,425	5,902	34.136	2	0.000683	0.002117	0	
	40–59	17,393,579	62,474	359.179	21	0.075427	0.233824	2	
	60–79	12,995,595	238,028	1,831.605	26	0.476217	1.476273	3	
	80–	2,033,533	65,458	3,218.930	1	0.032189	0.099786	1	
Male					50	0.584517	1.812003	6	331.13
Female	20–39	16,831,860	15,303	90.917	6	0.005455	0.016911	1	
	40–59	17,464,541	68,770	393.769	22	0.086629	0.268550	0	
	60–79	14,881,942	125,854	845.683	26	0.219877	0.681619	3	
	80–	4,305,564	64,687	1,502.405	2	0.030048	0.093149	1	
Female					56	0.342010	1.060231	5	471.60
Total		103,196,039	646,476	8,276.624	106	0.926527	2.872234	11	382.98

No. number, *Pts* patients, *Ca.* cancer, *IgG4-RD* IgG4-related disease, *SMART* Sapporo Medical University and Related institutes database for investigation and best Treatments of IgG4-RD

[a] Per 100,000 people

[b] The value for the standard population per year is regarded as 100

organs. Several IgG4-RD patients with pancreatic cancer have been reported over the past few years [5, 6, 8, 9].

It is known that PET is very useful for systemic evaluation in IgG4-RD [10, 11]. Whenever we make a diagnosis of IgG4-RD, we consult PET images. In some instances, we are presented with cases involving abnormal accumulation of FDG at lesion sites outside the involved organs; this is known as organic dysfunction of IgG4-RD. Upon further examination, we often find that the lesion is cancer. In such instances, PET is very useful for detecting cancer [12].

The present study demonstrated that malignancies occurred in 10.4% of IgG4-RD patients, approximately 3.5 times higher than the incidence of cancer in the general population. These results suggest that when diagnosing IgG4-RD, it is necessary not only to discriminate between the enlarged organs and cancers but also to consider the possibility of cancer complications in other parts of the body.

Malignancies as complications to IgG4-RD are categorized as lymphoma and non-lymphoid tumors. Lymphoma includes MALT lymphoma and non-Hodgkin lymphoma. Lymphoma can present as a background of chronic inflammation.

In SS, antigenic activation of B cells, together with oncogenic events, including p53 inactivation and bcl-2 activation, may play important roles in B-cell monoclonal proliferation and malignant transformation [13]. Zhang et al. reported that 2.2% of patients with primary SS developed malignancies during 4.4 years' follow-up [14]. The SIR for malignancies in SS was reported to be 1.5–3.3 [14, 15]. The SIR for lymphoma was higher, at 8.7–48.1 [14–16], but it was lower than that in IgG4-RD. The SIR for malignant lymphoma in SS showed an 18.8-fold risk [17], and that in IgG4-RD showed a 16.0-fold risk [18].

In our Case 1, it was difficult to interpret the temporal relationship between the onset of IgG4-RD and lymphoma, as the patient was retrospectively diagnosed with IgG4-RD; however, we assumed that the IgG4-RD was present before diagnosing lymphoma from the findings of the breast and lacrimal gland specimens. The SMART database revealed malignancies in two of the four patients in whom IgG4-RD progressed into lymphoma. Thus, it is suggested that lymphoma could occur in IgG4-RD as well as occurring in SS.

Various carcinomas were observed in the non-lymphoid tumors in our study. Cancers might be commonly associated in IgG4-RD patients. Case 2 was an example of the progression from IgG4-RD to cancer. Recently, it has been demonstrated that helper 2 and regulatory T cells play a role in the pathogenesis of IgG4-RD [19]. It is thus possible that regulatory T cells suppress not only the usual inflammation but also tumor immunity [20].

Considering the relationship between cancers and IgG4, it is known that in pancreatic cancer, but not AIP, there is an infiltration of IgG4-bearing plasmacytes in the normal pancreatic tissues surrounding cancers. Some patients with pancreatic cancer show elevated levels of serum IgG4 [21]. These phenomena do not apply only to pancreatic cancer. We found that pathological and serological phenomena associated with IgG4 in hepatocellular carcinoma resulted from chronic hepatitis and cirrhosis, scirrhous-type gastric cancer, and colorectal carcinoma (data not shown). Thus, we must avoid misdiagnosing a case that presents only with malignant neoplasms as IgG4-RD. We should recognize that IgG4 plays roles other than those in the pathogenesis of IgG4-RD and can be involved in tumor immunity. In the present analysis, we did not check whether the patients with malignancies had any relevant hereditary predisposition or environmental exposure factors, such as smoking for lung cancers, or human papillomavirus infection for oral cancers. We will have to analyze the relationships between IgG4-RD and malignancies by taking these factors into account.

In conclusion, malignancies are possible complications in patients with IgG4-RD. In this study, the complication rate of malignant neoplasms in patients with IgG4-RD was 10.4% and the SIR for malignancies in IgG4-RD was 383.0, which is substantially higher than that for the general population. As rheumatologists, we should consider the possibility that malignancies can be complications at the diagnosis or subsequent follow-up of IgG4-RD patients.

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Conflict of interest None.

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