Incidence of Malignancies in Patients with IgG4-related Disease

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Abstract

Objective It has been discussed whether IgG4-related disease (IgG4-RD), including autoimmune pancreatitis (AIP), is associated with malignancy; however, the issue has not been clarified.

Methods We analyzed 113 patients with IgG4-RD in whom malignancy was not diagnosed at the time of IgG4-RD onset and the follow-up period was longer than six months. A total of 95 patients had AIP. The mean follow-up period was 73 months. The incidence of the observed malignancies was compared with the expected incidence in an age- and sex-matched general Japanese population based on the Vital Statistics of Japan.

Results There were 15 malignancies (lung cancer in five patients, pancreatic cancer in two patients, gastric cancer in two patients, bile duct cancer in one patient, renal cancer in one patient, breast cancer in one patient, tongue cancer in one patient, malignant melanoma in one patient and acute myeloid leukemia in one patient) in 14 patients during the follow-up period. The calculated standardized incidence rate of the total malignancies was not significant, that is, 1.04 (95% CI 0.57-1.75).

Conclusion The incidence of total malignancies in IgG4-RD patients is similar to that observed in the general population. At present, it is reasonable to conclude that IgG4-RD is not associated with an increased incidence of total malignancies.

Key words: IgG4-related disease, autoimmune pancreatitis, malignancy, diabetes mellitus

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Introduction

Several case reports of malignancy in patients with autoimmune pancreatitis (AIP) and IgG4-related disease (IgG4-RD) have been published (1). For example, we previously reported the occurrence of malignancy in three of 42 patients with AIP (pancreatic cancer in one patient, lung cancer

in one patient and acute myeloid leukemia in one patient) (2). Kubota et al. described two cases of pancreatic cancer and two additional cases of other cancer (one case of breast cancer and one case of rectal cancer) (3). Takuma et al. reported the occurrence of cancer in six of 50 patients with AIP (lung cancer in four patients, esophageal cancer in one patient and prostate cancer in one patient) (4). Therefore, in addition to pancreatic cancer, several other malignancies

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nancies have been observed in patients with AIP. It is not unexpected that the processes of chronic inflammation and fibrosis observed in patients with IgG4-RD, including AIP, may increase the risk of malignancy. However, whether these malignancies are merely attributable to an older age remains unknown. In this study, we aimed to evaluate the incidence of malignancy in patients with IgG4-RD during follow-up, compared with that observed in the general Japanese population. We also aimed to clarify which factors are correlated with the occurrence of malignancy in IgG4-RD patients.

Materials and Methods

Since Yoshida et al. reported the concept of AIP in 1995 (5), various diagnostic criteria for AIP have been proposed (6-10). In this study, patients with type 1 AIP (IgG4-related AIP) whose diagnosis was eventually confirmed based on the international consensus diagnostic criteria (ICDC) (10) were enrolled. Among patients without AIP, those with IgG4-RD whose diagnosis was confirmed based on comprehensive diagnostic criteria for IgG4-RD (11) were enrolled. Patients in whom malignancy was diagnosed ≤ 6 months before or after the onset of IgG4-RD were excluded. Patients whose follow-up period was ≤ 6 months were also excluded.

In total, 126 patients were diagnosed with IgG4-RD at our institute and affiliated hospitals between January 1997 and September 2012. In seven patients, malignancy was diagnosed ≤ 6 months before or after the onset of IgG4-RD. The follow-up period was ≤ 6 months in six patients. After excluding these 13 patients, 113 patients were enrolled in this study. These patients were followed carefully every 3-6 months, and clinical data were prospectively collected. Chest and abdominal contrast-enhanced computed tomography (CT) was performed once or twice each year. Plain CT was performed when contrast medium could not be used. When patients showed any signs suggestive of malignancy, such as weight loss, anemia or tumor marker elevation, they underwent additional examinations, such as colonoscopy, gastro-duodenoscopy, chest X-ray, CT and positron emission tomography, according to the suspected malignancy. In patients without any signs or symptoms of malignancy, we recommended the use of a screening test once a year during the follow-up, particularly for cancers commonly found in the Japanese population. As a rule, pathological confirmation was obtained for the diagnosis of malignancy. When the recurrence of malignancy diagnosed before the onset of IgG4-RD was observed during follow-up of IgG4-RD, it was not regarded as an occurrence of malignancy.

Age-stratified (according to 5-year age groups) and sex-specific data for the incidence of cancer in Japan (Center for Cancer Control and Information Services, National Cancer Center, Japan, period 2007) were used to determine the expected number of cases of malignancy in the cohort (12). The standardized incidence rate (SIR) was calculated as the

ratio of the observed to the expected number of patients who developed malignancies. The 95% confidence interval (CI) of the SIR was estimated assuming a Poisson distribution (13).

Risk factors for malignancy were analyzed by comparing patients with and without malignancy. Possible risk factors included the age at onset of IgG4-RD, sex, number of lesions, diabetes mellitus, smoking and levels of IgG, IgG4 and IgE at the initial assessment.

Differences were analyzed using Student's *t*-test or Welch's *t*-test for continuous data and the χ^2 test or Fisher's exact test as required for categorical data. Continuous variables are reported as the mean $\pm$ SD. The cumulative incidence of malignancy was calculated according to the Kaplan-Meier method, and the effects of various variables on the risk of malignancy were evaluated using the log-rank test. Parameters proven to be significant in the univariate analysis were tested using a multivariate Cox proportional hazards model. All statistical analyses were performed using the JMP 7.0.1 software program (SAS Institute). All statistical tests were two-sided, and a *p* value of <0.05 was considered to be statistically significant.

This study was approved by the Institutional Review Board of our institution, and informed consent for all invasive procedures was obtained from each patient.

Results

Patient characteristics

In total, 113 patients with IgG4-RD (90 men and 23 women, mean age at onset: 65 years) were prospectively followed for >6 months. The mean and median follow-up periods were 73 and 64 months, respectively (range: 7-204 months). At the onset of IgG4-RD, pancreatic lesions (AIP), salivary and/or lacrimal gland lesions, periaortic lesions (including retroperitoneal lesions), extrapancreatic biliary lesions, pulmonary lesions, ophthalmologic lesions and pachymening lesions were observed in 82, 22, 20, nine, three, two and one patient, respectively. Five patients had three IgG4-related lesions, 16 patients had two lesions and 92 patients had one lesion. When the pancreatic lesions that appeared during follow-up were included, 95 patients (84%) had AIP. All of these patients had type 1 AIP according to the ICDC. Twenty patients were followed without steroid treatment (ST). Twenty-seven patients were initially followed without ST for at least six months but received ST thereafter. In the remaining 66 patients, the disease was diagnosed and treated with steroids within six months after the onset. In principle, maintenance therapy with 2.5-7.5 mg/day of prednisolone was administered for at least three years. Diabetes mellitus (DM), diagnosed before or around the diagnosis of IgG4-RD, was observed in 69 patients (61%). A diagnosis of DM was made when the fasting blood glucose level was ≥ 126 mg/dL and/or the hemoglobin A1c (HbA1c) level was $\geq 6.5\%$ (14). The extent of smoking was assessed based on

Table 1. Clinical Profile of 14 Patients Associated with Malignancy

Patient	Onset age of IgG4-RD	Sex (M/F)	Type of IgG4-RD	Type of malignancy	Period from the onset of IgG4-RD to malignancy (months)	Diabetes mellitus (Yes/No)	Brinkman index	IgG (mg/dL)	IgG4 (mg/dL)	IgE (IU/mL)	Introduction of steroid therapy before malignancy (Yes/No)
1	72	M	IgG4-SA	Lung cancer	12	Y	0	2,834	1,800	302	N
2	70	M	AIP	Lung cancer	20	Y	1,000	3,248	2,170	361	Y
3	59	M	AIP and RF	Lung cancer	26	Y	1,290	1,876	139	625	N
4	76	M	AIP	Lung cancer	32	Y	800	1,728	65.2	1,000	Y
5	73	M	AIP	Lung cancer	88	Y	0	1,647	360	290	Y
6	55	M	AIP	Gastric cancer	128	N	126	1,878	410	270	Y
7	58	M	AIP	Gastric cancer	43	Y	0	1,173	220	134	Y
7	58	M	AIP	Pancreatic cancer	119	Y	0	1,173	220	134	Y
8	70	M	AIP	Pancreatic cancer	162	Y	0	1,767	875	NA	N
9	71	M	AIP	Bile duct cancer	20	Y	0	2,318	470	1,915	Y
10	77	M	IgG4-SA	Renal cancer	10	Y	400	1,743	754	74	N
11	69	F	RF	Breast cancer	24	Y	40	1,717	562	1,230	N
12	65	M	IgG4-SC and AIP	Tongue cancer	186	Y	1,800	1,778	638	NA	Y
13	66	M	AIP and RF	Malignant melanoma	86	Y	900	2,220	525	1,380	Y
14	70	F	AIP	AML	26	Y	0	2,190	133	480	Y

IgG4-RD: IgG4 related disease, IgG4-SA: IgG4 related sialoadenitis, AIP: autoimmune pancreatitis, RF: retroperitoneal fibrosis, IgG4-SC: IgG4 related sclerosing cholangitis, AML: acute myeloid leukemia, NA: not available

One patient (Patient 7) developed gastric and pancreatic cancer metachronously.

Table 2. Comparison between Patients with and without Malignancy

Parameters	Malignancy (+) (n=14)	Malignancy (-) (n=99)	p value
Onset Age (mean) of IgG4-RD	67.9±6.6	64.1±10.1	0.179
Onset Age (≥65y / <65y)	11/3	52/47	0.087
Sex (male/female)	12/2	78/21	0.731
Number of lesions (1/ >1)	11/3	81/18	0.722
Brinkmann index (mean)	508±600	487±607 (n=95)	0.908
Brinkmann index (≥400 / <400)	7/7	45/50	1.0
DM (+/-)	13/1	56/43	0.0084
IgG (mg/dL) (mean)	1,976±549	1,999±775	0.912
IgG4 (mg/dL) (mean)	645±620	566±517	0.604
IgE (IU/mL) (mean)	689±569 (n=12)	729±1,161 (n=87)	0.908

IgG4-RD: IgG4 related disease, DM: diabetes mellitus, Ig: immunoglobulin

the Brinkman index (daily number of cigarettes×years). The index was <400 in 61 patients (54%).

Development of malignancy during follow-up

Fifteen malignancies developed in 14 patients (12%) during follow-up (Table 1). Lung cancer developed in five patients, pancreatic cancer developed in two patients, gastric cancer developed in two patients and bile duct cancer, renal cancer, breast cancer, tongue cancer, malignant melanoma and acute myeloid leukemia developed in one patient each. One patient metachronously developed gastric cancer and pancreatic cancer 43 months and 119 months after the onset of IgG4-RD, respectively. To calculate the SIR of the total malignancies, the earlier episode of gastric cancer was counted in this patient. The mean and median periods between the onset of IgG4-RD and the initial development of malignancy were 62 and 29 months, respectively.

The SIR of the total malignancies was 1.04 (95% CI 0.57-1.75). We also calculated the SIR of specific cancers that were observed in more than one patient. The SIR of lung cancer, pancreatic cancer and gastric cancer was 2.17 (95% CI 0.70-4.99), 3.46 (95%CI 0.40-11.9) and 0.75 (95% CI 0.086-2.59), respectively. When the patients were limited to those with AIP (n=95), the SIR of pancreatic cancer was 3.65 (95%CI 0.42-12.5).

Risk factors for malignancy in IgG4-RD patients

The results of the comparison between the patients with and without malignancy are summarized in Table 2. The number of patients with DM was significantly greater in the malignancy (+) group ($p=0.0084$). In addition, the number of patients with disease onset at an age of ≥65 years tended to be greater in the malignancy (+) group ($p=0.087$). According to the univariate analyses using the Kaplan-Meier method and log-rank test, “age at onset ≥65 years” ($p=0.029$) and “association with DM” ($p=0.031$) were significant risk factors for the incidence of malignancy (Figure). A multivariate analysis using the Cox proportional hazards model was performed using these two parameters. Consequently, “age at onset ≥65 years” was found to be the only risk factor (HR 3.82, 95% CI 1.028-14.20) (Table 3).

It was difficult to evaluate the effects of ST on the incidence of malignancy because 27 patients had a follow-up period both with and without ST. In these patients, we focused only on the follow-up period prior to the introduction of ST. Forty-seven patients (35 men and 12 women, mean age at onset: 64 years) had a follow-up period without ST. The mean and median follow-up periods were 62 and 37 months, respectively (range: 7-201 months). Malignancy occurred in five patients (lung cancer in two patients, pancreatic cancer in one patient, renal cancer in one patient and

Figure. A) Kaplan-Meier curves comparing the non-incidence rate of malignancy between the “age of onset <65 years group” and “age of onset ≥65 years group.” B) Kaplan-Meier curves comparing the non-incidence rate of malignancy between the “DM (+) group” and “DM (-) group.”

Table 3. Risk Factors for Malignancy in IgG4-RD (Multivariate Analysis by the Cox Proportional Hazards Model)

Parameters	Hazard ratio (95% CI)	p value
Onset age (≥65 y)	3.82 (1.03- 14.2)	0.045
Diabetes mellitus	6.71 (0.87-51.5)	0.067

breast cancer in one patient). The SIR of the total malignancies in this cohort was 1.05 (95% CI 0.34-2.40), which did not differ from the SIR of the total cohort (1.04). Therefore, ST does not appear to be a significant risk or protective factor for the incidence of malignancy in IgG4-RD patients.

Discussion

This is the largest-scale report of a systematic estimation of the incidence of malignancy in patients with IgG4-RD using a long-term follow-up period. In light of the chronic inflammation and frequent DM observed in such patients, it is anticipated that there would be a higher incidence of malignancy in patients with IgG4-RD. However, the incidence of total malignancies was similar to that observed in the age- and sex-matched Japanese controls. Evaluating specific malignancies is difficult because the number of cases is small. The SIR of pancreatic cancer (3.40) appeared to be a little high; therefore, it should be evaluated in a larger scale study.

Since we aimed to clarify whether IgG4-RD can cause malignancy, we selected patients with IgG4-RD who developed malignancy during the follow-up period. Therefore, we excluded seven patients in whom malignancy was diagnosed ≤6 months before or after the onset of IgG4-RD (gastric cancer in two patients, lung cancer in one patient, renal cancer in one patient, esophageal cancer in one patient, prostate cancer in one patient and concomitant pancreatic and colon cancer in one patient) and six patients whose follow-up pe-

riod was ≤6 months. Including these 13 patients, the incidence of total malignancies is 17% (21/126), which seems rather high. Considering the relationship between IgG4-RD and malignancy, it is very difficult to evaluate patients who develop IgG4-RD and malignancy around the same time (15). Of these seven patients, IgG4-RD was diagnosed during the close examination of malignancy in five cases. Because our institute is a tertiary hospital where many cancer patients are treated, various diseases may be diagnosed during the close examination of malignancy. In other words, a hospital examining a higher number of cancer patients may have a higher number of patients with IgG4-RD and malignancy. Although “seven patients” seems to be a comparatively large number, the effect of such selection bias cannot be denied.

As for the exclusion period of “six months,” we must admit that it was arbitrarily defined and may be insufficient. Unfortunately, this problem appears to be unavoidable. Selecting one or two years is possible instead of six months; however, whichever period is chosen will be arbitrary. If a longer period is adopted, the calculated SIR for total malignancies becomes smaller because more patients with malignancies are excluded. For example, if one year is adopted, the SIR for total malignancies is 0.90 (95%CI 0.47-1.56). Therefore, we chose to adopt a short period (six months) and obtained a conservative calculation of the SIR for our position.

Moreover, in this study, the follow-up period for calculating the SIR of total malignancies in the patients who developed malignancy was defined as the period between the onset of IgG4-RD and the occurrence of malignancy. Because calculating the SIR becomes impossible if patients whose follow-up period is zero are included, it is difficult to add patients who developed IgG4-RD and malignancy concurrently in the analysis.

Two recent studies evaluating the SIR support the association between IgG4-RD and total malignancies (16, 17). Yamamoto et al. reported the SIR for total malignancies to

be 3.8 in their series, which consisted primarily of patients with Mikulicz's disease (16), while Shiokawa et al. reported the SIR to be 2.7 in their series, which consisted of AIP patients only (17). Both studies concluded that the SIR was significantly high. However, both series included cases in which malignancies and IgG4-RD were diagnosed concurrently. In these two studies, the follow-up period of the patients who developed malignancy was not defined as the period between the onset of IgG4-RD and the occurrence of malignancy, but rather as the simple follow-up period, namely, the period between the diagnosis of IgG4-RD and the day of the last visit or death. If the SIR is calculated using this method, it follows that the timing of the occurrence of malignancy does not matter, whether it is at the time of diagnosis of IgG4-RD or during follow-up. This calculating method may overestimate the SIR when there are many patients in whom malignancy and IgG4-RD are diagnosed concurrently and the follow-up period is short. Therefore, in order to examine whether IgG4-RD causes malignancy, we believe that such cases should be excluded from the analysis. If IgG4-RD really causes malignancy, the results should be the same, regardless of the inclusion or exclusion of such cases.

In Shiokawa's series, 18 cancers were found in 108 AIP patients; however, eight cancers were diagnosed concurrently (17). Regarding this point, the authors speculated that AIP may develop as a paraneoplastic syndrome in some patients. They added that immunoreactions to cancer may induce AIP. This hypothesis is interesting and plausible; however, there appears to be inadequate evidence to support it at present. The problem of selection bias also cannot be denied. We aimed to clarify whether IgG4-RD is a risk factor for malignancy (= could cause malignancy) and cannot confirm or deny the authenticity of this hypothesis. For reference, we calculated the SIR of total malignancies using the same method as Shiokawa et al. That is, the data of all 126 patients were used for the analysis. As a result, the SIR of total malignancies was 1.56 (95%CI 0.99-2.34), which was barely significant. Our data and Shiokawa's data may be similar; however, the conclusions are quite opposite because we focused only on whether IgG4-RD can cause malignancy, while they considered both the possibility that "IgG4-RD causes malignancy" and "malignancy causes IgG4-RD."

A univariate analysis of the risk factors for malignancy in patients with IgG4-RD revealed that "age at onset of IgG4-RD $\geq$ 65 years" and "association with DM" were significant risk factors, with age at onset remaining significant in the multivariate analysis. These results are not unexpected (12, 18). Assuming that IgG4-RD itself is related to the increased incidence of malignancy, it is expected that IgG and IgG4, which reflect the disease activity (19), would be risk factors for malignancy. Treatment without steroids may increase the risk of malignancy. Because such results were not obtained, the hypothesis is not true. We also expected that IgE would be a protective factor for malignancy given the reports of an inverse association between the level

of IgE and cancer (20-22). However, this assumption also does not appear to be true.

The limitation of this study is that specifying the onset time of IgG4-RD is sometimes difficult. If there were preceding relevant symptoms before the final diagnosis of IgG4-RD, the timing of the appearance of the symptoms was regarded as the onset time. However, in patients without any symptoms, the onset time was regarded as the time of diagnosis. As for malignancies, the onset time was substituted for the time of diagnosis. Strictly speaking, it is difficult to determine the exact time of onset of IgG4-RD or malignancy in any case.

In conclusion, it is reasonable to conclude that IgG4-RD is not associated with an increased incidence of total malignancies. A larger scale study is needed to evaluate the incidence of specific cancers.

The authors state that they have no Conflict of Interest (COI).

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