

Risk of Cancer in Patients With Autoimmune Pancreatitis

Masahiro Shiokawa, MD¹, Yuzo Kodama, MD, PhD¹, Kenichi Yoshimura, MD, PhD², Chiharu Kawanami, MD³, Jun Mimura, MD⁴, Yukitaka Yamashita, MD, PhD⁵, Masanori Asada, MD, PhD⁶, Masataka Kikuyama, MD, PhD⁷, Yoshihiro Okabe, MD, PhD⁸, Tetsuro Inokuma, MD, PhD⁹, Masaya Ohana, MD, PhD¹⁰, Hiroyuki Kokuryu, MD¹¹, Kazuo Takeda, MD, PhD¹², Yoshihisa Tsuji, MD, PhD¹³, Ryuki Minami, MD¹, Yojiro Sakuma, MD¹, Katsutoshi Kuriyama, MD¹, Yuji Ota, MD¹, Wataru Tanabe, MD¹, Takahisa Maruno, MD¹, Akira Kurita, MD¹, Yugo Sawai, MD¹, Norimitsu Uza, MD, PhD¹, Tomohiro Watanabe, MD, PhD¹, Hironori Haga, MD, PhD¹⁴ and Tsutomu Chiba, MD, PhD¹

- OBJECTIVES:** Although simultaneous occurrences of autoimmune pancreatitis (AIP) and cancer are occasionally observed, it remains largely unknown whether cancer and AIP occur independently or these disorders are interrelated. The aim of this study was to examine the relationship between AIP and cancer.
- METHODS:** We conducted a multicenter, retrospective cohort study. One hundred and eight patients who met the Asian diagnostic criteria for AIP were included in the study. We calculated the proportion, standardized incidence ratio (SIR), relative risk, and time course of cancer development in patients with AIP. We also analyzed the clinicopathological characteristics of AIP patients with cancer in comparison with those without cancer.
- RESULTS:** Of the 108 AIP patients, 18 cancers were found in 15 patients (13.9%) during the median follow-up period of 3.3 years. The SIR of cancer was 2.7 (95% confidence interval (CI) 1.4–3.9), which was stratified into the first year (6.1 (95% CI 2.3–9.9)) and subsequent years (1.5 (95% CI 0.3–2.8)) after AIP diagnosis. Relative risk of cancer among AIP patients at the time of AIP diagnosis was 4.9 (95% CI 1.7–14.9). In six of eight patients whose cancer lesions could be assessed before corticosteroid therapy for AIP, abundant IgG4-positive plasma cell infiltration was observed in the cancer stroma. These six patients experienced no AIP relapse after successful cancer treatment.
- CONCLUSIONS:** Patients with AIP are at high risk of having various cancers. The highest risk for cancer in the first year after AIP diagnosis and absence of AIP relapse after successful treatment of the coexisting cancers suggest that AIP may develop as a paraneoplastic syndrome in some patients.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at <http://www.nature.com/ajg>

Am J Gastroenterol 2013; 108:610–617; doi:10.1038/ajg.2012.465; published online 15 January 2013

INTRODUCTION

Autoimmune pancreatitis (AIP) is a unique form of chronic pancreatitis characterized by immunological abnormalities, including elevated serum immunoglobulin 4 (IgG4) levels and IgG4-positive lymphoplasmacytic infiltration. In addition, AIP is associated with imaging abnormalities such as pancreatic parenchyma enlargement and pancreatic duct narrowing (1,2). Patients with AIP often exhibit IgG4-positive cell infiltration in not only

the pancreas but also in various extrapancreatic organs (3), suggesting that AIP is a manifestation of a systemic IgG4-related disease. Despite accumulating evidence of autoimmune features in this disease, however, the pathogenesis of AIP remains unknown.

Recent reports demonstrated that patients with AIP occasionally have various types of cancer, such as pancreatic cancer (4–6), lymphoma (7,8), bile duct cancer (9), gastric cancer (10), colon cancer (11), and thyroid cancer (12). Yamamoto *et al.* (13) reported

¹Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, Kyoto, Japan; ²Translational Research Center, Kyoto University Hospital, Kyoto, Japan; ³Department of Gastroenterology and Hepatology, Japanese Red Cross Otsu Hospital, Otsu, Japan; ⁴Department of Gastroenterology and Hepatology, Nishikobe Medical Center, Kobe, Japan; ⁵Department of Gastroenterology and Hepatology, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan; ⁶Department of Digestive Disease Center, Kitano Hospital, Osaka, Japan; ⁷Department of Gastroenterology and Hepatology, Shizuoka General Hospital, Shizuoka, Japan; ⁸Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital, Osaka, Japan; ⁹Department of Gastroenterology and Hepatology, Kobe City Medical Center General Hospital, Kobe, Japan; ¹⁰Department of Gastroenterology and Hepatology, Tenri Hospital, Tenri, Japan; ¹¹Department of Gastroenterology and Hepatology, Kyoto Katsura Hospital, Kyoto, Japan; ¹²Kyoto Industrial Health Association, Kyoto, Japan; ¹³Division of Radiology/Gastroenterology and Hepatology, Mayo clinic, Rochester, Minnesota, USA; ¹⁴Department of Diagnostic Pathology, Kyoto University Hospital, Kyoto, Japan. **Correspondence:** Yuzo Kodama, MD, PhD, Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, 54 Shogoin-kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan. E-mail: kodamayu@kuhp.kyoto-u.ac.jp

Received 23 April 2012; accepted 18 December 2012

that patients with IgG4-related disease are at high risk for cancer development based on an analysis of 105 patients, including 10 AIP patients. The precise prevalence of cancers in patients with AIP and the causal relationship between AIP and cancer, however, have not been elucidated.

In general, two mechanisms are proposed regarding co-occurrence of cancer and autoimmunity (14–16). First, sustained inflammation in the presence of autoimmune disease is considered to create the immunological environments for the development of cancer, e.g., lymphomas in Sjögren's syndrome or colitic cancers in inflammatory bowel diseases (17,18). In this case, the risk of cancer increases along with the duration of the underlying disease. Alternatively, cancers may induce autoimmune disease as a paraneoplastic syndrome, as represented by dermatomyositis (DM) and polymyositis (PM) (19–21). An important characteristic of paraneoplastic syndrome is that the risk of cancer is highest within the first year after diagnosis of the disease (14,22), and clinical improvement of the disease is frequently achieved after successful treatment of the accompanying cancer (23). Buchbinder *et al.* (20) reported that standardized incidence ratio (SIR) of cancer in the first year after diagnosis of myositis (DM/PM) was 4.4 (95% confidence interval (CI) 2.7–7.1) in the population-based cohort study.

In the present study, to examine the clinicopathological association between AIP and cancer, we conducted a multicenter, retrospective cohort study. We assessed the proportion of cancer in patients with AIP, the chronological relationship between the time of AIP diagnosis and diagnosis of cancers, IgG4 expression in cancer lesions in patients with AIP, and effects of cancer treatment on AIP.

METHODS

Patients

AIP patients. The study was approved by the institutional review boards of Kyoto University Hospital and affiliated hospitals of Kyoto University. Using K861 internal coding data, which includes AIP and chronic pancreatitis, we retrospectively identified 135 patients diagnosed as AIP between 2001 and 2011 at the Kyoto University Hospital or the affiliated hospitals of Kyoto University.

Patients who did not meet the Asian Criteria for AIP (see **Supplementary Table 1** online) (24) were excluded from the study. All the AIP diagnosis was made at the patients' initial visit or first admission for pancreatic examination. A total of 108 patients were included in this study (**Table 1**). According to the Asian diagnostic criteria, we diagnosed 94 AIP patients with criterion I (imaging) + II (serology), and 10 patients with criterion III (histopathology) alone in the resected pancreas, indicating the diagnosis of type I AIP (25). All of these patients fulfilled HISORT criteria in the United States (26). The remaining four patients were diagnosed with criterion I + optional criterion (response to steroid therapy). These four patients had no serology, no histology, and no extrapancreatic lesion, thus were considered to have type II AIP (25). The duration of the follow-up was defined as the period from the date of the diagnosis of AIP until death, the most recent contact, or the study closure date (31 October 2011), whichever occurred first.

Table 1. Characteristics of the 108 patients with AIP

Characteristic	Value
Male patients (%)	89 (82.4)
<i>Age (years at diagnosis of AIP)</i>	
Median	67
Range	21–86
<i>Follow-up (years)</i>	
Median	3.25
Range	0.3–11.7
<i>Serum IgG4 at diagnosis of AIP (mg/dl)</i>	
Median	259
Range	2.8–3640
Increased serum IgG4 (number of patients)	77 (11 NA)
<i>Asian diagnostic criteria for AIP (number of patients)</i>	
Criterion I + criterion II	94
Criterion III in the resected pancreas	10
Criterion I + optional (response to steroid therapy)	4
Number of patients with cancer	15
Number of cancers	18
Stomach	7
Lung	3
Non-Hodgkin lymphoma	2
Prostate	2
Colon	2
Bile duct	1
Thyroid	1

AIP, autoimmune pancreatitis, the normal values for serum IgG4 level; <135 mg/dl. NA, number of patients whose data were not available.

Ninety-one patients (84.2%) received corticosteroid treatment and all these patients showed an initial response. Twelve patients (11.1%) were observed without corticosteroid treatment. Ten of the 12 patients had spontaneous remission, and the remaining 2 patients showed deterioration of AIP and received corticosteroid treatment. The remaining five patients (4.6%) had surgical resection for suspicion of pancreatic cancer, and there was no relapse of AIP in the remaining pancreas after surgical resection of the AIP lesion without corticosteroid treatment. We defined AIP relapse as the recurrence of radiological manifestations of AIP with or without symptoms in the pancreas or extrapancreatic lesions after excluding other diseases (27,28). We expressed relapse rate of AIP by dividing the sum of AIP relapse by the follow-up period (person-years).

Gastric cancer patients without AIP. To compare gastric cancers with AIP and without AIP, we examined serum IgG4 levels in 20 gastric cancer patients without AIP, and IgG4-positive plasma cell infiltration in 40 gastric cancer patients without AIP. We randomly selected the patients, diagnosed between 2001 and 2011 at

Kyoto University Hospital, whose serum and/or tissues specimens were available.

Calculation of proportion of AIP patients with cancer and SIRs of cancer in AIP patients

We analyzed all cancers that were diagnosed concurrently with or after the diagnosis of AIP.

We calculated the proportion of AIP patients with cancer by dividing the number of AIP patients with cancer during the follow-up period by the number of all AIP patients. The result is expressed as a percentage.

We calculated the SIRs of cancer in AIP patients using the national cancer rates in the population of Japan, stratified by age, sex, and calendar period (29). We calculated SIR based on the number of cancers, and each cancer was counted once, so if a patient had two malignancies, they were each counted once. The SIR of cancer compared the incidence of cancer observed in the AIP cohort with that expected if the cohort developed cancer at the same rate as the standard population of Japan. An SIR greater than 1 indicates an elevated incidence of cancer in the AIP patients relative to the general population of Japan.

Calculation of relative risk of cancer in AIP patients and controls

The control population consisted of those who first had a medical checkup with the full examinations including blood examination, urine analysis, fecal occult blood, chest X-ray, abdominal ultrasonography, gastrointestinal endoscopy, and computed tomography (CT) in the lung in Kyoto Industrial Health Association. Control subjects not having AIP were matched to the cases for age (± 5 years) and gender with a 2:1 ratio, leading to the inclusion of 216 controls.

For calculation of relative risk of cancer, we analyzed cancers in AIP patients, which were diagnosed between 1 month before and 1 month after the AIP diagnosis. We analyzed cancers in controls that were diagnosed in the medical checkup.

We defined smoking as >10 pack-year and <10 year since smoking cessation. We defined alcohol intake as >30 g alcohol per day.

Immunohistochemical study

Immunohistochemistry of the cancer lesions was performed on two representative sections from each case, using antibodies against IgG4 (clone HP6025; dilution 1:500; Serotec, Oxford, UK). Immunostaining was performed on an autoimmunostainer (Ventana XT System Benchmark; Ventana Medical Systems, Tucson, AZ). We selected two sections in which IgG4-positive plasma cells infiltration was most abundant, and photographed them with $\times 20$ objective lens using a Nikon DX1200 digital camera (Nikon, Tokyo, Japan). We defined more than 29 cells per high-power field (HPF) as "abundant" infiltration of IgG4-positive plasma cells, between 10 and 29 cells per HPF as "moderate" infiltration, and fewer than 10 cells per HPF as "few" infiltration (30,31).

Statistical analysis

General characteristics are expressed as median and ranges. Differences concerning clinical characteristics were assessed using

Student's *t*-test for continuous data, and the χ^2 -test, the Fisher's exact test, and multiple logistic regression analysis for categorical data. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS version 17.0, Chicago, IL). All statistical tests were two-sided. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Proportion and sites of cancers in AIP patients

Table 1 summarizes the characteristics of the AIP patients. Among the 108 patients with AIP, 18 cancers were found in 15 patients either at the same time or after the diagnosis of AIP during the median follow-up period of 3.3 years. Three patients had multiple cancers. One patient had gastric cancer and lymphoma. Another patient had gastric cancer and colon cancer, and the other patient had bile duct cancer and lung cancer. The proportion of AIP patients with cancer was 13.9% (15/108).

The site of cancers in the AIP patients are shown in **Table 1**. Gastric cancer was the most common. Because of the small numbers of individual cancers, we were unable to determine whether the risk for any individual type of cancer was high compared with the general population.

SIRs of cancer in AIP patients

Eighteen cancers were found in the 108 AIP patients during the overall follow-up of 415.7 person-years. The incidence of cancer expected from the rates of Japanese population in this cohort was 6.7. Accordingly, the SIR of cancer in the patients after the diagnosis of AIP was 2.7 (95% CI 1.4–3.9; **Table 2**).

Time period between the diagnosis of cancer and AIP

Figure 1 shows the chronological relationship between the time of diagnosis of AIP and that for cancer. Of 18 cancers, 10 were detected within the first year after the diagnosis of AIP, including 8 cancers that were concurrently diagnosed. All the eight patients had no symptom/signs related to the cancer, and their cancers were incidentally diagnosed during the process of AIP diagnosis. The remaining 8 cancers were found after the first year of AIP diagnosis. The SIRs of cancer in the first year and in subsequent years after AIP diagnosis were 6.1 (CI 2.3–9.9) and 1.5 (CI 0.3–2.8), respectively (**Table 2**), indicating that the occurrence of cancer was significantly higher in the first year. The cancer sites stratified by time period between the diagnosis of AIP and cancer are shown in **Table 2**.

Relative risk of cancer at diagnosis of AIP

AIP patients underwent intensive testing, which may have enhanced the detection of cancer. Thus, it is possible that this intensive examination raised the SIR for cancer in our cohort, especially in the first year. To solve this concern, we calculated the relative risk of cancer at the diagnosis of AIP in our cohort in comparison with age- and sex-matched controls who first had a medical checkup with almost the same examinations as our cohort. The number of concurrent cancers at the diagnosis of AIP

Table 2. SIRs of cancer in patients with AIP

Variable	Follow-up (person-years)	Observed cases of cancer (no.)	Expected cases of cancer (no.)	Standardized incidence ratio (95% CI)	Site of cancers (no.)
Overall	415.7	18	6.7	2.7 (1.4–3.9)	
<i>Time since diagnosis of AIP</i>					
<1 year	103.6	10	1.6	6.1 (2.3–9.9)	Stomach (4)
					Lung (2)
					Prostate (2)
					Bile duct (1)
					Thyroid (1)
≥1 year	312.1	8	5.2	1.5 (0.3–2.8)	Stomach (3)
					Non-Hodgkin lymphoma (2)
					Colon (2)
					Lung (1)

AIP, autoimmune pancreatitis; CI, confidence interval; no., number of patients; SIR, standardized incidence ratio.

The overall SIR of cancer in the patients after the diagnosis of AIP was 2.7 (95% CI 1.4–3.9). The SIR in the first year and the subsequent years after the AIP diagnosis were 6.1 (95% CI 2.3–9.9) and 1.5 (95% CI 0.3–2.8), respectively. The site of cancers in the first year and following years after the AIP diagnosis were also shown.

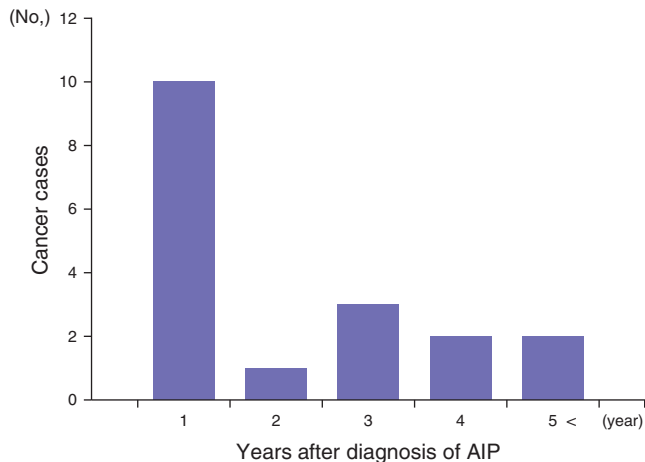


Figure 1. Time of cancer diagnosis in patients with AIP. Blue columns show the number of cancers diagnosed each year after the diagnosis of AIP. Ten cancers were diagnosed at or within 1 year after AIP diagnosis (eight cancers at the time of the diagnosis of AIP). AIP, autoimmune pancreatitis; no., number of cancers.

Table 3. Characteristics of the 108 patients with AIP and the 216 controls

Characteristic	AIP patients	Controls	P value
Number	108	216	
Number of cancers	8	3	0.008*
Male patients (%)	89 (82.4)	178 (82.4)	1
<i>Age (years at diagnosis of AIP)</i>			
Median	67	66	0.96
Range	21–86	19–83	
Familial history of cancer ^a	21.8 (30 NA)	32	0.36
Smoking ^a	34.5 (21 NA)	44.3	0.91
Alcohol intake ^a	9.4 (23 NA)	8	0.65

AIP, autoimmune pancreatitis; NA, number of patients whose data were not available.

^aData are expressed as percentages.

*Significant difference.

was eight (8/108) and the number of cancers in controls was three (3/216, $P=0.008$; **Table 3**). The incidence of malignancy in the control group (1,388 per 100,000 people) was higher than that in the overall population of Japan (551 per 100,000 people), but comparable to that in age- and sex-matched population according to data from the National Cancer Center in Japan (1,527 per 100,000 people) (29). Relative risk of cancer at AIP diagnosis was 4.9 (95% CI 1.7–14.9). In the eight AIP patients with cancer, no cancer was detected by abdominal CT or Positron Emission Tomography-CT, which were not included in the examinations in the controls. The differences of familial history of cancer, smoking, and alcohol intake between AIP patients and controls were not significant.

Clinicopathological characteristics of AIP patients with cancer

Serum IgG4 levels. Serum IgG4 levels at the diagnosis of AIP were significantly higher in AIP patients with cancers than in those without cancer (738 vs. 389, $P=0.02$).

Extrapaneatritic lesions. Extrapaneatritic lesions were found in 75 of the 108 (69.4%) patients with AIP. The frequencies of sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal fibrosis, renal involvement, and lung involvement were 52.8% (57 patients), 9.3% (10 patients), 9.3% (10 patients), 3.7% (4 patients), and 3.7% (4 patients), respectively. In the 15 AIP patients with cancer, extrapaneatritic lesions occurred in 11 (73.4%) patients. The frequencies of sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal

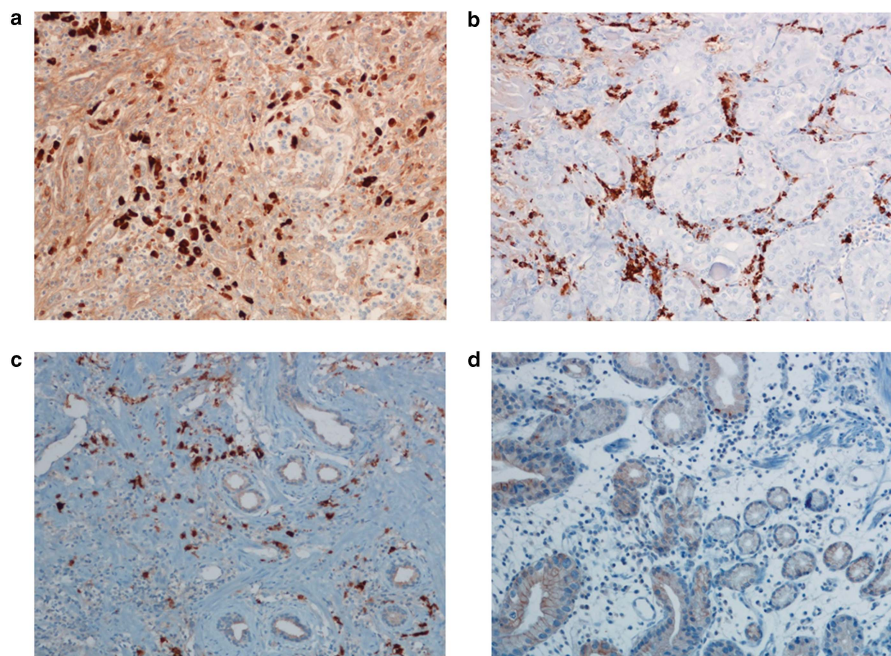


Figure 2. Infiltration of IgG4-positive plasma cells around the cancer before corticosteroid therapy. Representative cases of bile duct cancer (a), thyroid cancer (b), and prostate cancer (c) coexisting with AIP show abundant infiltration of IgG4-positive plasma cells before corticosteroid treatment (159, 214, and 50 cells/HPF, respectively). In contrast, one case of gastric cancer showed few infiltration of IgG4-positive cells before corticosteroid treatment (4 cells/HPF) (d). We defined more than 29 IgG4-positive cells/HPF as “abundant”, between 10 and 29 cells/HPF as “moderate” infiltration and less than 10 cells/HPF as “few”. AIP, autoimmune pancreatitis; HPF, high-power field.

fibrosis, renal involvement and lung involvement were 60% (nine patients), 13.3% (two patients), 20.0% (three patients), 0 and 6.7% (one patient), respectively. In the 93 AIP patients without cancer, extrapancreatic lesions occurred in 64 (68.9%) patients. The frequencies of sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal fibrosis, renal involvement, and lung involvement were 51.6% (48 patients), 8.6% (8 patients), 7.5% (7 patients), 4.3% (4 patients), and 3.2% (3 patients), respectively. Thus, frequencies of overall extrapancreatic lesions were similar between AIP patients with and without cancer. Moreover, univariate and multivariate analyses revealed no significant difference in the frequency of each extrapancreatic lesion between AIP patients with and without cancer. However, when we compared 8 patients concurrently diagnosed with AIP and cancer and 93 AIP patients without cancer, univariate ($P=0.04$) and multivariate analyses ($P=0.02$) revealed that frequency of retroperitoneal fibrosis was significantly higher in the patients concurrently diagnosed with AIP and cancer than AIP patients without cancer (3/8 vs. 8/93).

IgG4-positive plasma cell infiltration in the cancer lesions and relapse of AIP. Next, we evaluated IgG4-positive plasma cell infiltration in the cancer lesions by immunohistochemistry (Figure 2). To exclude the effect of corticosteroid therapy, we selected eight patients concurrently diagnosed with AIP and cancer, whose cancer lesions were assessed before corticosteroid treatment (Table 4). Of these eight cancer lesions, six showed abundant IgG4-positive plasma cell infiltration in the tissues surrounding the tumor cells, whereas the other two cancer lesions had few infiltration. All eight

patients were successfully treated for cancer (surgery, chemotherapy, or radiotherapy), followed by corticosteroid treatment for AIP. None of the six AIP patients with abundant IgG4-positive plasma cell infiltration around the cancers developed a relapse of AIP during the median follow-up of 4.7 years, whereas one of the two patients with few IgG4 plasma cell infiltration relapsed during the follow-up of 0.5 and 4.4 years and relapse rate was 0.20. Sixteen of 93 AIP patients without cancer had a relapse of AIP during the median follow-up of 3.1 years and relapse rate was 0.046.

As gastric cancer was the primary malignancy in our AIP patients, we examined serum IgG4 levels in 20 gastric cancer patients without AIP, and IgG4-positive plasma cell infiltration in the surrounding tissues in 40 gastric cancer patients without AIP. We found that serum IgG4 levels were above 135 mg/dl in 5 out of 20 gastric cancer patients with a maximum level of 227 mg/dl. On the other hand, moderate IgG4-positive plasma cell infiltration (10 to 29/HPF) were observed in only 2 out of 40 patients, and there were no gastric cancer with abundant IgG4-positive plasma cell infiltration (more than 29/HPF). The frequency of the patients with abundant IgG4-positive plasma cells around gastric cancer was significantly higher in AIP patients than non-AIP patients (2/3 vs. 0/40, $P=0.003$).

DISCUSSION

Although recent studies reported cases of AIP associated with cancers (4–12), no studies have examined the association between AIP and cancers in a large number of patients. In the present study

Table 4. IgG4-positive plasma cell infiltration in cancer stroma coexisting with AIP

Patients	Site of cancer	IgG4-positive cells (cells/HPF)	Serum IgG4 level (mg/dl)	AIP relapse	Follow-up period of AIP (years)
1	Stomach	332	360	(–)	5.8
2	Stomach	251	1,040	(–)	0.8
3	Stomach	4	194	(+)	4.4
4	Prostate	56	151	(–)	1.4
5	Prostate	4	1,170	(–)	0.5
6	Bile duct	159	NE	(–)	5.6
7	Thyroid	214	NE	(–)	4.7
8	Lung	55	528	(–)	1.9

AIP, autoimmune pancreatitis; NE, not examined; HPF, high-power field.

Numbers of IgG4-positive plasma cells showing infiltration around the cancer before corticosteroid treatments were counted (cells/HPF). Serum IgG4 levels at the diagnosis of AIP, and relapse of AIP after successful treatments for cancer were evaluated.

we analyzed a relatively large number of patients, and our findings demonstrated that cancer frequently occurs in patients with AIP. In a recent analysis of 105 patients with IgG4-related disease, including 10 AIP cases, Yamamoto *et al.* (13) reported that IgG4-related disease is a high-risk factor for cancer development. In their study, 20% of the patients with AIP had cancers, comparable to our data. Based on the findings of these two studies, patients with AIP are at high risk for cancer.

In previous reports, pancreatic cancer was the most common cancer found in patients with AIP (4–6). In contrast, none of the patients had pancreatic cancer in the present study. The reason for the discrepancy between our data and previous data is unknown. One possibility is that the awareness of differentiating AIP from pancreatic cancer may have enhanced the publication number of pancreatic cancer with AIP in previous studies. Another possibility is that AIP associated with pancreatic cancer might not have been diagnosed as AIP in our cohort, because we usually did not sample serum and tissue IgG4 levels in typical cases with pancreatic cancer. Nevertheless, no incidence of pancreatic cancer in patients with AIP in our cohort may support the notion that the cancer development in patients with AIP does not depend directly upon underlying chronic inflammation. In any event, patients with AIP have various type of cancers. The finding that the serum IgG4 levels were significantly higher in AIP patients with cancers than in those without cancers indicates that high IgG4 might be a useful marker for concurrent cancers.

The reason for the high risk of cancer in patients with AIP is unknown at present. In the present study, cancer tissues in AIP patients that were examined histologically before the administration of corticosteroids were frequently infiltrated with IgG4-positive plasma cells. This finding may suggest that the cancers in patients with AIP arise in the background of IgG4-related inflammation. It is well known that chronic inflammation has an important role in the development of various types of cancer, including *Helicobacter pylori*-induced gastric cancer, hepatitis C virus-related hepatocellular carcinoma, and colitic cancer (17,18,32,33). However, it should be noted in our study that no AIP patient developed

cancer in the pancreas, a major site of inflammation. This fact seems to contradict to an idea that chronic inflammation due to AIP is responsible for the development of cancer. In this context, it is worth noting that the risk of cancer development was the highest in the first year of AIP diagnosis in our study. Moreover, seven of eight patients, in whom cancer was histologically diagnosed before corticosteroid administration, did not have a recurrence of AIP after successful cancer treatment. In addition, curative cancer treatment prevented the relapse of AIP in the six patients whose cancer tissue showed abundant IgG4-positive plasma cell infiltration. Taken together, the data may indicate that the existing cancers have some roles in the development of AIP, raising an idea that AIP is a manifestation as a paraneoplastic syndrome in some patients. The fact that the relative risk of cancer at AIP diagnosis was significantly high in comparison with age- and sex-matched control subjects who received similar levels of examinations may further support an idea that certain portion of AIP is categorized as paraneoplastic syndrome.

Another well-known paraneoplastic syndrome that has an autoimmune nature is DM/PM (14–16). In patients with DM and PM, the SIR for cancers ranges from 3.7 to 8.8 and 1.7 to 2.2, respectively (20,21). AIP and PM/DM share several clinical findings as paraneoplastic syndrome. For instance, in our cohort with 108 patients, cancer was diagnosed concomitantly with AIP or within the first year after the AIP diagnosis in eight and two patients, respectively. Thus, similar to the previous reports on PM/DM (14,22), the risk for cancer diagnosis is highest within the first year after diagnosis of AIP, including the time of diagnosis of AIP. Notably, the cancers concurrently diagnosed with AIP were not detected by abdominal CT or Positron Emission Tomography-CT, which were not included in the examinations in the controls, excluding the possibility that the higher level of diagnostic work-up in AIP patients increased the probability of cancer diagnosis in our cohort. In addition, clinical and immunological abnormalities seen in both AIP and DM/PM are improved after successful treatment of the cancers (34). These similarities between DM/PM and AIP with regard to the relationship between

each disease and cancer further support the paraneoplastic nature of AIP, although we did not clarify the distinct immunological characteristics of AIP patients with cancers from those without cancers.

In DM/PM, the common cancers are different in different countries. The most common site of cancer is the stomach in Japan (35), whereas the ovary, lung, or gastrointestinal tracts are major sites of cancers in Western countries, and nasopharynx in Southeast Asia, South China, and North Africa (21). Similar to DM/PM, the most common cancer was gastric cancer in our cohort of Japanese patients with AIP. The high prevalence of gastric cancer in not only DM/PM but also AIP patients may reflect high incidence of gastric cancer in Japanese population (29).

In this study, we observed that the cancer tissues in AIP patients were frequently infiltrated with IgG4-positive plasma cells. The reason for the accumulation of IgG4-positive cells in the tumor tissues and the role of these cells in the pathophysiology of IgG4-related AIP, however, remain unknown. Previously, we reported that abnormal innate immune responses contribute to IgG4 production in B cells in patients with AIP (36). Moreover, tumor cells provoke innate immune responses by various mechanisms, such as release of various proinflammatory cytokines, or ligands for pattern-recognition molecules (37–39). Thus, it is possible that the tumor tissues or tumor cells activate IgG4-related immune responses. However, whether or not such immunological response contributes to the development of IgG4-related disease/AIP remains to be elucidated in future studies.

As for diagnosis of AIP, it has been reported that the specificity of AIP diagnosis was higher in HISORt criteria (97%) than in Japanese criteria (89%) or Asian criteria (89%) (40,41). In Asian criteria, AIP can also be diagnosed by response to steroid therapy (24), which might lead to the increased sensitivity and reduced specificity. Accordingly, we re-evaluated the AIP patients in our cohort by using Japanese or HISORt criteria. As a result, 94 out of the 108 AIP patients in our cohort fulfilled Japanese criteria. In the remaining 14 patients who did not meet Japanese criteria, AIP was diagnosed by Asian criteria with typical histology in resected pancreas in 10 patients or with optional criterion (image+response to steroid therapy) in 4 patients. On the other hand, 104 out of the 108 patients fulfilled HISORt criteria, and the remaining 4 patients were diagnosed by Asian criteria with optional criterion (image+response to steroid therapy). From these results, we believe that the accuracy of the AIP diagnosis was comparable to that made by Japanese or HISORt criteria, and therefore, that our cases of AIP were based on the accepted criteria.

Despite the importance of our findings, the present study has several limitations. Because we used national cancer rates as the control, SIR of cancer in the first year after diagnosis of AIP (6.1 (95% CI 2.3–9.9)) could be overestimated in our cohort who may be more carefully scrutinized than the general population. However, SIR of cancer in the first year after diagnosis of myositis (DM/PM) was reported 4.4 (95% CI 2.7–7.1) by the similar method of the population-based cohort study (20). These comparable values between AIP and myositis might support the high risk for

cancer in the first year after AIP diagnosis. Moreover, to solve this concern, we calculated the relative risk of cancer in comparison with age- and sex-matched control people who first had a medical checkup with almost the same examinations as our cohort. In additional limitation, the sample size was relatively small and retrospective studies are more prone to bias than prospective studies, and this may have contributed to the higher SIR and relative risk. A prospective study with a large number of patients should be performed.

In conclusion, patients who fulfilled the accepted criteria for AIP are at high risk for having cancer. The highest risk for cancer is in the first year after AIP diagnosis, including the time at the diagnosis of AIP, and there is a very low relapse rate of AIP after successful treatment of the accompanying cancer. These data might indicate that a certain portion of AIPs can be categorized as a paraneoplastic syndrome. Finally, more studies are needed to determine whether screening for neoplasia should be done in patients with AIP, and also to decide whether high prevalence of cancer in our cohort really reflects its paraneoplastic phenomenon or merely an epiphenomenon.

ACKNOWLEDGMENTS

This work was supported in part by the Health and Labour Sciences Research Grants for research on intractable diseases (Research on IgG4-related disease) from Ministry of Health, Labour and Welfare of Japan.

CONFLICT OF INTEREST

Guarantor of the article: Yuzo Kodama, MD, PhD.

Specific author contributions: Study concept and design, data acquisition, data analysis and interpretation, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, and study supervision: M.S., K.Y., and T.C. Statistical analysis, study supervision, data acquisition, and drafting of the manuscript: H.H. and K.Y. Patient enrollment, data acquisition, and drafting of the manuscript: J.M., C.K., M.K., S.Y., R.M., Y.S., K.K., Y.O., M.O., H.K., T.I., K.T., Y.O., W.T., T.M., S.K., Y.D., N.U., and T.W.

Competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Recent reports indicate that patients with autoimmune pancreatitis (AIP) occasionally have various cancers.
- ✓ It was also reported that patients with IgG4-related disease are at high risk for cancer.

WHAT IS NEW HERE

- ✓ Increased cancer risk was observed in patients with AIP during the first year after AIP diagnosis.
- ✓ Successful treatment for cancers with abundant IgG4-positive plasma cell infiltration may be associated with remission of AIP.
- ✓ These findings suggest that AIP may develop as a paraneoplastic syndrome in some patients.

REFERENCES

- Finkelberg DL, Sahani D, Deshpande V *et al*. Autoimmune pancreatitis. *N Engl J Med* 2006;355:2670–6.
- 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.
- Chiba T. Are immunoglobulin G4-positive multiorgan lymphoproliferative syndrome and autoimmune pancreatitis different manifestations of a common clinicopathologic entity? *Gastroenterology* 2010;138:781–4.
- Inoue H, Miyatani H, Sawada Y *et al*. A case of pancreas cancer with autoimmune pancreatitis. *Pancreas* 2006;33:208–9.
- Loos M, Esposito I, Hedderich DM *et al*. Autoimmune pancreatitis complicated by carcinoma of the pancreatobiliary system: a case report and review of the literature. *Pancreas* 2011;40:151–4.
- Pezzilli R, Vecchiarelli S, Di Marco MC *et al*. Pancreatic ductal adenocarcinoma associated with autoimmune pancreatitis. *Case Rep Gastroenterol* 2011;5:378–85.
- Kim T, Grobmyer SR, Dixon LR *et al*. Autoimmune pancreatitis and concurrent small lymphocytic lymphoma: not just a coincidence? *J Gastrointest Surg* 2008;12:1566–70.
- Takahashi N, Ghazale AH, Smyrk TC *et al*. Possible association between IgG4-associated systemic disease with or without autoimmune pancreatitis and non-Hodgkin lymphoma. *Pancreas* 2009;38:523–6.
- Oh HC, Kim JG, Kim JW *et al*. Early bile duct cancer in a background of sclerosing cholangitis and autoimmune pancreatitis. *Intern Med* 2008;47:2025–8.
- Arai O, Matsueda K, Katayama S *et al*. Case of autoimmune pancreatitis with various extrapancreatic fibrosclerosis followed by malignant diseases. *Nihon Shokakibyo Gakkai Zasshi* 2008;105:711–8.
- Nishino T, Toki F, Oyama H *et al*. Long-term outcome of autoimmune pancreatitis after oral prednisolone therapy. *Intern Med* 2006;45:497–501.
- Ito M, Naruke Y, Mihara Y *et al*. Thyroid papillary carcinoma with solid sclerosing change in IgG4-related sclerosing disease. *Pathol Int* 2011;61:589–92.
- Yamamoto M, Takahashi H, Tabeya T *et al*. Risk of malignancies in IgG4-related disease. *Mod Rheumatol* 2012;22:414–8.
- Bernatsky S, Ramsey-Goldman R, Clarke A. Malignancy and autoimmunity. *Curr Opin Rheumatol* 2006;18:129–34.
- Szekanecz E, Andras C, Sandor Z *et al*. Malignancies and soluble tumor antigens in rheumatic diseases. *Autoimmun Rev* 2006;6:42–7.
- Szekanecz Z, Szekanecz E, Bako G *et al*. Malignancies in autoimmune rheumatic diseases—a mini-review. *Gerontology* 2011;57:3–10.
- Ekbom A, Helmick C, Zack M *et al*. Ulcerative colitis and colorectal cancer—a population-based study. *N Engl J Med* 1990;323:1228–33.
- Itzkowitz SH, Harpaz N. Diagnosis and management of dysplasia in patients with inflammatory bowel diseases. *Gastroenterology* 2004;126:1634–48.
- Sandanayake NS, Church NI, Chapman MH *et al*. Presentation and management of post-treatment relapse in autoimmune pancreatitis/immunoglobulin G4-associated cholangitis. *Clin Gastroenterol Hepatol* 2009;7:1089–96.
- Buchbinder R, Forbes A, Hall S *et al*. Incidence of malignant disease in biopsy-proven inflammatory myopathy. A population-based cohort study. *Ann Intern Med* 2001;134:1087–95.
- Zahr ZA, Baer AN. Malignancy in myositis. *Curr Rheumatol Rep* 2011;13:208–15.
- Sigurgeirsson B, Lindelof B, Edhag O *et al*. Risk of cancer in patients with dermatomyositis or polymyositis. A population-based study. *N Engl J Med* 1992;326:363–7.
- Andras C, Ponyi A, Constantin T *et al*. Dermatomyositis and polymyositis associated with malignancy: a 21-year retrospective study. *J Rheumatol* 2008;35:438–44.
- Otsuki M, Chung JB, Okazaki K *et al*. Asian diagnostic criteria for autoimmune pancreatitis: consensus of the Japan-Korea Symposium on Autoimmune Pancreatitis. *J Gastroenterol* 2008;43:403–8.
- Okazaki K, Uchida K, Koyabu M *et al*. Recent advances in the concept and diagnosis of autoimmune pancreatitis and IgG4-related disease. *J Gastroenterol* 2011;46:277–88.
- Chari ST. Diagnosis of autoimmune pancreatitis using its five cardinal features: introducing the Mayo Clinic's HISORT criteria. *J Gastroenterol* 2007;42 (Suppl 18): 39–41.
- Chari ST, Murray JA. Autoimmune pancreatitis, Part II: the relapse. *Gastroenterology* 2008;134:625–8.
- Ghazale A, Chari ST. Optimising corticosteroid treatment for autoimmune pancreatitis. *Gut* 2007;56:1650–2.
- Matsuda T, Marugame T, Kamo KI *et al*. Cancer incidence and incidence rates in Japan in 2006: based on data from 15 population-based cancer registries in the monitoring of cancer incidence in Japan (MCIJ) project. *Jpn J Clin Oncol* 2012;42:139–47.
- Kamisawa T, Funata N, Hayashi Y *et al*. Close relationship between autoimmune pancreatitis and multifocal fibrosclerosis. *Gut* 2003;52: 683–7.
- Kamisawa T, Funata N, Hayashi Y *et al*. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003;38:982–4.
- Axon A. Review article: gastric cancer and *Helicobacter pylori*. *Aliment Pharmacol Ther* 2002;16 (Suppl 4): 83–8.
- Seeff LB. Natural history of chronic hepatitis C. *Hepatology* 2002;36: S35–46.
- Ponyi A, Constantin T, Garami M *et al*. Cancer-associated myositis: clinical features and prognostic signs. *Ann N Y Acad Sci* 2005;1051:64–71.
- Azuma K, Yamada H, Ohkubo M *et al*. Incidence and predictive factors for malignancies in 136 Japanese patients with dermatomyositis, polymyositis and clinically amyopathic dermatomyositis. *Mod Rheumatol* 2011;21: 178–83.
- Watanabe T, Yamashita K, Fujikawa S *et al*. Activation of toll-like receptors and NOD-like receptors is involved in enhanced IgG4 responses in autoimmune pancreatitis. *Arthritis Rheum* 2012;64:914–24.
- Apetoh L, Ghiringhelli F, Tesniere A *et al*. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. *Nat Med* 2007;13:1050–9.
- Curtin JF, Liu N, Candolfi M *et al*. HMGB1 mediates endogenous TLR2 activation and brain tumor regression. *PLoS Med* 2009;6:e10.
- Gotte M, Yip GW. Heparanase, hyaluronan, and CD44 in cancers: a breast carcinoma perspective. *Cancer Res* 2006;66:10233–7.
- Naitoh I, Nakazawa T, Ohara H *et al*. Comparative evaluation of the Japanese diagnostic criteria for autoimmune pancreatitis. *Pancreas* 2010;39:1173–9.
- Okazaki K, Uchida K, Matsushita M *et al*. How to diagnose autoimmune pancreatitis by the revised Japanese clinical criteria. *J Gastroenterol* 2007;42 (Suppl 18): 32–8.