1
2
3 **RELATIONSHIP BETWEEN AUTOIMMUNE PANCREATITIS AND PANCREATIC CANCER: A SINGLE-CENTER**
4 **EXPERIENCE**
5
6
7
8

9
10 Tsukasa Ikeura, MD, PhD, Hideaki Miyoshi, MD, PhD, Kazushige Uchida, MD, PhD, Toshiro Fukui, MD,
11 PhD, Masaaki Shimatani, MD, PhD, Yuri Fukui, MD, PhD, Kimi Sumimoto, MD, Mitsunobu Matsushita,
12 MD, PhD, Makoto Takaoka, MD, PhD, Kazuichi Okazaki, MD, PhD.
13
14
15

16 The third Department of Internal Medicine, Kansai Medical University, Osaka, Japan
17
18
19

20 **Running title:** Relationship between AIP and pancreatic cancer
21

22 **Keywords:** autoimmune pancreatitis, pancreatic cancer, chronic pancreatitis, carcinogenesis
23

24 **Disclosures:** The authors declare that there is no conflict of interest.
25

26 **Address for correspondence:** Tsukasa Ikeura
27

28 The Third Department of Internal Medicine
29

30 Kansai Medical University
31

32 2-3-1, Shinmachi, Hirakata
33

34 573-1191 Osaka – Japan
35

36 Phone: +81-72-804-0101
37

38 Fax: +81-72-804-2524
39

40 E-mail: ikeurat@takii.kmu.ac.jp
41
42
43
44

45 **AUTHOR CONTRIBUTIONS:**
46

47 The contributions of the Authors are the following:
48

- 49 1. Conception and design of the study: Tsukasa Ikeura, Hideaki Miyoshi, Yuri Fukui, and Kazuichi
50 Okazaki
51
- 52 2. Collection of data: Tsukasa Ikeura, Hideaki Miyoshi, Kazushige Uchida, Toshiro Fukui, Masaaki
53 Shimatani, Yuri Fukui, Kimi Sumimoto, and Makoto Takaoka
54
- 55 3. Drafting: Tsukasa Ikeura, Hideaki Miyoshi, and Yuri Fukui
56
- 57 4. Revision of the manuscript; Kazushige Uchida, Mitsunobu Matsushita, and Kazuichi Okazaki
58
- 59 5. Approval of the final version of the manuscript: Kazuichi Okazaki
60
61
62
63
64
65

ABSTRACT

Objectives: Ordinary chronic pancreatitis (CP), such as alcoholic CP, is well established to have the increased risk for pancreatic cancer (PaC), nevertheless an association between autoimmune pancreatitis (AIP) and PaC is still unknown. The aims of this study are to examine the frequency of patients who developed PaC during follow-up after being diagnosed with type 1 AIP and to compare the incidence rate of PaC between patients with type 1 AIP and CP.

Methods: Sixty-three patients with type 1 AIP and 41 patients with CP were enrolled. We examined development of PaC during follow-up from their clinical records.

Results: The mean follow-up period was 62.4 months in AIP group and 49.2 months in CP group. The occurrence of PaC was observed in 3 patients with AIP during the mean follow-up period of 94.7 months (range, 31-186), whereas a single CP patient developed PaC 38 months after CP diagnosis. The incident rate of PaC during follow-up was comparable between the 2 groups [4.8% (3/63) in type 1 AIP group vs. 2.4% (1/41) in CP group]. In all of 3 AIP patients who developed accompanying PaC, the clinical remission of AIP was achieved with maintenance steroid therapy, when tumors were discovered. In the histological examination of one surgical patient with PaC, lymphoplasmacytic infiltration in storiform fibrosis with

abundant IgG4-positive cell infiltration was observed around the PaC area.

Conclusions: Similar to patients with ordinary CP, surveillance for development of PaC is needed at regular interval during follow-up in AIP patients.

INTRODUCTION

Autoimmune pancreatitis (AIP), which was first proposed as a clinical entity by Yoshida et al. in 1995, is characterized by focal or diffuse pancreatic enlargement, irregular narrowing of the main pancreatic duct (MPD), and a dramatic response to steroid therapy¹⁻⁴. To date, 2 AIP subtypes have been recognized, type 1 and type 2⁵. The histological features of type 1 AIP include periductal infiltration of lymphocytes, abundant IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis, specifically lymphoplasmacytic sclerosing pancreatitis (LPSP). Type 2 AIP, on the other hand, is histologically characterized by the presence of granulocytic epithelial lesions without IgG4-positive plasma cell infiltration, specifically idiopathic duct-centric chronic pancreatitis (IDCP) or AIP with granulocyte epithelial lesions (GELs)^{6, 7}. Previous studies have reported the distinguishing characteristics in clinical profiles and outcomes of type 1 and type 2 AIP⁸⁻¹². Type 1 AIP is classified as a pancreatic manifestation of IgG4-related disease, and is probably a systemic disease with an abnormal immunological process¹³.

Currently, little is known about the natural clinical history of AIP. The prognosis of AIP is considered to be favorable because it is responsive to steroid therapy. However, reports indicate that 24-57% of the patients who receive steroid therapy experience a relapse¹³⁻¹⁵. Additionally, previous papers

1
2
3 have suggested an association between AIP and pancreatic cancer (PaC)¹⁶⁻²⁴. It is extremely important for
4
5
6
7 clinicians to recognize the validity and the magnitude of the association between AIP and PaC, although
8
9
10 whether patients suffering from AIP are more susceptible to PaC has not been clearly elucidated.
11
12

13
14 The aims of this study were to examine the frequency with which patients developed PaC during
15
16
17 follow-up after being diagnosed with type 1 AIP, to clarify the clinical and histological characteristics of
18
19
20 type 1 AIP patients with PaC, and to compare the incidence rate of PaC between patients with type 1 AIP
21
22
23 and ordinary chronic pancreatitis (CP), which is a well-established risk factor for PaC^{25, 26}.
24
25
26
27
28
29
30

31 **METHODS**

32
33
34
35
36
37
38

39 **Identification of type 1 AIP patients**

40
41

42 We reviewed data from all AIP patients included in our database starting in 2002. We applied the
43
44
45 international consensus diagnostic criteria (ICDC) to each patient based on clinical, serological,
46
47
48 radiological, and histological findings⁵. The current study included patients diagnosed with type 1 AIP who
49
50
51
52
53 were followed for more than 1 year using imaging modalities. These criteria led to inclusion of 63 patients
54
55
56 suffering from type 1 AIP (definitive type 1 AIP in 61 patients, and probable type 1 AIP in 2 patients) in the
57
58
59
60
61
62
63
64
65

study. Many of these patients were included in the previously published papers^{22, 27, 28}.

For the purpose of this study, we used clinical records to retrieve patient data, including age at the clinical onset of the disease, sex, length of observation period, and development of PaC or extrapancreatic cancer during the follow-up period. The observation period was defined as the time from the diagnosis of AIP until the final contact or, in cases accompanied by PaC, until the diagnosis of PaC. To allow further analysis of the clinical factors associated with development of PaC in type 1 AIP patients, we also collected the following information: alcohol and smoking habits, medical history, diabetes history, pancreatic parenchymal finding, pancreatic ductal finding, IgG4 serum levels, other organ involvement, therapy for the disease (steroid, resection, no treatment), and disease relapse.

Identification of ordinary CP patients

Clinical information of ordinary CP patients, including alcoholic CP and hereditary CP patients, who were observed at our institution from November 2002 to December 2011, were retrospectively reviewed to compare the incidence rate of PaC between patients with type 1 AIP and patients with ordinary CP. Of these CP patients, only CP patients who were followed for more than 1 year using imaging modalities were included in the current study. The diagnosis of CP was based on the clinical diagnostic criteria proposed by

the Japan Pancreas Society²⁹. We enrolled 41 CP patients (34 with definitive CP and 7 with probable CP).

Briefly, 34 patients diagnosed as definitive CP had multiple calcifications distributed in the entire pancreas on computed tomography (CT), and 7 patients diagnosed as probable CP had no calcification in the pancreas but irregular dilatation of the MPD throughout the entire pancreas plus pancreatic deformity with irregular contour on CT. As with type 1 AIP patients, clinical information of included CP patients was reviewed.

Definitions

Patients were divided into 2 groups based on their alcohol consumption: (1) teetotalers (non-drinkers), and (2) drinkers. They were also divided on the basis of smoking habits into non-smokers and smokers.

Diabetes was defined as a fasting glucose level > 126 mg/dL or a glucose level > 201 mg/dL 2 hours after an oral glucose tolerance test.

The upper limit of normal value of serum IgG4 was defined as 135 mg/dL³⁰.

Initial steroid therapy was performed with either conventional oral steroid therapy or steroid pulse therapy^{31, 32}. For conventional oral steroid therapy, prednisolone was administrated at an initial dose of 30 to 40 mg per day for 2 weeks, and was subsequently gradually tapered by 5 mg every 1 to 2 weeks until the

1
2
3 maintenance dosage was reached. Steroid pulse therapy involved intravenous administration of
4
5
6
7 methylprednisolone at a dose of 500 mg per day for 3 consecutive days per week for 2 straight weeks. After
8
9
10 steroid pulse therapy, we administered prednisolone at 20 mg per day, and it was gradually tapered until the
11
12
13 maintenance dosage was reached. After initial steroid therapy, if needed, maintenance steroid therapy was
14
15
16
17 performed for at least 6 months with prednisolone at a dose of 2.5 to 5.0 mg per day to prevent relapse.
18
19
20

21 AIP relapse was defined as the reappearance of pancreatic or extrapancreatic involvement after
22
23
24 steroid withdrawal.
25
26
27
28
29
30

31 **Statistical analysis**

32
33
34

35 Differences among the groups were analyzed using chi-squared test or Fisher's Exact test for
36
37
38 qualitative variables, and Mann-Whitney's U test for quantitative variables. A p-value > 0.05 was
39
40
41
42 considered statistically significant.
43
44
45
46
47
48

49 **RESULTS**

50
51
52
53
54
55

56 **Characteristics of type 1 AIP Patients**

57
58
59
60
61
62
63
64
65

The characteristics of the 63 patients with type 1 AIP are shown in Table 1. The mean follow-up period was 62.4 months (range, 12-195 months). All patients underwent imaging modalities, such as CT and magnetic resonance cholangiopancreatography (MRCP), for surveillance of AIP at least once a year during follow-up.

CT at the time of diagnosis of AIP revealed diffuse enlargement of the pancreas in 26 patients (41%), focal enlargement in 30 (48%), and a pancreatic mass without parenchymal enlargement in 7 (11%). Examination with endoscopic retrograde cholangiopancreatography (ERCP) or MRCP (available in 57 patients) revealed long or multiple strictures of the MPD in 30 patients (53%), focal narrowing of the MPD in 22 patients (39%), and no narrowing of the MPD in 5 patients (8%). IgG4 serum levels were measured in 61 patients at the time of diagnosis of AIP. IgG4 serum levels were higher than twice the upper normal limit in 40 patients (66%), 1 to 2 times the upper normal limit in 17 patients (28%), and normal in 4 patients (6%). Twenty patients (31%) had other organ involvement [biliary duct stricture in 9 patients (14%), enlargement of the salivary or lachrymal gland in 7 (11%), retroperitoneal fibrosis in 5 (8%), and renal involvement in 3 (5%)]. Fifty-one of the 63 patients (81%) were treated with steroid therapy (31 with conventional oral steroid therapy and 20 with steroid pulse therapy) as the initial treatment for AIP. After initial steroid therapy, 39 patients underwent maintenance steroid therapy. All patients who received steroid therapy

showed remission of the disease. Seven out of 63 patients (11%) underwent surgery because of suspected cancer. The remaining 5 patients (8%) were followed-up conservatively. Of 59 patients who underwent surgery or steroid therapy, 12 patients (19%) exhibited relapse of the disease.

Of 63 patients, 8 cancers were observed in 6 patients (9%), either synchronously or metachronously. The spectrum of malignancies included PaC (n = 3), gastric cancer (n = 2), colon cancer (n = 1), leukemia (n = 1), and melanoma (n = 1). All PaCs were found after the diagnosis of AIP.

Development of PaC in type 1 AIP patients

Case 1

A 61-year-old female presented with a mass-like enlargement of the pancreatic head with focal narrowing of the MPD (Fig. 1a). Her IgG4 serum level was 338 mg/dL. She was diagnosed with AIP based on these findings. Initial steroid therapy and subsequent maintenance therapy with prednisolone were performed and led to remission of the disease (Fig. 1b). Thirty-one months after the AIP diagnosis, she experienced jaundice due to a stricture in the lower bile duct despite being on maintenance steroid therapy. CT showed a low-density irregular mass in the pancreatic head (Fig. 1c), which endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) showed was adenocarcinoma. She underwent

pancreatoduodenectomy, and histological examination of the resected pancreata revealed a moderately differentiated ductal adenocarcinoma in the pancreatic head (Fig. 2a). Marked lymphoplasmacytic infiltration with storiform fibrosis surrounded the cancerous region (Fig. 2b). Immunohistochemical analysis revealed numerous IgG4-expressing plasma cells in the inflammatory area (Fig. 2c). Pancreatic intraepithelial neoplasia (PanIN) lesion was not seen in the non-cancerous region surrounding the PaC (Fig. 2d). After surgery, no morphological change was seen in the remnant pancreas on CT.

Case 2

A 39-year-old woman was diagnosed with AIP based on elevated serum levels of IgG4 and radiological abnormalities in the pancreatic tail such as focal enlargement of the pancreas and narrowing of the MPD. She had other autoimmune disorders, such as mixed connective tissue disease and Sjogren's syndrome. She underwent maintenance steroid therapy, which led to remission of the disease. One hundred eighty-six months after the diagnosis of AIP, a low-density mass was identified in the pancreatic body on contrast-enhanced CT performed for surveillance of AIP. EUS-FNA was used to obtain a sample from the mass, and the result of the cytological examination was positive for malignancy. She underwent distal pancreatectomy. Histological examination revealed a moderately differentiated ductal adenocarcinoma in the pancreatic body (Fig. 3a). The acinar cells around the cancerous region were replaced by massive inter-

and intralobular fibrosis with a pattern that was not storiform fibrosis (Fig. 3b). Obliterative phlebitis was not seen. Immunohistochemistry revealed scattered IgG4-positive cells (Fig. 3c). PanIN lesion was not seen in the non-cancerous region surrounding the PaC (Fig 3d).

Case 3

An 80-year-old male had obstructive jaundice due to a focal enlargement in the head of the pancreas (Fig. 4a). ERCP showed diffuse narrowing of the MPD. His IgG4 serum levels were 154 mg/dL. Based on the diagnosis of AIP, he was treated with a steroid, and it led to improvement of clinical and radiological findings (Fig. 4b). While being treated with maintenance steroid therapy (67 months after the diagnosis of AIP), a pancreatic body tumor with upstream dilatation of the pancreatic duct was detected (Fig. 4c). Cytological examination of material obtained by EUS-FNA from the tumor revealed adenocarcinoma, and the laparoscopic study identified peritoneal metastasis, leading to a diagnosis of unresectable PaC. He was treated with systemic chemotherapy.

Comparison of clinical characteristics between patients with or without PaC

There were no significant differences in age, observation period, incidence of drinking and smoking, or prevalence of diabetes between patients who developed and those who did not develop PaC (Table 2). A

1
2
3 higher proportion of patients who developed PaC had focal enlargement of the pancreas, focal narrowing of
4
5
6
7 the MPD, and marked elevation in IgG4 levels compared with patients who did not develop PaC, but there
8
9
10 were no significant differences between the 2 groups. The percentage of type 1 patients who underwent
11
12
13
14 initial steroid therapy and subsequent maintenance steroid therapy was comparable between the 2 groups.
15
16
17
18
19
20

21 **Comparison in incidence of PaC between type 1 AIP patients and CP patients**

22
23
24

25 Forty-one patients were included in CP group [29 males and 12 females; mean age at clinical onset,
26
27
28 60.2 years (range, 22-89)] (Table 3). The percentage of males, age at clinical onset, and observation period
29
30
31 were comparable between CP group and type 1 AIP group. There was a statistically significant difference in
32
33
34
35 the prevalence of alcohol drinkers between the 2 groups (8% in type 1 AIP group vs. 61% in CP group, $p <$
36
37
38 0.001). PaC occurred in a single patient 38 months after CP diagnosis. The incident rate of PaC in type 1
39
40
41
42 AIP group was 4.8% (3/63), which was higher than in CP group [2.4% (1/41)], although there was no
43
44
45
46 statistical difference. The annual incidence rates of PaC in type 1 AIP group and CP group were 0.92 % and
47
48
49 0.59 % per year, respectively.
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

DISCUSSION

This is the first paper to systematically assess the prevalence of PaC in patients with type 1 AIP. The results show that PaC occurred in 4.8% of type 1 AIP patients during the observation period. This incident rate was comparable to that of patients suffering from ordinary CP (2.4%).

Chronic inflammatory processes play a well-recognized role in carcinogenesis: e.g., liver cancer in chronic hepatitis B and C³³, gastric cancer in *Helicobacter pylori*-induced gastritis³⁴, and colon cancer in inflammatory bowel disease³⁵. Additionally, ordinary CP, such as alcoholic, hereditary, and tropical CP, has been established to increase the risk for developing PaC due to progressive and irreversible inflammation of the pancreas. Pre-existing ordinary CP result in about a 10-20-fold increased risk of pancreatic cancer^{25, 26}.

The previously held belief was that AIP, in contrast to CP, is a reversible disease with a favorable prognosis because of the dramatic improvement of clinical and radiological findings when steroid therapy is given.

However, persistently high IgG4 serum concentrations and relapses of pancreatic swelling and narrowing of the MPD occur in 60% and 58% of AIP patients, respectively, after steroid therapy, indicating that chronic inflammation of the pancreas in AIP patients may continue histologically even after remission of the disease is induced by steroid therapy^{36, 37}. Indeed, a recent paper reported that type 1 AIP patients with

1
2
3 pancreatic head swelling or MPD nonnarrowing in the pancreatic body may progress to an advanced stage
4
5
6
7 of CP due to pancreatic juice stagnation³⁸. As biologic evidence that supports an association between AIP
8
9
10 and PaC, the prevalence of PanIN in AIP patients was reported to be higher than that in non-autoimmune
11
12
13 forms of pancreatitis, although this comparison did not reach the level of statistical significance. Moreover,
14
15
16
17 significant K-ras mutations, which are known to be found in nearly all patients with pancreatic cancer, were
18
19
20
21 frequently detected in the pancreas of patients suffering from AIP^{17, 39}. Taking the above into consideration,
22
23
24
25 AIP might have malignant potential for development of PaC, as has been observed with ordinary CP.
26
27

28 A recent study by Shiokawa et al. reported that the risk of developing various cancers was highest
29
30
31 during the first year after AIP diagnosis, and that most patients diagnosed with cancer prior to the diagnosis
32
33
34
35 of AIP did not experience relapse of AIP after the successful treatment of the cancer⁴⁰. From these data, they
36
37
38
39 speculate that AIP may be a manifestation of paraneoplastic syndrome, which is a rare condition triggered
40
41
42 by an altered immune system response to a neoplasm⁴¹. In our cohort, 3 PaCs were found during the mean
43
44
45
46 follow-up period of 94.7 months (range, 31-186 months), indicating that the process of carcinogenesis had
47
48
49
50 not yet occurred in the pancreas at the time of the diagnosis of type 1 AIP, and that our cases were not
51
52
53
54 associated with paraneoplastic syndrome.
55
56
57
58
59
60
61
62
63
64
65

Although case reports and studies regarding synchronous or metachronous development of PaC in AIP patients have been published before, there have been only a few papers that have used resected pancreatic tissue to examine the histological association between PaC and the parenchyma surrounding the PaC^{23, 24}. This is because patients with PaC frequently have unresectable disease due to late clinical presentation. In this study, we were able to use resected pancreata to histologically evaluate in detail 2 AIP patients who developed accompanying PaC. One patient (Case 1) demonstrated not only dense lymphoplasmacytic infiltration in storiform fibrosis, but also infiltration of numerous IgG4-positive plasma cells around the PaC, fulfilling histological Level 1 Criteria for type 1 AIP according to ICDC⁵. This finding that PaC occurred in the background of LPSP suggested that carcinogenesis can be attributed to longstanding pancreatic inflammation. The other patient (Case 2) exhibited dense fibroinflammation with acinar atrophy accompanied by rather mild inflammatory infiltration around the PaC area. IgG4 immunostaining of this area showed scanty IgG4-positive cell infiltration. These changes were consistent with those observed in obstructive pancreatitis caused by PaC⁴². Therefore, the process of pancreatic carcinogenesis in the 2 cases appears to be different. On the other hand, Gupta et al. reported that the prevalence of PanIN in type 1 AIP and non-autoimmune forms of CP was 64% and 63%, respectively, suggesting the possibility that the risk of malignancy in type 1 AIP and ordinary CP may be equivalent.

1
2
3 However, PanIN lesion was not seen in the non-cancerous region surrounding the PaC in these 2 patients.
4
5

6
7 Further histological investigation about pancreatic carcinogenesis in AIP is needed.
8
9

10 Three multicenter surveys reported that PaC occurred less commonly after the diagnosis of AIP,
11
12 which is in contrast to the result of our single-center study^{10, 13, 43}. The most recent study also demonstrated
13
14 that patients with AIP had a high risk of developing various cancers, such as gastric cancer, prostate cancer,
15
16 and colon cancer, but none of the AIP patients had PaC⁴⁰. Although the incidence rate for the development
17
18 of PaC in AIP patients might be overestimated in this study owing to population bias, we should be careful
19
20 to monitor for the development of PaC during long-term follow-up.
21
22
23
24
25
26
27
28
29
30

31 Interestingly, all 3 AIP patients who developed PaC were recognized as focal type AIP at the onset
32
33 of the disease and receiving low-dose maintenance therapy with prednisolone at the diagnosis of PaC. The
34
35 previous study about clinical differences between the focal and diffuse AIP reported that the mean serum
36
37 levels of IgG4 were significantly higher in focal than in diffuse AIP, and that recurrences occurred more
38
39 frequently in focal AIP than in diffuse AIP³. This data may suggest the possibility that the pancreatic
40
41 inflammation may be more likely to be sustained even after steroid therapy in focal type AIP more than in
42
43 diffuse type AIP. From the standpoint that chronic inflammatory processes play a critical role in
44
45 carcinogenesis, patients with focal type AIP may be likely to develop PaC. Moreover, the
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3 immunosuppressed state of the patients that is produced by longstanding steroid therapy is also possibly
4
5
6
7 related to the development of PaC in AIP patients⁴⁴. However, in the comparison between AIP patients with
8
9
10 and those without PaC, focal form of the disease and maintenance steroid therapy were not statistically
11
12
13 identified as a clinical predictor for the development of PaC in AIP patients. This may be because the study
14
15
16 sample size was small. Larger prospective studies are needed to clarify whether or not focal form of the
17
18
19 disease and maintenance steroid therapy are closely related to carcinogenesis of the pancreas in AIP.
20
21
22
23

24 Diagnosing AIP can be challenging, because AIP and PaC share clinical and radiological
25
26
27 characteristics, such as age of disease onset, mass formation in the pancreas, and painless obstructive
28
29
30 jaundice. While AIP is responsive to steroid therapy, surgical resection is the only curative treatment for
31
32
33 PaC⁴⁵. Therefore, it is extremely crucial to differentiate between AIP and PaC in order to avoid
34
35
36 inappropriate treatment. In the patients who had AIP accompanied by PaC, tumors were incidentally
37
38
39 discovered as new findings, such as mass formation and stricture of the lower bile duct, on CT or MRCP
40
41
42 performed as surveillance for AIP. These findings in imaging studies of AIP patients during follow-up may
43
44
45
46 lead to a mistaken diagnosis of relapsed AIP. In order to avoid inappropriate treatment, it is important to
47
48
49 recognize the possibility that PaC can develop in AIP patients during the observation period, and
50
51
52
53 pathological examination using EUS-FNA is needed. However, there may also be a concern that patients
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3 with PaC may be misdiagnosed with AIP due to insufficient biopsy specimens by fine needle aspiration,
4
5
6
7 and because pancreatic cancer sometimes shows histological findings mimicking those of AIP, such as
8
9
10 marked infiltration with IgG4-positive plasma cells⁴⁶⁻⁴⁸. Furthermore, in steroid trials that use conventional
11
12
13 oral steroid therapy or steroid pulse therapy, it is essential to confirm the partial or complete resolution of
14
15
16 the disease with tests for radiological and serological abnormalities, even after a negative workup for
17
18
19 cancer by EUS-FNA^{5, 32, 49}.
20
21
22
23

24 In conclusion, patients with type 1 AIP have a higher risk of PaC, similar to patients with ordinary
25
26
27 CP, although the result we offered was not sufficient to categorically link type 1 AIP with an elevated risk of
28
29
30 carcinoma. Nonetheless, surveillance not only for relapse of AIP but also for development of PaC is needed
31
32
33 at regular intervals during follow-up of type 1 AIP patients. Long-term prospective studies in large cohorts
34
35
36 of AIP patients are required to determine the exact relationship between AIP and PaC.
37
38
39
40
41
42
43
44

45 **ACKNOWLEDGMENT**

46
47
48

49 The authors thank Dr. Sakagami Junichi, Kyoto Prefectural University of Medicine, for providing clinical
50
51
52 data of a patient included in this study.
53
54
55

56 This study was partly supported by (1) Grant-in-Aid for Scientific Research of Ministry of Culture and
57
58
59
60
61
62
63
64
65

1
2
3 Science of Japan (23591017,24591020), (2) Grant-in-Aid for “Research for Intractable Disease” Program
4
5
6
7 from the Ministry of Health, Labour and Welfare of Japan, (3) grants-in-aid from CREST Japan Science
8
9
10 and Technology Agency, and (4) NEXT-Supported Program for the Strategic Research Foundation at
11
12
13
14 Private Universities.
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

REFERENCES

1. Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K, Hayashi N. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. *Dig Dis Sci* 1995;40:1561-8.
2. Finkelberg DL, Sahani D, Deshpande V, Brugge WR. Autoimmune pancreatitis. *N Engl J Med* 2006;355:2670-6.
3. Frulloni L, Scattolini C, Falconi M, Zamboni G, Capelli P, Manfredi R, et al. Autoimmune pancreatitis: differences between the focal and diffuse forms in 87 patients. *Am J Gastroenterol* 2009;104:2288-94.
4. Okazaki K, Uchida K, Koyabu M, Miyoshi H, Takaoka M. Recent advances in the concept and diagnosis of autoimmune pancreatitis and IgG4-related disease. *J Gastroenterol* 2011;46:277-288.
5. Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas* 2011;40:352-8.
6. Notohara K, Burgart LJ, Yadav D, Chari S, Smyrk TC. Idiopathic chronic pancreatitis with

- periductal lymphoplasmacytic infiltration: clinicopathologic features of 35 cases. *Am J Surg Pathol* 2003;27:1119-27.
7. Zamboni G, Luttges J, Capelli P, Frulloni L, Cavallini G, Pederzoli P, et al. Histopathological features of diagnostic and clinical relevance in autoimmune pancreatitis: a study on 53 resection specimens and 9 biopsy specimens. *Virchows Arch* 2004;445:552-63.
8. Sah RP, Chari ST, Pannala R, Sugumar A, Clain JE, Levy MJ, et al. Differences in clinical profile and relapse rate of type 1 versus type 2 autoimmune pancreatitis. *Gastroenterology* 2010;139:140-8; quiz e12-3.
9. Maire F, Le Baleur Y, Rebours V, Vullierme MP, Couvelard A, Voitot H, et al. Outcome of patients with type 1 or 2 autoimmune pancreatitis. *Am J Gastroenterol* 2011;106:151-6.
10. Kamisawa T, Kim MH, Liao WC, Liu Q, Balakrishnan V, Okazaki K, et al. Clinical characteristics of 327 Asian patients with autoimmune pancreatitis based on Asian diagnostic criteria. *Pancreas* 2011;40:200-5.
11. Detlefsen S, Zamboni G, Frulloni L, Feyerabend B, Braun F, Gerke O, et al. Clinical features and relapse rates after surgery in type 1 autoimmune pancreatitis differ from type 2: a study of 114 surgically treated European patients. *Pancreatology* 2012;12:276-83.

- 1
2
3
4 12. Okazaki K, Uchida K, Ikeura T, Takaoka M. Current concept and diagnosis of IgG4-related
5
6
7 disease in the hepato-bilio-pancreatic system. J Gastroenterol 2013;48:303-14.
8
9
10
11 13. Kamisawa T, Shimosegawa T, Okazaki K, Nishino T, Watanabe H, Kanno A, et al. Standard
12
13
14 steroid treatment for autoimmune pancreatitis. Gut 2009;58:1504-7.
15
16
17
18 14. Kubota K, Watanabe S, Uchiyama T, Kato S, Sekino Y, Suzuki K, et al. Factors predictive of
19
20
21 relapse and spontaneous remission of autoimmune pancreatitis patients treated/not treated with
22
23
24 corticosteroids. J Gastroenterol 2011;46:834-42.
25
26
27
28 15. Sandanayake NS, Church NI, Chapman MH, Johnson GJ, Dhar DK, Amin Z, et al. Presentation
29
30
31 and management of post-treatment relapse in autoimmune pancreatitis/immunoglobulin
32
33
34 G4-associated cholangitis. Clin Gastroenterol Hepatol 2009;7:1089-96.
35
36
37
38
39 16. Gupta R, Khosroshahi A, Shinagare S, Fernandez C, Ferrone C, Lauwers GY, et al. Does
40
41
42 autoimmune pancreatitis increase the risk of pancreatic carcinoma?: a retrospective analysis of
43
44
45 pancreatic resections. Pancreas 2013;42:506-10.
46
47
48
49 17. Kamisawa T, Tsuruta K, Okamoto A, Horiguchi S, Hayashi Y, Yun X, et al. Frequent and
50
51
52 significant K-ras mutation in the pancreas, the bile duct, and the gallbladder in autoimmune
53
54
55 pancreatitis. Pancreas 2009;38:890-5.
56
57
58
59
60
61
62
63
64
65

- 1
2
3
4 18. Loos M, Esposito I, Hedderich DM, Ludwig L, Fingerle A, Friess H, et al. Autoimmune
5
6
7 pancreatitis complicated by carcinoma of the pancreatobiliary system: a case report and review
8
9
10 of the literature. *Pancreas* 2011;40:151-4.
11
12
13
14 19. Ghazale A, Chari S. Is autoimmune pancreatitis a risk factor for pancreatic cancer? *Pancreas*
15
16
17 2007;35:376.
18
19
20
21 20. Inoue H, Miyatani H, Sawada Y, Yoshida Y. A case of pancreas cancer with autoimmune
22
23
24 pancreatitis. *Pancreas* 2006;33:208-9.
25
26
27
28 21. Pezzilli R, Vecchiarelli S, Di Marco MC, Serra C, Santini D, Calculli L, et al. Pancreatic ductal
29
30
31 adenocarcinoma associated with autoimmune pancreatitis. *Case Rep Gastroenterol*
32
33
34 2011;5:378-85.
35
36
37
38 22. Fukui T, Mitsuyama T, Takaoka M, et al. Pancreatic cancer associated with autoimmune
39
40
41 pancreatitis in remission. *Intern Med* 2008;47:151-155.
42
43
44
45 23. Motosugi U, Ichikawa T, Yamaguchi H, Uchida K, Matsushita M, Okazaki K. Small invasive
46
47
48 ductal adenocarcinoma of the pancreas associated with lymphoplasmacytic sclerosing
49
50
51 pancreatitis. *Pathol Int* 2009;59:744-7.
52
53
54
55 24. Witkiewicz AK, Kennedy EP, Kenneyon L, Yeo CJ, Hruban RH. Synchronous autoimmune
56
57
58
59
60
61
62
63
64
65

- pancreatitis and infiltrating pancreatic ductal adenocarcinoma: case report and review of the literature. *Hum Pathol* 2008;39:1548-51.
25. Lowenfels AB, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. *N Engl J Med* 1993;328:1433-7.
26. Chari ST, Mohan V, Pitchumoni CS, Viswanathan M, Madanagopalan N, Lowenfels AB. Risk of pancreatic carcinoma in tropical calcifying pancreatitis: an epidemiologic study. *Pancreas* 1994;9:62-6.
27. Uchida K, Yazumi S, Nishio A, Kusuda T, Koyabu M, Fukata M, et al. Long-term outcome of autoimmune pancreatitis. *J Gastroenterol* 2009;44:726-32.
28. Sumimoto K, Uchida K, Mitsuyama T, Fukui Y, Kusuda T, Miyoshi H, et al. A proposal of a diagnostic algorithm with validation of International Consensus Diagnostic Criteria for autoimmune pancreatitis in a Japanese cohort. *Pancreatology* 2013;13:230-7.
29. Shimosegawa T, Kataoka K, Kamisawa T, Miyakawa H, Ohara H, Ito T, et al. The revised Japanese clinical diagnostic criteria for chronic pancreatitis. *J Gastroenterol* 2010;45:584-91.
30. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4

- concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001;344:732-8.
31. Matsushita M, Yamashina M, Ikeura T, Shimatani M, Uchida K, Takaoka M, et al. Effective steroid pulse therapy for the biliary stenosis caused by autoimmune pancreatitis. *Am J Gastroenterol* 2007;102:220-1.
32. Tomiyama T, Uchida K, Matsushita M, Ikeura T, Fukui T, Takaoka M, et al. Comparison of steroid pulse therapy and conventional oral steroid therapy as initial treatment for autoimmune pancreatitis. *J Gastroenterol* 2011;46:696-704.
33. Koike K. Hepatocarcinogenesis in hepatitis viral infection: lessons from transgenic mouse studies. *J Gastroenterol* 2002;37 Suppl 13:55-64.
34. Asaka M, Takeda H, Sugiyama T, Kato M. What role does *Helicobacter pylori* play in gastric cancer? *Gastroenterology* 1997;113:S56-60.
35. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001;48:526-35.
36. Kubota K, Iida H, Fujisawa T, Yoneda M, Inamori M, Abe Y, et al. Clinical factors predictive of spontaneous remission or relapse in cases of autoimmune pancreatitis. *Gastrointest Endosc* 2007;66:1142-51.

- 1
2
3
4 37. Kawa S, Hamano H, Ozaki Y, Ito T, Kodama R, Chou Y, et al. Long-term follow-up of
5
6
7 autoimmune pancreatitis: characteristics of chronic disease and recurrence. Clin Gastroenterol
8
9
10 Hepatol 2009;7:S18-22.
11
12
13
14 38. Maruyama M, Arakura N, Ozaki Y, Watanabe T, Ito T, Yoneda S, et al. Type 1 autoimmune
15
16
17 pancreatitis can transform into chronic pancreatitis: a long-term follow-up study of 73 Japanese
18
19
20 patients. Int J Rheumatol 2013;2013:272595.
21
22
23
24 39. Almoguera C, Shibata D, Forrester K, Martin J, Arnheim N, Perucho M. Most human
25
26
27 carcinomas of the exocrine pancreas contain mutant c-K-ras genes. Cell 1988;53:549-54.
28
29
30
31 40. Shiokawa M, Kodama Y, Yoshimura K, Kawanami C, Mimura J, Yamashita Y, et al. Risk of
32
33
34 cancer in patients with autoimmune pancreatitis. Am J Gastroenterol 2013;108:610-17.
35
36
37
38 41. Tai P, Yu E, Joseph K, Miale T. A review of autoimmune diseases associated with cancer. Front
39
40
41 Biosci (Elite Ed) 2010;2:122-6.
42
43
44
45 42. Suda K, Mogaki M, Oyama T, Matsumoto Y. Histopathologic and immunohistochemical
46
47
48 studies on alcoholic pancreatitis and chronic obstructive pancreatitis: special emphasis on
49
50
51 ductal obstruction and genesis of pancreatitis. Am J Gastroenterol 1990;85:271-6.
52
53
54
55 43. Hart PA, Kamisawa T, Brugge WR, Chung JB, Culver EL, Czakó L, et al. Long-term outcomes
56
57
58
59
60
61
62
63
64
65

of autoimmune pancreatitis: a multicentre, international analysis. Gut 2013;62:1771-6.

44. Nishino T, Toki F, Oyama H, Shimizu K, Shiratori K. Long-term outcome of autoimmune pancreatitis after oral prednisolone therapy. Intern Med 2006;45:497-501.
45. Egawa S, Toma H, Ohigashi H, Okusaka T, Nakao A, Hatori T, et al. Japan Pancreatic Cancer Registry; 30th year anniversary: Japan Pancreas Society. Pancreas 2012;41:985-92.
46. Zhang L, Notohara K, Levy MJ, Chari ST, Smyrk TC. IgG4-positive plasma cell infiltration in the diagnosis of autoimmune pancreatitis. Mod Pathol 2007;20:23-8.
47. Bang SJ, Kim MH, Kim dH, Lee TY, Kwon S, Oh HC, et al. Is pancreatic core biopsy sufficient to diagnose autoimmune chronic pancreatitis? Pancreas 2008;36:84-9.
48. Fukui Y, Uchida K, Sumimoto K, Kusuda T, Miyoshi H, Koyabu M, et al. The similarity of Type 1 autoimmune pancreatitis to pancreatic ductal adenocarcinoma with significant IgG4-positive plasma cell infiltration. J Gastroenterol 2013;48:751-61.
49. Moon SH, Kim MH, Park DH, Hwang CY, Park SJ, Lee SS, et al. Is a 2-week steroid trial after initial negative investigation for malignancy useful in differentiating autoimmune pancreatitis from pancreatic cancer? A prospective outcome study. Gut 2008;57:1704-12.

1
2
3 **FIGURE LEGEND**
4
5
6
7
8
9

10 Fig. 1
11
12

13
14 (a) CT revealed a focal enlargement in the head of pancreas (arrow). (b) Steroid therapy led to marked
15
16
17 improvement of pancreatic enlargement. (c) While being treated with maintenance steroid therapy, a
18
19
20
21 low-density mass in the pancreatic head was detected (arrowhead).
22
23
24
25
26

27
28 Fig. 2
29
30

31
32 Histological findings of Case 1. (a) Histological examination revealed a moderate-differentiated ductal
33
34
35 adenocarcinoma (H&E, $\times 100$). (b) Marked lymphoplasmacytic infiltration with storiform fibrosis was
36
37
38 observed around the PaC area (H&E, $\times 100$). (c) Immunohistochemically, abundant IgG4-positive cells
39
40
41
42 were detected (IgG4, $\times 100$). (d) PanIN lesion was absent in the non-cancerous region surrounding the PaC
43
44
45
46 (H&E, $\times 400$).
47
48
49
50
51
52

53 Fig. 3
54
55

56 Histological findings of Case 2. (a) Histological examination revealed a moderate-differentiated ductal
57
58
59
60
61
62
63
64
65

adenocarcinoma (H&E, $\times 100$). (b) Massive fibrosis with acinar atrophy and less severe infiltration of lymphocytes were observed around the PaC area (H&E, $\times 100$). (c) Scant IgG4-positive cells were detected (IgG4, $\times 100$). (d) PanIN lesion was absent in the non-cancerous region surrounding the PaC (H&E, $\times 400$).

Fig. 4

Figure 4. (a) MRI showed a focal enlargement in the head of the pancreas (arrow). (b) Steroid therapy led to improvement of pancreatic enlargement. (c) While being treated with maintenance steroid therapy, a pancreatic body tumor with upstream dilatation of the pancreatic duct was detected (arrowhead).

Table 1. Characteristics of patients with type 1 AIP

	All patients (N=63)
Male sex	45 (71%)
Mean age at AIP diagnosis, y	62.6 (19 -80)
Mean observation period, mo	62.4 (12 - 195)
Drinkers	5 (8%)
Smokers	26 (41%)
Diabetes	22 (35%)
Enlargement of pancreas	
Diffuse	26 (41%)
Focal	30 (48%)
None	7 (11%)
Narrowing of MPD	
Long or multiple	30/57 (53%)
Focal	22/57 (39%)
None	5/57 (8%)
Elevated serum IgG4	
>2x upper limit of normal value	40/61 (66%)
1-2x upper limit of normal value	17/61 (28%)
None	4/61 (6%)
OOI	
Sclerosing cholangitis	9 (14%)
Enlarged salivary/lachrymal glands	7 (11%)
Retroperitoneal fibrosis	5 (8%)
Renal involvement	3 (5%)
Initial therapy	
Steroid	51 (81%)
Resection	7 (11%)
Conservative follow-up	5 (8%)
Maintenance steroid therapy	39/51 (76%)
Relapse	12 (19%)
Development of malignancies	
Pancreatic cancer	3 (5%)
Gastric cancer	2 (3%)
Colon cancer	1 (2%)
Leukemia	1 (2%)
Melanoma	1 (2%)

Table 2. Clinical characteristics of type 1 AIP patients with or without development of PaC during follow-up

	AIP patients with PaC (n=3)	AIP patients without PaC (n=60)	p
Male sex	1 (33%)	44 (73%)	0.193
Mean age at AIP diagnosis, y	59 (30 - 77)	62.8 (19 - 80)	0.662
Mean observation period, mo	94.7 (31 - 186)	60.8 (12 - 195)	0.561
Drinkers	0	5 (8%)	1.000
Smokers	1 (33%)	25 (42%)	1.000
Diabetes	1 (33%)	21 (35%)	1.000
Enlargement of pancreas	0	26 (43%)	0.102
Diffuse	3 (100%)	27 (45%)	
Focal	0	7 (12%)	
None			
Narrowing of MPD	0	30/54 (56%)	0.053
Long or multiple	3 (100%)	19/54 (35%)	
Focal	0	5/54 (9%)	
None			
Elevated serum IgG4			0.544
>2x upper limit of normal value	3 (100%)	37/58 (64%)	
1-2x upper limit of normal value	0	17/58 (29%)	
None	0	4/58 (7%)	
OOI	0	19 (33%)	0.547
Initial therapy	3 (100%)	48 (80%)	1.000
Steroid	0	7 (12%)	
Resection	0	5 (8%)	
No treatment			
Maintenance steroid therapy	3 (100%)	36/48 (75%)	0.439
Relapse	0	12 (20%)	1.000

Table 3. Comparison in incidence of PaC between patients with type 1 AIP and CP

	Type 1 AIP (N=63)	CP (N=41)	p
Male sex	45 (71%)	29 (73%)	0.938
Mean age at diagnosis, y	62.6 (19 - 80)	60.2 (22 - 89)	0.185
Mean observation period, mo	62.4 (12 - 195)	49.2 (13 - 88)	0.085
Drinkers	5 (8%)	25 (61%)	<0.001
Smokers	26 (41%)	21 (51%)	0.319
Incidence of PaC	3 (4.8%)	1 (2.4%)	1.000

Figure

Figure

Figure

Figure