Tumor-like Chronic Pancreatitis Is Often Autoimmune Pancreatitis

SARI RÄTY[1*], JUHANI SAND[1*], ISTO NORDBACK[1], IRINA RINTA-KIIKKA[2], KAIJA VASAMA[3], JAANA HAGSTRÖM[4], STIG NORDLING[4], JUKKA SIRÉN[5], TUULA KIVILUOTO[5] and CAJ HAGLUND[5,6]

Departments of [1]Gastroenterology and Alimentary Tract Surgery, [2]Clinical Radiology and [3]Laboratory Center, Tampere University Hospital, Tampere, Finland; Departments of [4]Pathology and [5]Surgery, Helsinki University Hospital, Helsinki, Finland; [6]Research Programs Unit, Translational Cancer Biology, University of Helsinki, Helsinki, Finland

Abstract. *Background: Distinguishing between pancreatic cancer and chronic pancreatitis (CP) is often difficult. Certain (5-6%) CP cases are autoimmune in nature, and these patients respond to corticosteroid treatment, making surgery avoidable. Our aim was to evaluate the incidence of autoimmune pancreatitis (AIP) among patients operated on for a pancreatic mass with a final histology of CP. Patients and Methods: A total of 33 patients were operated on at the Tampere or Helsinki University Hospital for suspicion of cancer, but with final histopathological diagnosis of CP. The median age was 58 (31-81) years; 26 patients (79%) were male. There were 28 pancreaticoduodenectomes and five left pancreatic resections. Surgical specimens were re-evaluated by experienced pathologists, with representative samples chosen for immunohistochemistry Each sample was scored as positive or negative for immunoglobulin G4 (IgG4) independently by two pathologists. Honolulu consensus criteria served for AIP sub-typing. Results: Out of the 33 specimens, 10 (30%) were positive for IgG4. Histopathological re-evaluation of these revealed all to be type 1 AIP. Conclusion: The proportion of AIP, according to IgG4-positive immunohistochemistry and histological re-evaluation, was much higher than expected. This suggests that by focusing on diagnosis of AIP preoperatively, certain patients might be treated with corticosteroids and possibly avoid unnecessary surgery.*

*These Authors contributed equally to this study.

Correspondence to: Juhani Sand, MD, Ph.D., Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, P.O. BOX 2000, FIN-33521 Tampere, Finland. Tel: +358 33116111 (office), e-mail: juhani.sand@pshp.fi

Key Words: autoimmune pancreatitis, chronic pancreatitis, IgG4.

Preoperatively, it is sometimes difficult to distinguish between pancreatic cancer and chronic pancreatitis (CP); patients may thus undergo radical surgery with clinical suspicion of pancreatic malignancy, but histology may reveal only chronic inflammatory process. In about 5-6% of such patients with CP, the final diagnosis may be autoimmune pancreatitis (AIP) (1-3). At imaging, AIP may manifest as a diffuse, sausage-like pancreas or as focal enlargement of the pancreas (4). Infocal-type AIP especially, the large focal fibrotic areas may mimic pancreatic cancer. If patients with AIP respond to corticosteroid treatment, surgery can be avoided. The typical patient with pancreatic cancer is male and 60 years old or more, similarly to patients with AIP (2). Suspicion of AIP thus has to be strong before start of treatment with corticosteroids, for instance a finding of high serum immunoglobulin G4 (IgG4). In one Japanese study, the serum IgG4 was elevated in 92% of patients with AIP, and serum levels decreased significantly after 4 weeks of corticosteroid therapy (5). In other series, however, sensitivity and specificity of serum IgG4 for diagnosis of AIP were only 60% to 65% (6, 7).

Ever since Sarles and colleagues described an unusual lymphoplasmacytic sclerosing inflammatory disease involving the whole pancreas in 1961 (8), the different types of AIP have attracted lively debate. Consensus criteria on histological and clinical types of AIP have appeared in Asia and the United States (9, 10). In Japanese reports, AIP diagnosis is based mainly on clinical phenotype without focus on histology, whereas in Europe and the United States, at least two histopathological patterns are described: lymphoplasmacytic sclerosing pancreatitis (LPSP), meaning AIP without granulocyte epithelial lesions (GELs), and idiopathic duct-centric pancreatitis (IDCP), meaning AIP with GELs (10). In 2009, experts in pathology, surgery, gastroenterology, and radiology from Japan, Korea, Europe (the United Kingdom, Germany, Sweden, and Italy), and from the United States organized an assembly in Honolulu

to define new criteria for AIP (11). Although no consensus was reached, most experts agreed that clinical phenotypes associated with the histopathological patterns of AIP without GELs and AIP with GELs should be referred to as type 1 and type 2 AIP, respectively. Type 1 AIP is associated with high serum IgG4 levels, other organ involvement, and a typical radiological image (sausage-like pancreas) (12). Type 2 AIP, more often than in type I, shows no typical lymphoplasmacytic infiltration, appearing as focal changes (84% *vs*. 16%), thus leading to a higher rate of surgical resection (68% *vs*. 32%) (12). The diagnosis of type 2 AIP requires histological confirmation and its clinical spectrum and long-term outcome is less often reported (12, 13).

Our aim was to evaluate the proportion of AIP in patients operated on for suspicion of pancreatic cancer, but with final histopathological diagnosis of CP.

Patients and Methods

The study comprised 33 patients operated on at Tampere or Helsinki University Hospital between 1987 and 2009 for suspicion of cancer, but in whom final histopathological diagnosis revealed CP. The median age was 58 years (range=31-81); 26 patients (79%) were male. Surgical procedures were pancreaticoduodenectomy in 28 and left pancreatic resection in five. All 33 surgical specimens were re-evaluated by experienced pathologists (K.V., J.H., S.N.), with representative samples chosen for immunohistochemistry (IHC). Sections 4 μm-thick from formalin-fixed and paraffin-embedded tissue samples were stained for IgG4 (MCA2098G, 1:100; Serotec, Oxford, UK). For antigen retrieval, slides were treated in a pretreatment module (LabVision Corp., Fremont, CA, USA) with Tris-EDTA for 20 min at 98˚C. IHC was performed in an Autostainer 480 (LabVision Corp.) using the Dako REAL EnVision Detection System, Peroxidase/DAB+, Rabbit/Mouse (Dako, Glostrup, Denmark). Each sample was scored as positive or negative for IgG4 independently by two pathologists (J.H., S.N.) blinded to the clinical data. IgG4 IHC was considered positive if there was intensive infiltration of 50 or more IgG4-positive plasma cells per high power field. The pathologists also evaluated storiform fibrosis, GELs, and periductal lymphocyte infiltration, in order to divide samples into type 1 and 2 AIP according to the Honolulu consensus criteria (11).

Statistics. For statistical analysis, we used IBM SPSS 20.0 (IBM, Computer Software, Chicago, IL, USA) and Fisher's exact test. A *p*-value of less than 0.05 was considered statistically significant.

Results

Out of 33 samples, 10 (30%) were positive for IgG4. Positive cells covered the whole sample area or were clustered at a minimum of 50 positive cells per high power field (Figure 1). At histopathological re-evaluation, all 10 IgG4-positive samples were diagnosed as type 1 AIP, with no difference in storiform fibrosis, GELs, or lymphoplasmacytic infiltration between patients with and without AIP (Table I). Table II shows the histopathological features of the 10 AIP patients. Patients number 4 and 10 were considered type 1 AIP despite positive GELs, since their IgG4 and lymphoplasmacytic cells were positive.

Table I. *Histopathological findings in patients with autoimmune pancreatitis (AIP) versus no AIP; patients were divided according to IgG4 positivity.*

Finding	AIP N=10	No AIP N=23	*p*-Value
IgG4-positive	10 (100%)	0	
Storiform fibrosis	6 (60%)	13 (57%)	0.293
Granulocyte epithelial lesions	2 (20%)	3 (13%)	0.310
Lymphoplasmocytic infiltration	3 (30%)	4 (17%)	0.249

Discussion

In this retrospective study of surgical samples from 33 patients with CP undergoing surgery for suspected pancreatic cancer, re-evaluation revealed 10 (30%) patients with positivity for IgG4 by IHC, suggesting a final diagnosis of AIP. We found a higher proportion of IgG4-positive samples than most reports, but in series including only patients with benign final histology, the proportion of IAP was similar to ours (3, 14). Improved IHC and clarification of histological criteria of AIP may, in part, explain our higher figures.

The Honolulu Consensus Document divides AIP into two subclasses, types 1 and 2 AIP (12). All of our 10 AIP cases were classified as type 1. In two patients, tissue specimens were positive for GELs, which is atypical for type 1 AIP (11), but positivity for IgG4 at IHC and lymphoplasmacytic infiltration allowed classification of these cases also as type 1. The lack of type 2 AIP in our series is surprising, as type 2 is said to more often appear as a focal lesion (12).

Gupta and colleagues reported that AIP represents a risk for pancreatic cancer. They found that out of 28 patients, two (7%) developed pancreatic cancer after their 6- and 10-year follow-up (15). Hart and colleagues have recently shown that the cancer risk before and after diagnosis of AIP is similar to that of control subjects (16). Specifically, there is no increased risk of cancer immediately preceding or following AIP diagnosis. Further validation studies should show whether surgical removal of an AIP lesion is to be recommended to avoid development of cancer. On the other hand, although 30-day mortality after pancreatic surgery is low today (2%), the morbidity of major surgery is still high (30%) (17-20). All our patients with AIP had focal-type lesions mimicking pancreatic cancer. Back during the era of their surgery, knowledge of AIP was limited, which explains why all these patients were surgically treated. Today, awareness of the possibility of AIP,

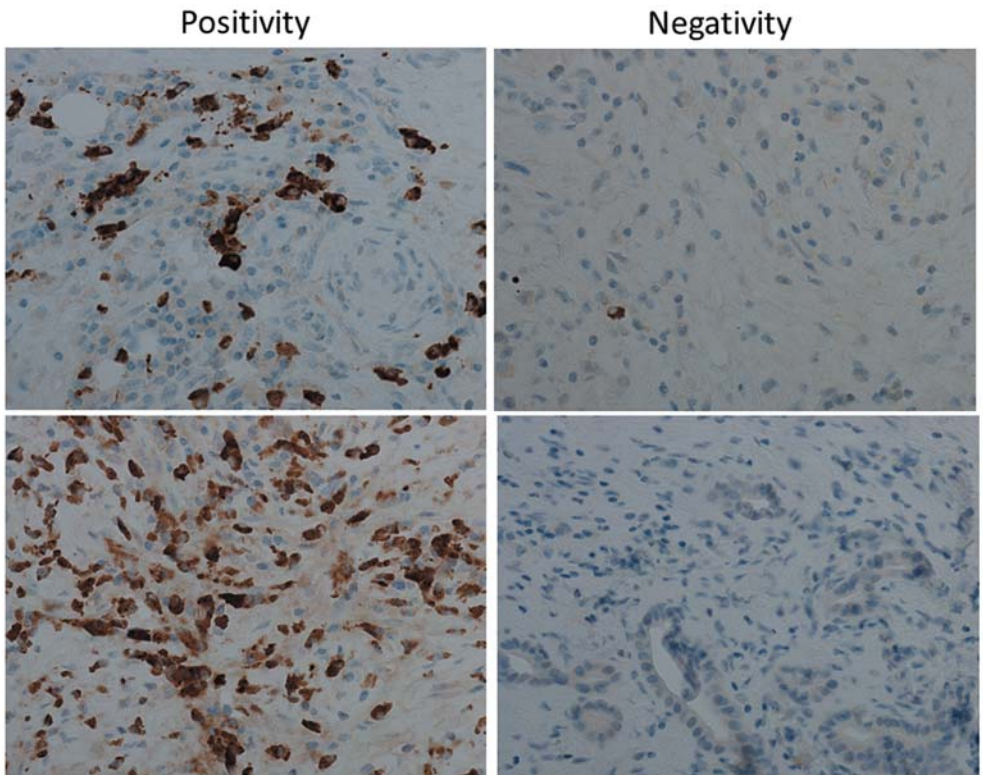

Figure 1. *IgG4-positive plasma cells visible in the periductal area. Samples were considered positive when positively stained cells covered the whole sample area or when a cluster of ≥50 positive cells were counted per high-power field (magnification ×400).*

Table II. *Histopathological features in 10 patients with autoimmune pancreatitis.*

Patient number	IgG4	Storiform fibrosis	GELs	Lymphoplasmocytic infiltration
1	+	+	–	–
2	+	+	–	–
3	+	–	–	–
4	+	–	+	+
5	+	+	–	–
6	+	–	–	–
7	+	+	–	–
8	+	–	–	–
9	+	+	–	+
10	+	+	+	+

GELs: Granulocyte epithelial lesions.

combined with modern computed tomography, magnetic resonance imaging, endoscopic ultrasound, and preoperative histology will aid in preoperative evaluation of patients with pancreatic lesions of unknown nature. This will allow, especially in benign diseases such as CP and AIP, avoidance of unnecessary surgery. Instead, we can attempt to treat AIP conservatively by corticosteroids.

AIP sometimes relapses making surgery unavoidable, such as for Sah and colleagues, who in 2010 reported a relapse rate of 47% during a 42-month follow-up of patients with type 1 AIP; none of their patients with type 2 AIP experienced relapse, although pancreaticoduodenectomy, interestingly, reduced their relapse rate (12). It is debated whether steroid therapy should be continued after resection of AIP. Wu and

colleagues do not recommend steroid therapy unless there exists evidence of residual AIP after resection (21).

In conclusion, the proportion of AIP, based on IgG4-positive IHC and histological re-evaluation in our series, was much higher than expected. This suggests that today, because of growing knowledge of and focus on diagnosis of AIP preoperatively, certain patients can be treated with corticosteroids and possibly avoid unnecessary surgery.

Acknowledgements

This study was financially supported by the Competitive State Research Financing of the Expert Responsibility area of Tampere and Helsinki University Hospitals (Grant number: 9P048) and the Sigrid Jusélius Foundation.

References

1 Lin L, Huang P, Ho K and Tung J: Autoimmune chronic pancreatitis. J Chin Med Assoc *71*: 14-22, 2008.

2 Cavallini G and Frulloni L: Autoimmunity and chronic pancreatitis: a concealed relationship. J Pancreas *2*: 61-68, 2001.

3 Abraham SC, Wilentz RE, Yeo CJ, Sohn TA, Cameron JL, Boitnotti JK and Hruban RH: Pancreaticoduodenectomy (Whipple resections) in patients without malignancy: Are they all chronic pancreatitis? Am J Surg Pathol *27*: 110-120, 2003.

4 Wakabayashi T, Kawaura Y, Satomura Y, Watanabe H. Motoo Y, Okai T and Sawabu N: Clinical and imaging features of autoimmune pancreatitis with focal pancreatic swelling or mass formation: comparison with so-called tumour-forming pancreatitis and pancreatic carcinoma. Am J Gastroenterol *98*: 2679-2687, 2003.

5 Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, Fukushima M, Nikaido T, Nakayama K, Usuda N and Kiyosawa K: High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med *344*: 732-738, 2001.

6 Hirano K, Shiratori Y, Komatsu Y, Yamamoto N, Sasahira N, Toda N, Isayama H, Tada M, Tsujino T, Nakata R, Kawase T, Katamoto T, Kawabe T and Omata M: Involvement of biliary system in autoimmune pancreatitis: A follow-up study. Clin Gastroenterol Hepatol *1*: 453-454, 2003.

7 Okazaki K: Autoimmune pancreatitis is increasing in Japan. Gastroenterology *125*: 1557-1558, 2003.

8 Sarles H, Sarles JC, Muratore R and Guien C: Chronic inflammatory sclerosis of the pancreas-an autonomous pancreatic disease? Am J Dig Dis *6*: 688-698, 1961.

9 Otsuki M, Chung JB, Okazaki K, Kim M-H, Kamisawa T, Kawa S, Park SW, Shimosegawa T, Lee K, Ito T, Nishimori I, Notohara K, Naruse S, Ko SBH and Kihara Y: Asian diagnostic criteria for autoimmune pancreatitis: consensus of the Japan-Korea Symposium on Autoimmune Pancreatitis. J Gastroenterol *43*: 403-408, 2008.

10 Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Zhang L, Clain JE, Pearson RK, Petersen BT, Vege SS and, Farnell MB: Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. Clin Gastroenterol Hepatol *4*: 1010-1016, 2006.

11 Chari ST, Kloeppel G, Zhang L, Notohara K, Lerch MM, Shimosegawa T and The Autoimmune Pancreatitis International Cooperative Study Group (APICS: Histopathologic and Clinical Subtypes of Autoimmune Pancreatitis: The Honolulu Consensus Document. Pancreas *39*: 549-554, 2010.

12 Sah RP, Chari ST, Pannala R, Sugumar A, Clain JE, Levy MJ, Pearson RK, Smyrk TC, Petersen BT, Topazian MD, Takahashi N, Farnell MB and Vege SS: Differences in clinical and relapse rate of type 1 *versus* type 2 autoimmune pancreatitis. Gastroenterology *139*: 140-148, 2010.

13 Kamisawa T, Chari ST, Lerch MM, Kim MH, Gress TM and Shimosegawa T: Recent advances in autoimmune pancreatitis: type 1 and type 2. Gut *62*: 1373-1380, 2013.

14 van Heerde MJ, Biermann K, Zondervan PE, Kazemier G, van Eijck CH, Pek C, Kuipers EL and van Buurden HR: Prevalence of autoimmune pancreatitis and other benign disorders in pancreaticoduodenectomy for presumed malignancy of the pancreatic head. Dig Dis Sci *57*: 2458-2465, 2012.

15 Gupta R, Khosroshahi A, Shinagare S, Fernandez C, Ferrone C, Lauwers GY, Stone JH and Deshpande V: Does autoimmune pancreatitis increase the risk of pancreatic carcinoma?: a prospective analysis of pancreatic resections. Pancreas *42*: 506-510, 2013.

16 Hart PA, Law RJ, Dierkhising RA, Smyrk TC, Takahashi N and Chari ST: Risk of cancer in autoimmune pancreatitis: a case-control study and review of the literature. Pancreas *43*: 471-421, 2014.

17 Birkmeyer JD, Siewers AE, Finlayson EV, Tsukel TA, Lucas FL, Batista I, Welch HG and Wannberg DE: Hospital volume and surgical mortality in the United States. N Engl J Med *346*: 1128-1137, 2002.

18 Büchler MW, Wagner M, Schmied BM, Uhl W, Friess H and Z'graggen K: Changes in morbidity after pancreatic resection: toward the end of completion pancreatectomy. Arch Surg *138*: 1310-1314, 2003.

19 Nordback I, Parviainen M, Räty S, Kuivanen H and Sand J: Resection of the head of the pancreas in Finland: Effects of hospital and surgeon on short-term and long-term results. Scand J Gastroenterol *12*: 1454-1460, 2002.

20 Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, Hodgin MB, Sauter PK, Hruban RH, Riall TS, Schulick RD, Choti MA, Lillemoe KD and Yeo CJ: 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. J Gastrointest Surg *10*: 1199-1210, 2006.

21 Wu W, Yao X, Lin C, Jin D1, Wang D, Lou W and Qin X: Should Steroid Therapy Be Necessarily Needed for Autoimmune Pancreatitis Patients with Lesion Resected due to Misdiagnosed or Suspected Malignancy? Gastroenterol Res Pract 253471, 2014.

Received June 30, 2015
Revised August 4, 2015
Accepted September 9, 2015