Application of international consensus diagnostic criteria to an Italian series of autoimmune pancreatitis

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Abstract

Background: International consensus diagnostic criteria (ICDC) have been proposed to classify autoimmune pancreatitis (AIP) in type 1, type 2, or not otherwise specified.

Objective: Aim was to apply the ICDC to an Italian series of patients to evaluate the incidence and clinical profiles among different subtypes of AIP.

Methods: we re-evaluated and classified 92 patients diagnosed by Verona criteria, according to the ICDC.

Results: Out of 92 patients, 59 (64%) were diagnosed as type 1, 17 (18%) as type 2, and 15 (16%) as not otherwise specified according to the ICDC. A significant difference between type 1 and type 2 were found for age (54.5 ± 14.5 vs. 34.4 ± 13.9 respectively; $p < 0.0001$), male sex (76 vs. 47%; $p = 0.007$), jaundice (66 vs. 18%; $p = 0.002$) and acute pancreatitis (9 vs. 47%; $p < 0.0001$), elevated serum IgG4 levels (85 vs. 7%; $p < 0.0001$), inflammatory bowel disease (8 vs. 82%; $p < 0.0001$), and relapse of the disease (34 vs. 6%; $p = 0.058$). Imaging and response to steroids in the not-otherwise-specified group were similar to type 1 and 2.

Conclusions: Type 1 has a different clinical profile from type 2 autoimmune pancreatitis. The not-otherwise-specified group has peculiar clinical features which are shared both with type 1 or type 2 groups.

Keywords

Autoimmunity, diagnosis, imaging, pancreatic diseases, pathology

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Introduction

Autoimmune pancreatitis (AIP) is a unique chronic inflammation of the pancreas.^{1–4} Radiologically, the disease is characterized by focal or diffuse pancreatic enlargement and irregular narrowing of the main pancreatic duct (MPD).^{5,6} The main clinical finding is a dramatic response to steroid.^{2,7,8} Two histological subtypes in AIP have been recognized, type 1 and type 2.^{4,9,10} The histological pattern of type 1 AIP is characterized by periductal infiltration of lymphocytes, abundant IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis. Patients with type 1 AIP are often elderly men, with elevated levels of serum IgG4 and extrapancreatic lesions (e.g. sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis). In

contrast, type 2 AIP is histologically characterized by the presence of granulocytic epithelial lesions^{11,12} and absence of IgG4-positive plasma cells in pancreatic tissue. Patients with type 2 AIP are often younger with normal serum levels of IgG4 and frequently suffer from inflammatory bowel diseases, particularly ulcerative colitis.^{13–16}

The diagnosis of AIP is challenging because several cases of AIP may closely mimic the pancreatic cancer.¹⁷

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Since AIP responds dramatically to steroid treatment, diagnostic criteria with a high accuracy are essential to avoid an unnecessary surgery. Up to now, several diagnostic criteria for AIP have been proposed.^{3,9,18–20} In 2011, the International Association of Pancreatology proposed International Consensus Diagnostic Criteria (ICDC) to identify type 1 and type 2 AIP.²¹ These criteria are composed of five cardinal features such as imaging of the pancreatic parenchyma and duct, serology, other organ involvement, histology, and response to steroid therapy, categorized as level 1 or 2 findings depending on the diagnostic reliability. Different from other criteria, the ICDC can diagnose type 1 and type 2 AIP independently. In addition, the ICDC defined the criteria for AIP not otherwise specified (AIP-NOS) for cases not diagnosed as type 1 and type 2 AIP.

In the present study, patients diagnosed as having AIP by Verona criteria³ were reviewed and reclassified according to the ICDC. The aims were to examine the frequency of patients classified into type 1, type 2, and AIP-NOS by the ICDC and to compare clinical, radiological, and serological parameters among these groups.

Patients and methods

We included all patients enrolled in our prospectively collected database of AIP patients from January 2002 to March 2012 who met Verona criteria (Table 1).³ Some patients had been included in previously published papers.^{3,22,23} For the purpose of this study, these patients were reassessed radiologically and histologically and classified according to the ICDC.

Pathological findings were re-evaluated by two expert pathologists (GZ and PC). In operated patients,

the diagnosis of subtype of AIP was based on histological findings on surgical specimens, according to the ICDC. In non-operated patients, the classification of AIP was based on the combination of the five cardinal features according to the ICDC.

Two expert radiologists (RM and RN) separately reviewed the findings on the computed tomography (CT) and/or magnetic resonance imaging (MRI) at the clinical onset and after steroids, when used. They categorized parenchymal and ductal changes into level 1 or 2 findings according to the ICDC. Furthermore, possible other organ involvement in abdomen was also carefully evaluated. According to the classification of other organ involvement in the ICDC, segmental/multiple proximal (hilar/intrahepatic) bile duct stricture, and retroperitoneal fibrosis were categorized as level 1 and renal involvement as level 2. In case of disagreement, the final decision was made by consensus.

Presence or history of symmetrically enlarged salivary/lachrymal glands (level 2 in other organ involvement of type 1) and inflammatory bowel disease (level 2 in other organ involvement of type 2) and the histological findings of biopsies were retrieved from the clinical records of patients.

Serum levels of IgG4 were evaluated at the clinical onset of the disease. The upper limit of normal value was 135 mg/dl, in accordance with the previous papers.^{3,24,25}

If patients were treated with steroid as the initial therapy, the response was also retrieved. Response to steroid was defined as clinical and morphological resolution of the pancreatic changes or other organ involvement.

Finally, two clinicians (LF and TI) separately evaluated the five cardinal features and classified AIP

Table 1. Verona criteria for autoimmune pancreatitis

Category	Verona criterion
Suggestive radiological features (CT or MRI)	Diffuse or focal involvement of the pancreas Delayed enhancement in the involved parenchyma No dilation of the main pancreatic duct in diffuse form No extra-pancreatic or vascular involvement
Association with autoimmune diseases	Ulcerative colitis, Crohn's disease, Sjögren's syndrome, primary biliary cirrhosis, primary sclerosing cholangitis, retroperitoneal fibrosis, autoimmune thyroiditis, tubulointerstitial nephritis, uveitis, and Mikulicz's disease
Consistent cytological or histological features	Periductal lymphoplasmacytic infiltration Presence of granulocytic epithelial lesions Negative for epithelial atypia
Response to steroid therapy	Clinical: resolution of symptoms/signs of AIP Radiological (CT or MR): disappearance/significant reduction in the size of the involved pancreas, normalization of the main pancreatic duct

CT, computed tomography; MR, magnetic resonance.

patients according to the ICDC. In case of disagreement, the final decision was made by consensus.

The patients were therefore classified in the following four groups: type 1 AIP (definitive or probable); type 2 AIP (definitive or probable); AIP-NOS; probable AIP (that fulfilled the Verona criteria but not the ICDC).

To compare the clinical profiles and outcomes of the different groups of patients, we evaluated the following variables: age at the clinical onset of the disease and sex; alcohol and smoking habits; medical history; symptoms at the clinical onset of the disease (acute pancreatitis, abdominal pain, weight loss, jaundice, steatorrhoea, none); diabetes; pancreatic exocrine insufficiency; association with other autoimmune diseases; initial therapy for the disease (steroid, resection, no treatment); relapse of the disease; use of immunosuppressant drugs. Patients were divided on the basis of alcohol consumption in two groups: teetotalers (no drinkers) and drinkers. Patients were also divided on the basis of smoking habits: non-smokers and smokers.

The diagnosis of diabetes was defined as fasting glucose level higher than 127 mg/dl. Pancreatic exocrine insufficiency was diagnosed on the basis of clinical steatorrhoea or faecal elastase $1 < 100 \mu\text{g/g}$ of stool. Acute pancreatitis was diagnosed in the presence of epigastric pain and serum pancreatic amylase or lipase higher than $3 \times$ the upper normal limit. Autoimmune diseases other than other organ involvement reported in the ICDC were recorded as other autoimmune diseases.

Steroid therapy was performed with the oral administration of prednisone. The initial dose of prednisone was 1 mg/kg of body weight per day for 2–3 weeks. It was then tapered by 5 mg every week up to suspension.

Relapse of AIP was defined as the reappearance of pancreatic or extrapancreatic involvement after steroid withdrawal.

Statistical analysis

Differences among each group were analysed using the chi-squared test or Fisher's Exact test for qualitative variables and Kruskal–Wallis test for quantitative variables. A p -value >0.05 was considered statistically significant. Mean and standard deviation are reported.

Results

Patient characteristics

A total of 123 patients were in our prospective database of AIP. Thirty-one patients were excluded from this study (22 did not meet Verona criteria, three underwent surgery in other institutions, and six were referred to our centre after steroid therapy). A total of 92 patients (60 males and 32 females, mean age at the clinical onset

49.3 ± 16.2 years) were studied. The characteristics of analysed patients are summarized in Table 2.

Diabetes was observed in 11 patients (12%; seven at clinical onset, four during steroid treatment) and pancreatic exocrine insufficiency was observed in 29 (32%).

CT or MRI revealed diffuse enlargement of the pancreas in 42 patients (46%) and focal enlargement in 50 (54%). On magnetic resonance cholangiopancreatography with secretin stimulation (available in 61 patients), long or multiple strictures of MPD was observed in 50 patients (82%) and short (focal) narrowing of MPD in 11 patients (18%).

Table 2. Patient characteristics

Parameter	Patient population ($n = 92$)
Male sex	60 (65)
Age at onset (years)	49.3 ± 16.2
Drinkers	21 (23)
Alcohol/day (g)	23.1 ± 24.8
Smokers	22 (24)
Cigarettes/day	15.9 ± 6
Symptom at clinical onset	
Body weight loss	66 (72)
Jaundice	49 (53)
Acute pancreatitis	19 (21)
Abdominal pain	8 (9)
Diabetes	7 (8)
Steatorrhoea	10 (11)
None	7 (8)
PEI	29 (32)
Enlargement of pancreas	
Diffuse	42 (46)
Focal	50 (54)
Narrowing of MPD	
Long or multiple stricture	50 (82)
Focal narrowing	11 (18)
Elevated serum IgG4	
$>2 \times$ upper normal limit	28 (37)
$1-2 \times$ upper normal limit	14 (18)
None	34 (45)
Other organ involvement	34 (37)
Inflammatory bowel disease	20 (22)
Initial therapy	
Steroid	74 (80)
Resection	16 (17)
No treatment	2 (3)
Relapse	24 (26)

Values are n (%) or mean $\pm$ SD.

MPD, main pancreatic duct; PEI, pancreatic exocrine insufficiency.

Serum levels of IgG4 at the clinical onset of the disease were available in 76 out of 92 patients (83%). Serum levels of IgG4 were higher than $2\times$ upper normal limit in 28 (37%) patients, $1-2\times$ upper normal limit in 14 (18%), and normal in 34 (45%).

Other organ involvement was observed in 34 (37%). Twenty patients (22%) had inflammatory bowel disease. The association with other autoimmune diseases was observed in 11 patients (12%). The spectrum of autoimmune diseases included autoimmune gastritis ($n=2$), autoimmune thyroiditis ($n=4$), erythema nodosum ($n=1$), systemic lupus erythematosis ($n=1$), autoimmune thrombocytopenia ($n=1$), retro-ocular fibrosis ($n=1$), pulmonary fibrosis ($n=1$), celiac disease ($n=1$), autoimmune prostatitis ($n=1$), autoimmune neuritis ($n=1$), and autoimmune encephalitis ($n=1$).

Sixteen out of 92 patients (17%) underwent surgery. Out of the remaining 76 patients, 74 patients (97%) were treated with steroid. Immunosuppressant drugs

were used in 28 patients (31%), mainly azathioprine ($n=22$), cyclosporine ($n=2$), tamoxifen ($n=2$), methotrexate ($n=1$), and 6-mercaptopurin ($n=1$). The indications for the use of immunosuppressant drugs were relapse of AIP in 19 patients, associated autoimmune diseases in six, and high levels of serum IgG4 after steroid treatment in three.

Recurrence of the disease was observed in 24 out of 92 patients (26%), in 19 out of 76 (25%) non-operated, and in five out of 16 operated patients (31%). All operated patients with recurrence were treated with steroids.

Diagnosis according to the ICDC for AIP

According to the ICDC, 59 patients (64%) were diagnosed as type 1 AIP, 17 (18%) as type 2, 15 (16%) as AIP-NOS, and one (1%) as probable AIP. The algorithms following the ICDC for the diagnosis of AIP type 1, type 2, and NOS are reported in Figures 1 and 2.

Figure 1. Flow chart of diagnosis according to the ICDC algorithm for type 1 AIP.

*Level 2D is counted as level 1 in this setting.

Definitive diagnosis of type 1 or type 2 AIP was made in 63 out of 76 not operated patients (83%). All but one of the 59 patients (98%) with type 1 were classified as 'definitive', in 11 based on histology in surgical specimens and in 48 based on the other the ICDC. Five out of 17 patients (29%) with type 2 were classified as 'definitive' on the basis of histology in surgical specimens and the remaining 12 non-operated patients (71%) as 'probable'.

Five type 1 AIP patients with ulcerative colitis fulfilled the diagnostic criteria of probable type 2 as well. However, these patients were included in type 1 AIP according to algorithm of the ICDC.¹⁸

Pancreatic biopsies or aspiration cytology were performed in 57 out of 76 non-operated patients (75%). The histological findings excluded pancreatic cancer and showed only suggestive findings for AIP (lymphoplasmacytic infiltration and fibrosis).

Comparison of cardinal features in the ICDC among type 1 AIP, type 2 AIP, and AIP-NOS

The results of classification in five ICDC cardinal features are shown in Table 3. The frequency of levels 1 and 2 in parenchymal and ductal imaging criteria is not different among groups. The frequency of levels 1 and 2 in serology criterion was significantly higher in type 1

compared to type 2 AIP (56 and 7% in level 1, 29 and 0% in level 2, respectively, $p < 0.0001$).

Other organ involvement was observed in 34 patients (58%) with type 1 AIP, whereas inflammatory bowel disease was diagnosed more frequently in type 2 (84%) compared to type 1 AIP (8%; $p < 0.0001$).

Response to steroid was observed in all non-surgical patients.

Comparison of clinical profiles and outcomes among type 1 AIP, type 2 AIP, and AIP-NOS

The demographic characteristics, clinical profile, laboratory data, and pancreatic imaging of type 1, type 2, and AIP-NOS are summarized in Table 4. The single patient with probable AIP by the ICDC was excluded.

Males were more frequently observed in type 1 compared to type 2 and AIP-NOS (76, 47, and 40%, respectively; $p = 0.007$). Type 2 patients were significantly younger (34.4 ± 13.9 years) than type 1 (54.5 ± 14.5 years; $p < 0.0001$) and AIP-NOS (45.7 ± 14.9 ; $p < 0.0001$). The frequency of drinkers and smokers was comparable among groups, as well as the mean consumption of alcohol and cigarette smoking in drinkers and smokers (Table 4). The frequency of jaundice at the onset in type 1 was significantly higher than that in type 2 (66 vs. 18%, respectively; $p = 0.002$).

Figure 2. Flow chart of diagnosis according to the ICDC algorithm for type 2 AIP and AIP-NOS.

Table 3. Cardinal features of the international consensus diagnostic criteria in the study population according to final classification of autoimmune pancreatitis

Cardinal features	AIP type 1 (n = 59)	AIP type 2 (n = 17)	AIP-NOS (n = 15)	p-value
Parenchymal imaging				
Level 1	28 (47)	8 (47)	5 (33)	NS
Level 2	31 (53)	9 (53)	10 (67)	
Ductal imaging				
Level 1	30 (86)	8 (80)	11 (73)	NS
Level 2	5 (14)	2 (20)	4 (27)	
Serology IgG4				
Level 1	27 (56)	1 (7)	0	<0.0001
Level 2	14 (29)	0	0	
Normal	7 (15)	14 (93)	12 (100)	
Other organ involvement				
Level 1	26 (44)	0	0	<0.0001
Level 2	8 (14)	0	0	
No	25 (42)	17 (100)	15 (100)	
Inflammatory bowel disease				
Level 2	5 (8)	14 (82)	0	<0.0001
No	54 (92)	3 (18)	15 (100)	
Histology of surgical specimens				
Level 1	11 (19)	5 (29)	0	<0.0001
No	46 (81)	12 (71)	15 (100)	
Response to steroid in non-operated patients				
Yes	47 (98)	12 (100)	15 (100)	NS
No	1 (2)	0	0	

Values are n (%).

AIP, autoimmune pancreatitis; NOS, not otherwise specified.

Acute pancreatitis developed more frequently in type 2 AIP and AIP-NOS compared with type 1 AIP (47 and 40 vs. 9%; $p < 0.0001$). Asymptomatic patients were observed only in type 1 AIP (11%). A higher proportion of patients suffered from diabetes and pancreatic exocrine insufficiency in type 1 than in the two other groups, but there was no significant difference among each group. Relapse of the disease after steroid therapy was observed in 20 of 59 patients (34%) with type 1, in three of 15 patients (20%) with AIP-NOS, and in one operated patient (6%) with type 2 ($p = 0.058$).

Discussion

The results of this study described the application of the ICDC in AIP patients diagnosed by Verona criteria.

Firstly, all but one of the patients diagnosed as suffering from AIP by Verona criteria fulfilled the ICDC. Therefore, a positive AIP diagnosis by Verona criteria correctly identifies AIP, without discriminating between the subtypes. A patient who fulfilled Verona criteria (suggestive radiology, consistent pathological findings on pancreatic biopsies and association with ulcerative

colitis) did not meet the ICDC because she did not undergo steroid treatment (intolerance previously documented) and a spontaneous remission was later observed. Some cases of AIP have been reported in the literature showing spontaneous clinical and radiological remission without steroid therapy.²³ Since response to steroid treatment is included as cardinal feature, some AIP cases with spontaneous resolution may be misclassified by the ICDC. In such patients, histology obtained by core needle biopsy may be needed for the diagnosis of AIP.

Secondly, type 1 AIP was the most frequent subtype in this Italian series. It is known that type 1 and type 2 AIP substantially differ in terms of demography, symptoms at clinical onset, and relapse. The distinctions of these clinical profiles and outcome between two subtypes were largely in agreement with those reported in previous studies.^{9,13–16} However, some aspects (sex distribution in type 2 and mean age at the onset in type 1) are different.^{10–13} A possible explanation for this discrepancy may be that only 17% of patients had a histologically proven type 1 and type 2 AIP diagnosed in surgical specimens.

Table 4. Epidemiological and clinical findings of the groups of patients classified by the international consensus diagnostic criteria

Parameters	AIP type 1 (n = 59)	AIP type 2 (n = 17)	AIP-NOS (n = 15)	p-value
Male sex	45 (76)	8 (47)	6 (40)	0.007
Age at onset (years)	54.5 ± 14.5	34.4 ± 13.9	45.7 ± 14.9	<0.0001
Drinkers	14 (24)	3 (18)	3 (20)	NS
Alcohol/day (g)	25.4 ± 29.1	18.3 ± 12.6	18.3 ± 18.9	NS
Smokers	10 (17)	6 (35)	5 (33)	NS
Cigarettes/day (n)	16.7 ± 4.5	15 ± 7.7	13.4 ± 6.1	NS
Symptom at clinical onset				
Body weight loss	45 (76)	11 (65)	9 (60)	NS
Jaundice	39 (66)	3 (18)	7 (47)	0.002
Acute pancreatitis	5 (9)	8 (47)	6 (40)	<0.0001
Abdominal pain	4 (7)	3 (18)	1 (7)	NS
Diabetes	5 (8)	1 (6)	1 (7)	NS
Steatorrhea	8 (14)	2 (12)	0	NS
None	6 (11)	0	0	0.048
Other autoimmune diseases	8 (14)	1 (6)	2 (13)	NS
PEI	21 (36)	5 (29)	3 (20)	NS
Relapse	20 (34)	1 (6)	3 (20)	0.058
Immunosuppressant drugs	25 (42)	0	3 (20)	0.002

Values are n (%) or mean ± SD.

AIP, autoimmune pancreatitis; MPD, main pancreatic duct; NOS, not otherwise specified; PEI, pancreatic exocrine insufficiency.

Parenchymal and ductal the ICDC are similar and not statistically different between type 1 and type 2 AIP, as well as the response to steroids. Therefore, in clinical practice, imaging and response to steroids cannot distinguish type 1 from type 2 AIP. On the contrary, serum IgG4, other organ involvement, and histology are significantly different in the two groups. Recent papers reported a low sensitivity of serum IgG4 levels for the diagnosis of AIP (53–90%),^{14,24,26,27} ranging from 63 to 76% in type 1 and 0 to 23% in type 2 AIP.^{13–16,28} Applying the ICDC, elevation of serum IgG4 levels was more frequently observed in type 1 AIP (85%) than in type 2 AIP patients (7%). A single patient with a histological definitive diagnosis of type 2 AIP had marked elevation of serum IgG4 levels (290 mg/dl). We do not have any explanation for that, but we may only postulate an overlap syndrome between the two subtypes.

Inflammatory bowel disease in the ICDC addressed to a diagnosis of type 2 AIP. The prevalence of inflammatory bowel diseases, particularly ulcerative colitis, in patients with type 2 AIP ranges between 16 and 33%,^{3,9,14,28–30} only occasionally in type 1 AIP (up to 6%).^{15,28,30,31} In the current study, all five of 59 patients (8%) classified as type 1 AIP with ulcerative colitis meet the ICDC for type 2 AIP. Since the ICDC suggest that such patients are firstly classified into type 1 disease, the ICDC may misclassify the type 2 disease.

This is the first study, to our knowledge reporting the clinical, radiological, and serological features of AIP-NOS, and this study classified 16% of the patients as AIP-NOS.²¹ Other organ involvement, serology, and histology were lacking in this group, as expected. Imaging features and response to steroids in AIP-NOS group were similar to those in type 1 and 2 AIP groups. The clinical and epidemiological parameters in AIP-NOS group were different from those in type 1 and type 2 AIP. While the frequency of AIP-NOS patients presenting with jaundice as initial symptom was intermediate between those of type 1 and type 2 AIP, type 2 and AIP-NOS were similar in prevalence of acute pancreatitis. Moreover, AIP-NOS patients suffer from clinical relapse similarly to type 1, as confirmed by the use of immunosuppressant drugs. The clinical characteristics of AIP-NOS are unknown, and the only data available are clinical profiles of seronegative AIP patients for serum IgG4 levels.^{32–34} The most recent study reported that, among the seronegative AIP group, patients were more likely to have type 1 rather than type 2 AIP if they are older than 50 years or have other organ involvement or disease relapse.³⁴ We can postulate that some AIP-NOS patients are IgG4-seronegative type 1 AIP. However, we cannot exclude an undiagnosed type 2 AIP or an overlap syndrome.

Pancreatic core needle biopsy is reported to be a good method to diagnose both type 1 and type

2 AIP.^{35–37} In our study, core biopsy or aspiration cytology was performed in 75% of non-operated patients. Histology excluded pancreatic adenocarcinoma but did not meet the ICDC. Suggestive pathology is a Verona criterion for the diagnosis of AIP but do not reach level 1 or 2 for the ICDC. This reflects the aim of Verona criteria, used for the diagnosis of AIP, but not the ICDC, used to define the subtypes of the disease. Despite the lack of histological cardinal feature, we were able to classify the subtype of AIP in most part of patients (84%).

The limitation of the study is the lack of serum levels of IgG4 at the clinical onset in 17%, leading probably to misclassification of AIP. However, since 11 out of these patients lacking serum IgG4 levels were classified as type 1 AIP, the diagnosis of subtype of AIP may be mistaken in only five patients: two with type 2 AIP and three with AIP-NOS.

In conclusion, patients diagnosed as type 1 AIP by the ICDC have different clinical profiles and outcomes from those as type 2 AIP. Clinical features of AIP-NOS are sometimes similar to those observed in type 1 AIP and other times with type 2 AIP. We cannot exclude an overlap syndrome as a separate entity. The ICDC may misclassify AIP cases with a spontaneous remission and patients with inflammatory bowel disease.

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Conflict of interest

The authors declare that there is no conflict of interest.

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