Features of Autoimmune Pancreatitis Associated With Inflammatory Bowel Diseases

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BACKGROUND & AIMS: **Few people know of autoimmune pancreatitis (AIP), a rare disorder associated with inflammatory bowel diseases (IBD). We aimed to describe phenotype and outcomes of IBD and AIP when associated.**

METHODS: **We performed a retrospective study of cases of AIP in IBD identified from the multicenter Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif in Belgium and France from July 2012 through July 2015. Patients were diagnosed with AIP based on the International Consensus Diagnostic Criteria for AIP. A definitive AIP diagnosis was based on histological analysis of pancreatic resection specimens or samples collected by fine-needle aspiration during endoscopic ultrasound. Patients with probable type 1 AIP were identified based on imaging findings, clinical and/or radiologic responses to steroids, level of serum immunoglobulin G4, and involvement of other organs. Patients with probable type 2 AIP were identified based on imaging findings, clinical and/or radiologic responses to steroids, and association with IBD. The primary objective was to collect information on the characteristics of AIP in patients with IBD. We also compared features of patients with IBD with and without AIP in a case-control analysis, using multivariate analysis.**

RESULTS: **We analyzed data from 91 individuals with AIP and IBD (47 women) seen at 23 centers (58 had ulcerative colitis [UC] and 33 Crohn's disease [CD]). Eighty-nine patients had type 2 AIP, and 2 patients had type 1 AIP. The mean age at diagnosis of AIP was 35 ± 12 years, and for IBD it was 32 ± 12 years. AIP preceded IBD in 19 patients (21%). Over a mean follow-up period of**

[c]List of members of GETAID-AIP study group in Appendix 1.

Abbreviations used in this paper: AIP, autoimmune pancreatitis; CD, Crohn's disease; CI, confidence interval; CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; GETAID, Groupe d'etudes et therapeutiques des affections inflammatoires du tube digestif; IBD, inflammatory bowel disease; ICDC, International Consensus Diagnostic Criteria; IDCP, idiopathic duct-centric pancreatitis; Ig, immunoglobulin; LPSP, lymphoplasmacytic sclerosing pancreatitis; MRI, magnetic resonance imaging; OR, odds ratio; TNF, tumor necrosis factor; UC, ulcerative colitis.

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5.7 ± 4.9 years, 31 patients (34%) relapsed, 11 patients (12%) developed diabetes, and 17 patients (19%) developed exocrine pancreatic insufficiency. In patients with UC, factors independently associated with AIP included proctitis (odds ratio [OR], 2.9; 95% confidence interval [CI], 1.3–6.3; $P = .007$) and colectomy (OR, 7.1; 95% CI, 2.5–20; $P = .0003$). In patients with CD, AIP was significantly associated with fewer perianal lesions (OR, 0.16; 95% CI, 0.03–0.77; $P = .023$), non-stricturing non-penetrating CD (OR, 6.7; 95% CI, 1.25–33.3; $P = .0029$), and higher rate of colectomy (OR, 27.8; 95% CI, 3.6–217; $P = .0029$).

CONCLUSIONS: **In a multicenter retrospective analysis of patients with AIP and IBD, followed for an average of 5.7 ± 4.9 years, we found most to have type 2 AIP. Two-thirds of patients have UC, often with proctitis. One-third of patients have CD, often with inflammatory features. Patients with IBD and AIP have higher rates of colectomy than patients with just IBD.**

Keywords: GETAID Study; Pancreas; Long-term Outcome; Surgery.

Autoimmune pancreatitis (AIP) associated with inflammatory bowel disease (IBD) is a rare and poorly known disease. Pancreatitis associated with IBD has been initially reported from histopathologic studies.[1] In 1995, Yoshida et al[2] named "autoimmune pancreatitis" the steroid-responsive chronic pancreatitis. In 2001, identification of immunoglobulin (Ig) G4 antibody contributed to a better understanding of this disease.[3] During the last decade, several classifications of AIP have been proposed.[4,5] Histologic and clinical profiling of patients with AIP revealed 2 distinct subtypes, lymphoplasmacytic sclerosing pancreatitis (LPSP) (type 1 AIP) and idiopathic duct-centric pancreatitis (IDCP) (type 2 AIP).[6–8] Recently, Shimosegawa et al[8] published the International Consensus Diagnostic Criteria for AIP. Type 1 AIP is an IgG4-related disease affecting mostly men older than 50 years. IgG4 level is commonly high, and there is multi-organ involvement.[3,8,9] Type 2 AIP is an idiopathic centric pancreatitis with granulocytic epithelial lesions, affecting young patients from 30 to 40 years old with equal gender ratio. IgG4 level is normal, and IBD is associated in 20%–30%.[7,10–12]

Few data are available regarding incidence and prevalence of AIP in IBD. Published series of patients with AIP and IBD are heterogeneous, and most of them included a small number of cases.[11,13–17] A recent Japanese study identified 7 cases of AIP among 1741 IBD patients, with a prevalence of 0.4%.[15] Barthet et al[13] reported 6 cases of AIP in IBD patients. In the study by Maire et al,[10] 5 patients with IBD were identified among 16 patients with type 2 AIP. Kawa et al[14] assessed 52 IBD patients, 11 of whom had confirmed type 2 AIP. Hart et al[17] recently published the Mayo Clinic experience with 19 IBD patients among 43 with type 2 AIP.

The aims of this study were to describe AIP associated with IBD and to determine the phenotype and outcomes of IBD when associated with AIP.

Methods

Selection of Patients

A retrospective multicenter study was performed in French and Belgian tertiary referral centers belonging to the Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif (GETAID). Gastroenterologists belonging to the GETAID were asked to report any cases of AIP in IBD patients. Patients were recruited from July 2012 to July 2015. The procedure used was approved by the ethics committee of Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (CCTIRS no. 14.442) and CNIL (French Commission on Information Technology and Liberties).

Inclusion Criteria

All patients had both IBD and AIP. IBD diagnosis was established according to ECCO guidelines.[18] For inclusion, we considered only patients who fulfilled the diagnostic criteria of AIP as defined by the International Consensus Diagnostic Criteria (ICDC) published in 2011.[8] The ICDC used 5 cardinal features of AIP, namely imaging of pancreatic parenchyma and ducts, serum IgG4 level, other organ involvement, histology, and response to steroid therapy. Each feature was categorized as level 1 and 2 findings, depending on the diagnostic certainty. The diagnosis of type 1 and type 2 AIP can be definitive or probable. All the files were reviewed before inclusion to check AIP criteria through a diagnostic grid and expert opinion in AIP (F.M.).[8]

Exclusion Criteria

To rule out other causes of pancreatitis, patients with the following criteria were excluded: alcohol consumption (>1 glass/day), gallstones, serum calcium level >3 mmol/L, history of abdominal radiotherapy, trauma to the epigastric region, tumoral duct obstruction, and positive search for mutation of cystic fibrosis transmembrane conductance regulator, serine protease inhibitor Kazal-type 1, or cationic trypsinogen genes.[10] Suspected cases of drug-induced pancreatitis were excluded[19] as well as cases of acute pancreatitis observed in patients starting thiopurines or salicylates (<3 months). Moreover, patients

had abdominal computed tomography (CT) scan and/or magnetic resonance imaging (MRI) and/or endoscopic ultrasound (EUS) to exclude other causes of pancreatitis.

Definitions

A definitive AIP diagnosis was confirmed by histologic analysis of pancreatic resection specimen or EUS–fine-needle-aspiration (EUS-FNA).[8] LPSP defined type 1 AIP, and IDCP defined type 2 AIP. In LPSP, there is periductal lymphoplasmacytic infiltrate with obliterative phlebitis, storiform fibrosis, and more than 10 IgG4-positive cells per high-power field on IgG4 immunostaining.[8] In IDCP, there is periductal lymphoplasmacytic infiltrate, storiform fibrosis, and granulocyte epithelial lesions.[6,8]

A probable type 1 AIP diagnosis was based on imaging criteria, clinical and/or radiologic response to steroids, high level of serum IgG4 >140 mg/dL (immunonephelometry),[3] and other organ involvements (cholangitis, sialadenitis, retroperitoneal fibrosis).[8]

A probable type 2 AIP diagnosis was based on imaging criteria, clinical and/or radiologic response to steroids (if introduced for pancreatic manifestations), and association with IBD, which is a diagnostic criterion for type 2 AIP.[8]

Imaging criteria for AIP according to ICDC[8] on CT scan and/or MRI and/or EUS were diffuse or focal enlargement with delayed enhancement in parenchymal imaging; long (one-third length of main pancreatic duct), or multiple strictures or segmental narrowing without marked upstream dilatation or irregular narrowing of the main pancreatic duct in association with wall thickening in ductal imaging (ductitis).[8] All images had to be analyzed by a radiologist with expertise in AIP.

Cholangitis associated with AIP was considered by the presence of significant bile duct wall thickening or irregular narrowing bile duct (extrahepatic or intrahepatic) on imaging.[8] Bile duct stenosis in the head of pancreas was not considered as cholangitis. Cholangitis healing with steroid was required.[8]

Primary sclerosing cholangitis associated with IBD diagnosis was based on liver histologic analysis. Primary sclerosing cholangitis does not respond to steroids. Patients are treated with ursodeoxycholic acid.

Data Collected

A standardized anonymous questionnaire was used to collect data on each patient, which were stored in a database (FileMaker Pro 12; Apple Inc, Cupertino, CA).

Inflammatory Bowel Disease

The following characteristics were recorded on each patient: gender, age at IBD diagnosis, smoking status, family history, IBD duration, location and behavior of Crohn's disease (CD) and extent of ulcerative colitis (UC) according to Montreal classification,[20] extraintestinal manifestations, surgeries, occurrence of cancer, and prior and present treatments.

Autoimmune Pancreatitis

The following characteristics were recorded on each patient: age at AIP diagnosis, AIP type, other organ involvement, treatments received for AIP, relapses, evolution (diabetes, exocrine pancreatic insufficiency), and duration of follow-up.

Corticosteroid treatment for AIP was usually a daily dose of 40 mg during 4 weeks and gradually tapered by 5 mg every week. All patients with acute AIP had initial medical management including fasting, intravenous hydration, and analgesics. Steroids were given for AIP only in patients with persisting symptoms after few days. AIP remission was defined as the resolution of AIP-related symptoms and radiologic abnormalities.

AIP relapse was defined as a reappearance of related AIP event (pancreatic pain, obstructive jaundice, extrapancreatic manifestation).[10] At the latest news, information regarding exocrine and endocrine functions was collected. Exocrine pancreatic insufficiency was defined by fecal elastase <200 μg/g stool or cessation of fatty stools with pancreatic enzyme substitution. Diabetes was defined by serum levels of glucose >7 mmol/L or glycosylated hemoglobin A1C >6%.[10]

Study Design

First part of the study was description of AIP and IBD characteristics and outcomes.

Second part was a case-control study with comparison of IBD patients with and without AIP. Each case of IBD with AIP was compared with 2 controls without AIP, matched by IBD type, gender, and age at IBD diagnosis. Control cases were drawn from a multicentric prospective IBD database from tertiary referral centers (Focus_MICI).

Statistical Analysis

Descriptive statistics were used to analyze patients' characteristics. Data were expressed as mean $\pm$ standard deviation. The association between IBD characteristics and AIP was evaluated in univariate and multivariate analysis. The Student t test for quantitative variables and χ^2 or Fisher exact tests for qualitative variables were used in the univariate analysis. Multivariable analysis was performed to determine the strength of associations. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by using regression analysis. All statistical analyses were performed by using SPSS software program (version 18.0; IBM, Armonk, NY). A 2-tailed P value <.05 determined a statistically significant result.

Results

Patient Characteristics

One hundred fourteen suspected cases of AIP in IBD patients were identified in 23 GETAID centers. After exclusion of 23 patients with insufficient imaging criteria for AIP (N = 21) or another cause of pancreatitis (N = 2), 91 patients (47 women) were finally analyzed in the present study (Figure 1). Eighty-nine patients had type 2 AIP, and 2 patients had type 1 AIP. Fifty-eight patients (64%) had UC, and 33 (36%) had CD.

Characteristics of patients with IBD and AIP are shown in Table 1. Mean age at AIP diagnosis was 35 ± 12 years, and mean age at IBD diagnosis was 32 ± 12 years. Mean IBD duration was 8.2 ± 7 years, and mean AIP follow-up was 5.7 ± 4.9 years. Among patients with known IBD at the time of AIP diagnosis (N = 72), 52 (72%) had an active IBD. Eighteen patients (20%) underwent colectomy, which was performed after AIP diagnosis in 11 of 18 patients (61%). Seven patients (8%) had first-degree family history of IBD. At AIP diagnosis, 21 patients (23%) were active smokers.

At the latest news, 25 patients (27%) have had extraintestinal manifestations of IBD including rheumatologic (N = 22), ophthalmologic (N = 2), and dermatologic (N = 1) manifestations.

Four patients had histologically proven primary sclerosing cholangitis associated with IBD. Primary sclerosing cholangitis diagnosis was made before AIP first manifestation, with a delay from 1 to 4 years.

Description of Inflammatory Bowel Disease

Ulcerative colitis. Fifty-eight patients (64%) had UC. Extent was rectal, left-sided, or pancolitis in 20 (34%), 18 (32%), and 20 (34%) patients, respectively. Thirteen UC patients (22%) (left-sided extent [N = 2], pancolitis [N= 11]) had colectomy; indications of colectomy were acute severe colitis (N = 12) and non-adenoma dysplastic lesion (N = 1). Colectomy was performed after AIP diagnosis in 10 of 13 UC patients (77%).

Crohn's disease. Thirty-three patients (36%) had CD. Location was ileal, ileocolonic, colonic, and upper digestive in 8 (22%), 13 (40%), 12 (38%), and 4 (12%) patients, respectively. Six patients (18%) had perianal disease. Behavior was inflammatory, structuring, and penetrating in 29 (87%), 2 (6%), and 2 (6%) patients, respectively.

Seven patients (21%) had intestinal surgery: colectomy or proctocolectomy (N = 5), small bowel surgery (N = 1), ileocolic resection (N = 1). Indications of colectomy were acute severe colitis (N = 4) and colonic fistula (N = 1). Four CD patients had colectomy before AIP. Two patients had perianal surgery for fistula.

Table 1. Characteristics of Patients With IBD and AIP

Characteristics	N = 91
Age (*y*)	
Mean age at AIP diagnosis ± SD	35 ± 12
Mean age at IBD diagnosis ± SD	32 ± 12
Gender	
Men	44 (48%)
Women	47 (52%)
Type of IBD	
CD	33 (36%)
UC	58 (64%)
CD location	
Ileal (L1)	8 (24%)
Colonic (L2)	13 (39%)
Ileocolonic (L3)	12 (36%)
Upper digestive (L4)	4 (12%)
CD behavior	
Non-stricturing non-penetrating (B1)	29 (88%)
Stricturing (B2)	2 (6%)
Penetrating (B3)	2 (6%)
Perianal disease	6 (18%)
UC location	
Rectal (E1)	20 (35%)
Left-sided (E2)	18 (31%)
Extensive UC (E3)	20 (35%)
Active IBD at AIP diagnosis	
Harvey-Bradshaw index ≥ 4	28 (64% of CD)
Partial Mayo score[a] ≥ 2	43 (46% of UC)
Treatments (past and present)	
Mesalamine	62 (68%)
Immunosuppressors	45 (50%)
Azathioprine	36 (40%)
Methotrexate	9 (10%)
Anti-TNF	35 (38%)
Colectomy	
CD	5 (15%)
UC	13 (22%)
AIP (ICDC)	
Definitive	14 (16%)
Probable (imaging, steroids, IBD)	77 (84%)
AIP location	
Diffuse	29 (32%)
Focal	62 (68%)
AIP manifestation	
Acute pancreatitis	73 (80%)
Abdominal pain	10 (11%)
Jaundice	6 (7%)
Incidental diagnosis	2 (2%)

AIP, autoimmune pancreatitis; CD, Crohn's disease; IBD, inflammatory bowel disease; ICDC, International Consensus Diagnostic Criteria; SD, standard deviation; TNF, tumor necrosis factor; UC, ulcerative colitis.
[a]Mayo score without endoscopy.

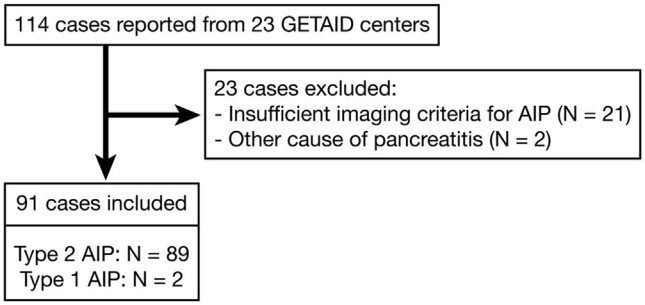

Figure 1. Flow chart.

Description of Autoimmune Pancreatitis

AIP characteristics are shown in Table 1. Diagnosis of AIP was definitive for 14 patients (16%) (histologic confirmation on 5 surgical specimens and 9 EUS-FNA) and probable for 77 patients (84%). All patients had typical AIP imaging features. One to 3 imaging examinations were performed per patient. CT scan, pancreatic MRI, and EUS were performed in 87 (96%), 77 (85%), and 75 (82%) patients, respectively. Focal enlargement of pancreatic parenchyma, diffuse enlargement of pancreatic parenchyma, and a pancreatic mass were observed in 29 (32%), 47 (52%), and 23 (25%) patients, respectively. Patients could have 1 or more parenchymal lesions. Main pancreatic duct was altered in all patients. Pancreatic ductitis, segmental stricture of main pancreatic duct, and multiple or long strictures of main pancreatic duct were present in 53 (58%), 38 (42%), and 28 (31%) patients, respectively. Strictures and ductitis could be associated.

Initial AIP manifestations were acute pancreatitis (N = 73, 80%), abdominal pain (N = 10, 11%), jaundice (N = 6, 7%), or incidental diagnosis (2%). No pancreatitis was severe. AIP preceded IBD in 19 patients (21%), was synchronous in 23 patients (26%), and occurred after IBD in 49 patients (54%). In patients with AIP preceding IBD, mean delay of IBD diagnosis was 2.2 ± 2.7 years. In patients with IBD before AIP, mean delay of AIP diagnosis was 5.6 ± 6.5 years, and among them, 22 (44.8%) developed AIP 2 years after IBD.

AIP was initially treated with corticosteroids in 44 patients (48%), with 100% response. Five patients (6%) underwent pancreatic surgery for initial suspicion of cancer. Forty-two patients (46%) received conservative care because of benign symptoms.

Cholangitis associated with AIP was diagnosed in 14 patients (15%) including type 1 AIP (N = 1) and type 2 AIP (N = 13). Cholangitis responded to steroids, with complete recovery in all cases. Five patients had irregular narrowing bile duct with 1 or multiple stenoses on MRI, and 11 patients had significant bile duct wall thickening on EUS.

After a mean follow-up of 5.7 ± 4.9 years, 31 patients (34%) have had at least 1 relapse. Mean number of relapses was 2.1 ± 1.6. Fourteen patients (45%) had 1 relapse, 7 patients (22.5%) had 2 relapses, and 10 patients (32.5%) had more than 2 relapses. Manifestations of relapses were acute pancreatitis (77%), abdominal pain (23%), and cholangitis (10%).

Eighteen patients (20%) had steroid-dependent AIP. Among them, 5 received azathioprine for AIP (UC, 3; CD, 2), with complete efficacy in 4. AIP evolved toward diabetes in 11 patients (12%) and to an exocrine pancreatic insufficiency in 17 patients (19%). No case of pancreatic or colorectal cancer was observed.

Azathioprine and Mesalamine Treatment in Patients with Inflammatory Bowel Disease and Autoimmune Pancreatitis

Twenty patients received azathioprine for IBD before AIP; azathioprine was stopped before AIP onset in these patients. Seven patients were treated with azathioprine at the time of AIP, all of them for more than 6 months. Mean duration of azathioprine treatment at the time of AIP was 28.7 months. All of these patients had active IBD. Nine patients (10%) started azathioprine after AIP onset, including 5 for steroid dependence for AIP; none of these patients had azathioprine-induced pancreatic symptoms.

Eighteen patients (20%) received mesalamine for IBD before AIP; mesalamine was stopped before AIP onset in these patients. Twenty patients (22%) were treated with mesalamine at the time of AIP, all of them for more than 3 months. Mean duration of mesalamine treatment at the time of AIP was 70 months. Twenty-four patients (26%) started mesalamine after AIP onset.

Case-Control Study

Inflammatory bowel disease with autoimmune pancreatitis compared with inflammatory bowel disease without autoimmune pancreatitis. Comparison of IBD patients with and without AIP is shown in Table 2. There was no difference between cases and control groups regarding time periods of IBD diagnosis (before 1990, 1990–2000, 2000–2010, after 2010) ($P = .96$). In univariate analysis, patients with AIP had significantly less first-degree family history of IBD ($P = .045$) and more colectomy procedures ($P < .0001$).

In multivariate analysis, colectomy (OR, 6.5; 95% CI, 2.39–17.8; $P < .0001$) was significantly associated with AIP. There was no difference between cases and controls in the proportions with colectomy before and after anti-tumor necrosis factors (TNF) availability in 2000.

Ulcerative colitis with autoimmune pancreatitis compared with ulcerative colitis without autoimmune pancreatitis. Comparison of UC patients with and without AIP is shown in Table 3.

In univariate analysis, UC patients with AIP were less likely to have first-degree family history of UC ($P = .032$) and immunosuppressive therapy ($P = .042$). Rectal location ($P = .024$) and colectomy ($P = .001$) were significantly associated with the presence of AIP. In multivariate analysis, independent factors associated with AIP were rectal location (OR, 2.9; 95% CI, 1.3–6.3; $P = .007$) and history of colectomy (OR, 7.1; 95% CI, 2.5–20; $P = .0003$).

Crohn's disease with autoimmune pancreatitis compared with Crohn's disease without autoimmune pancreatitis. Comparison of CD patients with and without AIP is shown in Table 4.

Table 2. Factors Associated With AIP in IBD Patients

	IBD with AIP (N = 91)	IBD without AIP (N = 182)	Univariate (*P* value)	Multivariate OR (95% CI)	Multivariate (*P* value)
UC	58 (64%)	116 (64%)	NS		
CD	33 (36%)	66 (36%)	NS		
Female	47 (52%)	94 (52%)	NS		
Active smoker	21 (23%)	35 (19%)	NS		
Age at IBD diagnosis (*y*)	32 ± 12	33 ± 12	NS		
IBD duration (*y*)	8.2 ± 7	9.5 ± 7	NS		
Active smoker	21 (23%)	35 (19%)	NS		
Family history of IBD	7 (8%)	30 (17%)	**.045**	2.5 (0.96–6.3)	.06
Extraintestinal manifestations	25 (28%)	68 (37%)	NS		
Acute severe colitis	19 (21%)	28 (15%)	NS		
Ileocolic surgery	20 (22%)	26 (29%)	NS		
Colectomy	18 (20%)	9 (5%)	**<.0001**	6.5 (2.39–17.8)	**<.0001**
Treatments (past and present)					
Mesalamine	62 (68%)	161 (88%)	NS		
Immunosuppressors	55 (60%)	122 (67%)	NS		
Azathioprine	36 (40%)	94 (52%)	NS		
Anti-TNF	35 (38%)	81 (35%)	NS		

NOTE. Boldface indicates significant results.
AIP, autoimmune pancreatitis; CD, Crohn's disease; IBD, inflammatory bowel disease; TNF, tumor necrosis factor; UC, ulcerative colitis.

In univariate analysis, CD patients with AIP were less likely to have perianal disease ($P < .0001$) and stricturing and penetrating behavior ($P = .0029$) but significantly more likely to have colectomy ($P = .001$). CD patients with AIP had received more immunosuppressors ($P = .014$) and more mesalamine ($P < .00001$).

In multivariate analysis, independent factors associated with AIP were inflammatory behavior (OR, 6.7; 95% CI, 1.25–33.3; $P = .023$) and colectomy (OR, 27.8; 95% CI, 3.6–217; $P = .001$). Perianal disease was associated with the absence of AIP (OR, 0.16; 95% CI, 0.03–0.77; $P = .023$).

Discussion

To our knowledge, this study is the largest series of patients with AIP and IBD. Nearly all patients (89 of 91) had type 2 AIP. This was expected in a population of IBD patients, because the association between both diseases is a diagnostic criterion for type 2 AIP in the ICDC.[8] Hart et al[17] recently reported that patients with definitive type 2 AIP (histology of IDCP) and those with probable type 2 AIP associated with IBD have similar demographic profiles and disease-related outcomes. Authors suggested that the co-occurrence of IBD as a supportive diagnostic criterion for type 2 AIP appears valid. Histologic diagnosis of AIP is often missing. With the progress of imaging, differential diagnosis with pancreatic cancer is easier, and surgery is required less often. EUS-FNA can help to confirm AIP with variable diagnostic value in the literature.[8,17,21] Two patients had type 1 AIP. Even if association of type 1 AIP and IBD is less frequent, it has already been reported.[7,11,22,23]

Demographic data of our population exhibited young onset age and equal gender ratio, in accordance with the

Table 3. Factors Associated With AIP in UC Patients

	UC with AIP (N = 58)	UC without AIP (N = 116)	Univariate (*P* value)	Multivariate OR (95% CI)	Multivariate (*P* value)
Family history of IBD	3 (5%)	20 (17%)	**.032**	0.33 (0.09–1.22)	.097
Active smoker	10 (17%)	17 (15%)	**NS**		
Location					
Rectal (E1)	20 (35%)	22 (19%)	**.024**	2.9 (1.3–6.3)	**.007**
Left-sided (E2)	18 (31%)	45 (39%)	NS		
Extensive UC (E3)	20 (35%)	49 (42%)	NS		
Acute severe colitis	15 (26%)	17 (15%)	.072	1.2 (0.39–3.7)	.75
Colectomy	13 (22%)	6 (5%)	**.001**	7.1 (2.5–20)	**.0003**
Treatments					
Mesalamine	47 (82%)	105 (91%)	NS		
Immunosuppressors	22 (38%)	63 (54%)	**.042**	0.66 (0.29–1.5)	.33
Anti-TNF	16 (28%)	39 (34%)	NS		

NOTE. Boldface indicates significant results.
AIP, autoimmune pancreatitis; IBD, inflammatory bowel disease; TNF, tumor necrosis factor; UC, ulcerative colitis.

Table 4. Factors Associated With AIP in CD Patients

	CD with AIP (N = 33)	CD without AIP (N = 66)	Univariate (*P* value)	Multivariate OR (95% CI)	Multivariate (*P* value)
Extraintestinal manifestations	14 (42%)	36 (55%)	NS	0.38 (0.12–1.17)	.094
Active smoker	11 (33%)	18 (27%)	NS		
Location					
Ileal (L1)	8 (24%)	19 (29%)	NS		
Colonic (L2)	13 (39%)	29 (44%)	NS		
Ileocolonic (L3)	12 (36%)	18 (27%)	NS		
Upper digestive (L4)	4 (12%)	7 (11%)	NS		
Perianal disease	6 (18%)	38 (58%)	**<.0001**	0.16 (0.03–0.77)	**.023**
Behavior					
Non-stricturing non-penetrating (B1)	29 (88%)	35 (53%)	**.0029**	6.7 (1.25–33.3)	**.023**
Stricturing (B2)	2 (6%)	15 (23%)			
Penetrating (B3)	2 (6%)	16 (24%)			
Ileocolic surgery	7 (21%)	20 (30%)	NS		
Colectomy	5 (15%)	3 (9%)	**.001**	27.8 (3.6–217)	**.001**
Treatments					
Mesalamine	15 (45%)	56 (85%)	**<.00001**	0.55 (0.11–2.83)	.47
Immunosuppressors	23 (70%)	59 (89%)	**.014**	0.83 (0.25–2.78)	.760
Anti-TNF	19 (58%)	42 (64%)	NS		

NOTE. Boldface indicates significant results.
AIP, autoimmune pancreatitis; CD, Crohn's disease; TNF, tumor necrosis factor.

literature.[7,10,11,17,24] Acute pancreatitis was the most common clinical presentation in our study (80%). Other studies have also reported that acute pancreatitis is more common in type 2 AIP compared with type 1 AIP.[11,17] Hart et al[11] reported acute pancreatitis in 64% of patients with type 2 AIP vs 27% in patients with type 1. Interestingly, we observed a 15% rate of associated cholangitis, which is higher than in the literature. Usually cholangitis is more common in type 1 AIP,[5,8,11,14] but it has also been reported in association with type 2 AIP.[13,14,25–27] A recent study reported 5 cases of autoimmune cholangitis characterized by the presence of granulocyte epithelial lesions in liver biopsies; all patients went to remission with steroid therapy.[28] Four of these 5 patients had IBD.[28] Unfortunately, histologic analysis of biliary duct was not available in our patients, but cholangitis was demonstrated by using MRI and/or EUS. We excluded patients with bile duct compression by large/pseudotumoral pancreatitis. EUS, which was not systematically performed in other studies, could identify early signs of cholangitis such as wall thickening ($\geq$1.5 mm), irregular wall structure, and changes of caliber of the common bile duct.[21,29] A second argument for the diagnosis of cholangitis in our patients was the remission observed after steroid treatment in all of them.

In our study, 31 patients (34%) had at least 1 AIP relapse. In the literature, relapse rate varies between 6% and 55%,[30,31] significantly higher in type 1 than in type 2 AIP.[24,30,31] In the Mayo Clinic study[17] cumulative relapse rate of type 2 AIP was 10.6% at 3 years. Our relapse rate was higher, but the mean follow-up was longer (>5 years), and our patients underwent fewer pancreatic surgery procedures.

We observed endocrine and exocrine pancreatic insufficiency in 12% and 19% of patients, respectively. These rates are lower than those previously reported.[10,17] Two explanations could be proposed. First, almost all studies have considered both type 1 and type 2 AIP, and diabetes is more frequent in type 1 AIP (40%–70%)[10,32]; second, in our study few patients had pancreatic surgery, which is a risk factor of diabetes and exocrine pancreatic insufficiency.[10,32]

There were no cases of colorectal or pancreatic cancer within the 5-year period of follow-up. In the literature, some pancreatic cancers have been described in AIP patients, but a significantly increased risk of pancreatic cancer has not been demonstrated.[33] A survey of patients with AIP in Japan reported pancreatic cancer in 0.8% and colorectal cancer in 1.7%.[34]

In our cohort, AIP preceded IBD in 21%, which is similar to other series.[17] At the time of AIP diagnosis, 72% of our patients had active IBD, suggesting the role of systemic inflammation in AIP onset. In our series, two-thirds of patients had UC, and one-third had CD, in accordance with the literature.[13,14,16,24] Our patients with IBD and AIP had an increased risk of colectomy. We did not detect any temporal bias; colectomy rates before and after anti-TNF availability were similar.

In our patients with UC, multivariate analysis showed that rectal location and colectomy were associated with AIP. A high rate of colectomy in patients with UC and AIP (43%) was also reported by Hart et al.[17] In our study, all colectomies were performed in patients with extensive UC. Our results suggested that there are 2 groups of UC patients at risk of AIP, one with rectal location and mild disease and the second with extensive and active disease not responding to biologic treatments.

Our patients with CD and AIP had more inflammatory behavior, less perianal disease, and more colectomies than

controls. No data are available in the literature regarding location and behavior of CD associated with AIP.

Our study has several strengths. To our knowledge, it is the largest series of patients with IBD and AIP. It is a case-control study of patients with IBD and AIP assessing phenotype and outcomes of IBD when associated with AIP. Some limitations should be taken into consideration. This study was retrospective with some missing data. Histologic diagnosis of AIP was often missing. Because of the declarative nature of the cases, we could not assess the total number of patients with IBD followed during the same period, and so we could not evaluate the prevalence of AIP in IBD patients. Ueki et al[15] recently reported the frequency of AIP in Japanese IBD patients was 0.5% in UC and 0.3% in CD.

Conclusion

Most patients with IBD had type II AIP. A third of AIP patients relapsed, with an excellent response rate to steroid treatment. Two-thirds of patients had UC and one-third CD. AIP diagnosis preceded IBD in 20% of patients. Patients with AIP and UC were more likely to have rectal disease whereas those with CD had non-stricturing and non-penetrating behavior than comparison groups without AIP. Patients with both IBD and AIP have increased rates of colectomy.

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Conflicts of interest
The authors disclose no conflicts.

Appendix 1. Collaborators of the GETAID-AIP Study Group

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