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Original Article

Idiopathic acute pancreatitis in patients with inflammatory bowel disease: A multicenter cohort study

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ABSTRACT

Background: Idiopathic acute pancreatitis (IAP) in patients with inflammatory bowel disease (IBD) is not well characterized. Our purpose was to better understand this condition and its natural history.
Methods: Retrospective cohort study conducted at nine Spanish IBD referral centers. Patients with IBD and a first episode of acute pancreatitis (AP) between 1998 and 2018 were included. Patients with a previous episode of AP or a diagnosis of chronic pancreatitis were excluded. IAP and non-IAP were compared by multivariate logistic regression and survival analysis.
Results: We identified 185 patients with IBD (68.7% Crohn's disease) and a first episode of AP. Thirty-eight of those 185 (20.6%) fulfilled criteria for IAP. There were no severe cases of IAP. On multivariate analysis, AP before IBD diagnosis (21.1% vs. 3.4%, $p = 0.04$) and ulcerative colitis (52.6% vs. 23.1%, $p = 0.002$) were significantly more common in IAP. Further work-up was performed in 16/38 (42%) IAP patients, and a cause was identified in 6/16 (37.5%). Median time from AP to the end of follow-up was 6.3 years (3.1–10). Five-year risk of AP recurrence was significantly higher in IAP group (28% vs. 5.1%, log-rank $p = 0.001$), with a median time to first recurrence of 4.4 months (2.9–12.2).
Conclusions: IAP represents the second cause of AP in patients with IBD. It is more frequent in ulcerative colitis, and presents a high risk of recurrence. Additional imaging work-up after a first episode of IAP in IBD patients is highly advisable, as it identifies a cause in more than one-third of cases.

Introduction

Acute pancreatitis (AP) is one of the most frequent gastrointestinal conditions, with an annual incidence between 13 and 45 cases per 100,000 habitants [1]. Approximately 20% of patients

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suffer more than one episode [2]. In most cases, a cause is identified after a targeted anamnesis (alcohol abuse, drug exposure, etc.), routine blood tests (including complete liver profile, calcium, and triglycerides), and an abdominal ultrasound [3]. However, in 20–30% of patients with a first episode of AP, this initial evaluation fails to disclose a cause, and those are classified as idiopathic acute pancreatitis (IAP) [3,4]. It is still a matter of debate if additional work-up should be performed after a first episode of IAP [2,3].

Patients with inflammatory bowel disease (IBD) appear to be at an increased risk of AP [5]. This risk is higher in patients with Crohn's disease (CD) [5,6]. Drugs, particularly thiopurines, are the main cause of AP in IBD [6,7]. Thiopurine-induced pancreatitis characteristically appears within the first weeks after exposure, has a mild course and a higher incidence in patients with CD [6,8,9]. Gallstone disease is second in frequency, particularly in patients with CD, who have a higher prevalence of cholelithiasis than the general population [10]. Regarding IAP, its incidence seems greater in patients with IBD than in the general population, varying from 15 to 83% [6,11,12].

IBD is a multisystemic disease with a prevalence of extra-intestinal manifestations of 21–47%, sometimes preceding the diagnosis of the intestinal involvement [13]. The probability of presenting an extraintestinal manifestation increases with disease duration and in patients who already have one [9]. Some authors have suggested that a number of IAP cases could be classified as true extraintestinal manifestations [9,11,14]. Furthermore, some case series have linked the onset of AP with the activity of IBD, and describe the resolution of the pancreatic inflammation after adequately treating the underlying IBD [15]. However, few studies have focused on characterizing IAP in IBD.

Another point of interest is the role that corresponds in this situation to autoimmune pancreatitis, specifically type 2, which has been associated with IBD [16]. Up to 30–40% of patients with type 2 autoimmune pancreatitis have IBD and, in this context, its presentation in form of AP is significantly more frequent than the classic form of painless jaundice and pancreatic mass [17]. However, it is not uncommon to reach a diagnosis only after several episodes of AP initially considered idiopathic.

The main aim of the present study was to describe the clinical characteristics and natural history of AP classified as idiopathic in IBD patients. Secondarily, we aimed to compare the features and outcomes of IAP with other causes of AP in this population.

Materials and methods

Study design

This was a retrospective analytical cohort study conducted at nine academic hospitals in Spain. The study protocol adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee for Clinical Research of the steering center (Hospital Universitario Ramón y Cajal; IRB number: 353/18. HRC-PANCREATITIS-EII-01; approval date: October 30, 2018). Exemption of individual informed consent for the inclusion in the study was granted due to its retrospective design.

Patients with IBD diagnosis and history of a first episode of AP between January 1998 and January 2018 were included. Patients with a previous episode of AP or a known diagnosis of chronic pancreatitis at the moment of AP were excluded.

Study definitions

AP was diagnosed according to the International Association of Pancreatology criteria, and it was defined as fulfillment of 2 out of 3 of the following criteria: (1) clinical (upper abdominal pain); (2) laboratory (serum amylase or lipase three times greater than normal); (3) radiological evidence of pancreatitis [2]. Cause of AP was established in accordance with the guidelines of the American College of Gastroenterology; AP was labelled as idiopathic when the cause remained unexplained after directed anamnesis, initial laboratory studies, and abdominal ultrasound according to current guidelines [3]. Additional tests performed after the first episode (magnetic resonance cholangiopancreatography [MRCP] or endoscopic ultrasound [EUS]) were registered. Severity of AP was graded according to the Revised Atlanta Classification into the following categories: mild (absence of organ failure and absence of local or systemic complications), moderate (transient organ failure <48 h or presence of local complications), and severe (persistent organ failure >48 h) [3]. Recurrent pancreatitis was diagnosed if the patient presented a new episode of AP, as defined above. Chronic pancreatitis was defined by the presence of typical findings at imaging [18]. Autoimmune pancreatitis was determined according to the diagnostic criteria of the International Consensus [19]. The Charlson index was used to assess comorbidity. IBD diagnosis and extension, and extraintestinal manifestations were defined according to ECCO guidelines [9,20,21]. Due to the retrospective design of the study, IBD severity was indirectly assessed by 1) occurrence of moderate/severe flares, and 2) IBD related-surgeries (perianal, intestinal resection, abscess drainage or proctocolectomy). These items were assessed 12 months after the index episode of AP and at the end of follow-up.

Study endpoints

The primary endpoint was to describe the clinical characteristics and evolution of AP initially classified as idiopathic according to current guidelines in patients with IBD. As secondary endpoints, we evaluated: 1) the proportion of IAP in which a cause was found after additional work-up; 2) the course of IBD after IAP; and 3) the risk of IAP recurrence, progression to chronic pancreatitis, and diagnosis of autoimmune pancreatitis during follow-up after a first episode of IAP.

Data collection

Patients with IBD diagnosis and record of a first episode of AP between January 1998 and January 2018 were identified through the ENEIDA registry. ENEIDA is a prospectively maintained registry of the Spanish Working Group in Crohn's disease and Ulcerative Colitis (GETECCU), which includes patients with IBD. Hospital and primary health care clinical records of patients included were also reviewed. Study data were collected and managed using AEG-REDCap electronic data capture tools; this is a secure, web-based application created to support data capture for research studies providing semiautomatic data quality control [22].

Statistical analysis

If additional work-up study (MRCP, EUS) performed after the initial episode found a cause in patients with pancreatitis initially classified as idiopathic, pancreatitis remained classified as idiopathic for analysis as we intended to evaluate the course of a first episode of AP labelled as idiopathic according to current guidelines. Continuous variables were reported as mean and standard deviation (SD) when normality was met, and as median and interquartile range (IQR) for non-normally distributed variables. The *t*-Student test was used to compare differences between groups for normally distributed variables, and the U Mann-Whitney test for non-normally distributed variables. Categorical variables were described as absolute and relative frequencies, and $\chi 2$ test or Fisher

exact test when necessary were used for intergroup comparisons. Variables with a p value < 0.15 in bivariate analysis entered multivariate logistic regression via backward stepwise regression. No sample size estimation was performed for the descriptive analysis. To conduct the multivariate analysis assuming 20% of IAP, an alpha risk of 0.05, and following the standard of one explanatory variable for every 10 events, a sample size of 150 patients was estimated to analyze a minimum of three independent factors associated with IAP [6]. We plotted the five-year cumulative incidence of recurrence of IAP, diagnosis of autoimmune pancreatitis, and chronic pancreatitis by using the Kaplan-Meier survival function estimates. The log-rank test assessed differences between groups. All analyses were two-tailed, and significance was set at $p < 0.05$. Statistical analyses were performed using Stata/IC 14.0.

Results

Study population

Of a total population of 12,171 IBD cases registered at nine IBD referral centers, we identified 185 patients (53% males; 68.7% CD) with a first episode of AP within the study period. Drug-induced AP represented more than half of AP causes (109, 59%), of which 83.4% were due to azathioprine, 9.2% to 5-aminosalicylates (5-ASA), and 7.4% to mercaptopurine. Of the thiopurine-induced AP, 88% were CD patients. IAP was the second most common cause of AP (38, 20.6%). Clinical characteristics are summarized in Table 1. Median time from AP to the end of follow-up was 6.3 years (3.1–10).

Idiopathic acute pancreatitis versus other causes

The study population was divided into two groups: IAP (38 patients) and non-IAP (147 patients), detailed in Table 2. On multivariate analysis, ulcerative colitis (UC) (Odds Ratio (OR) 3.6; confidence interval (CI) 95%: 1.64–7.9; $p = 0.001$) and absence of extraintestinal manifestations at the end of follow-up (OR 0.26; CI 95%: 0.06–0.98; $p = 0.005$), were independently associated with IAP. Two patients with IAP (5.2%) died during follow-up (one due to metastatic breast cancer and one to chronic obstructive pulmonary disease exacerbation) and another two in the non-IAP group (1.3%; one due to lung cancer and another to cholangiocarcinoma in the context of primary sclerosing cholangitis [PSC]).

Acute pancreatitis characteristics

Most AP episodes were mild, and specifically, ninety-five of the 99 (96%) thiopurine-related AP. There were no severe cases registered in IAP patients, and there were no significant differences in severity between IAP and non-IAP group after multivariate adjustment. Similarly, no significant differences were found in the rate of local complications (Table 2). None of the IAP patients required intensive care unit admission, and there were no AP-related deaths.

Additional work-up

Further diagnostic work-up was performed in 16/38 (42%) patients without an identifiable cause at presentation: MRCP in 9, EUS in 3, and both in 4 patients. A cause for IAP was identified in 6 of the 16 patients (37.5%) who did undergo additional work-up: two biliary etiology, one groove pancreatitis, and three patients with probable autoimmune pancreatitis type 2. MRCP achieved a diagnosis in 5/13 patients (38.4%): two biliary, one groove pancreatitis, and two probable autoimmune pancreatitis. EUS was performed in seven patients with an initially labelled IAP, and a cause was found in two patients (28.7%): an enlarged pancreas suggestive of autoimmune pancreatitis, one of which had also undergone MRCP with similar findings. Serum IgG4 was determined in 34% of IAP patients, and they all presented normal levels.

Relationship between inflammatory bowel disease and acute pancreatitis

Occurrence of AP before IBD diagnosis was significantly more frequent in IAP patients (OR 6.71; CI 95%: 1.77–25.35, $p = 0.04$) as detailed in Table 2, with a median time from IAP to IBD diagnosis of 7.5 months (1.7–18). In the 13 patients in which AP preceded IBD identification, UC was eventually diagnosed in 7 patients, CD in 5, and unclassified colitis in one. In patients who presented with IAP after the diagnosis of IBD, time from IBD diagnosis to AP was 3.4 years (0.8–10.8). IBD was diagnosed coincidentally with IAP in one patient. Forty-five patients (24.3%) developed AP during a flare of the underlying IBD, without significant differences between the two groups (29% in the IAP group and 23% in the non-IAP group, $p = 0.49$).

The course of IBD during the year that followed the first episode of AP did not differ among the two groups. Likewise, there were no differences between IAP and non-IAP patients regarding IBD activity at the end of follow-up (Table 2).

Course of pancreatic disease

The risk of IAP recurrence, progression to chronic pancreatitis, and diagnosis of autoimmune pancreatitis during follow-up after a first episode of IAP are depicted in Fig. 1.

IAP patients presented a significantly higher five-year risk of AP recurrence (28% vs. 5.1%, log-rank $p = 0.001$), with a median time to first recurrence of 4.4 months (2.9–12.2). Eleven patients in the IAP group presented at least one recurrence of AP during follow up: five patients presented one recurrence; four patients two recurrences; one patient three recurrences, and one patient four recurrences. The causes of the first recurrence were: drug-related in three patients; autoimmune in two patients, and idiopathic in six patients. In the non-IAP group there were seven patients with recurrence of AP: one gallstone pancreatitis (the index AP was also biliary), two alcohol AP (index AP were also alcohol-related), and four azathioprine-induced pancreatitis (index AP was biliary in one and 5-ASA related in the remaining three). Three out of the ten patients with 5-ASA-related index AP went on to develop azathioprine-induced AP during follow-up.

IAP patients also presented a significantly higher five-year risk of developing chronic pancreatitis (5.2% vs. 0.6%, log-rank $p = 0.02$). Two patients were diagnosed with idiopathic chronic pancreatitis in the IAP group of which none had PSC, and one patient in the non-IAP group was diagnosed with alcoholic chronic pancreatitis. In all three cases the diagnosis was made based on pancreatic calcifications.

Probable autoimmune pancreatitis type 2 (idiopathic duct-centric chronic pancreatitis) was diagnosed in 5/38 patients of the IAP group (in three patients the diagnosis was made because they underwent additional work-up after the first episode of AP and the other two were diagnosed during follow-up) and in one patient of the non-IAP group. Of these 6 patients, there were three with UC (all with left-sided colitis) and three with CD (2/3 with inflammatory phenotype and 1/3 with perianal disease). Only one of the six patients had concomitant PSC and none had previous colectomy. There were no other forms of autoimmune pancreatitis in the cohort. Five-year risk of being diagnosed with autoimmune pancreatitis was higher in IAP patients (14.1% vs. 0.7%, log-rank $p < 0.001$). We performed an exploratory sensitivity analysis excluding the five patients eventually diagnosed of autoimmune pancreatitis from the idiopathic acute pancreatitis group. UC remained significantly associated with IAP as detailed in Table 3.

Table 1
Patient baseline characteristics at first episode of acute pancreatitis.

	n = 185
Male gender	98 (53%)
Age, years	41.8 (17.3)
AP cause	
Drug-induced	109 (59%)
Idiopathic	38 (20.6%)
Gallstones	34 (18.4%)
Alcohol	2 (1%)
Post-ERCP	2 (1%)
Comorbidity	
Active smoking	74 (40%)
Diabetes mellitus	4 (2.1%)
Autoimmune diseases	11 (5.9%)
Prior cholecystectomy	13 (7%)
Charlson index	0 (0–2)
Family history of IBD	31 (16.7%)
IBD phenotype and disease extent[a]	
Crohn's disease	127 (68.7%)
A1/A2/A3	3.1%/66.2%/30.7%
L1/L2/L3/L4	49.6%/21.2%/29.2%/11.8%
B1/B2/B3	61.4%/21.3%/17.3%
Duodenal involvement	6 (4.7%)
Perianal involvement	30 (23.6%)
Ulcerative colitis	54 (29.2%)
E1/E2/E3	13%/46.2%/40.8%
S0/S1/S2/S3	22.2%/35.1%/29.7%/13%
Perianal involvement	2 (12.5%)
Unclassified	4 (2.1%)
Number of patients with extraintestinal manifestations	36 (19.5%)
Musculoskeletal	17
Dermatologic	10
Ocular	5
Primary sclerosing cholangits	4
Others	4
IBD-related surgery prior to AP	34 (18.4%)
IBD treatment within 12 months prior to AP	
5-ASA	97 (52.4%)
Steroids	117 (63.2%)
Immunomodulators	111 (60%)
Anti-TNF	10 (5.4%)

Quantitative variables are provided as mean and standard deviation in brackets or median and interquartile range when appropriate. Qualitative variables are provided as absolute values and percentages. AP: acute pancreatitis; ERCP: endoscopic retrograde cholangiopancreatography; IBD: inflammatory bowel disease; 5-ASA: 5-aminosalicylic acid; anti-TNF: anti-tumor necrosis factor.

[a] In the 13 patients that developed AP before the establishment of IBD diagnosis, IBD extension and severity were registered at the time of IBD diagnosis.

Discussion

This study represents the largest cohort of AP in IBD patients and contributes to better understanding of IAP in this specific context. Our data provide information regarding IAP preferential association with UC and a higher likelihood of pancreatic disease during follow-up. Besides, we observed that a cause for AP is found in a significant proportion of patients without an identifiable etiology at presentation, provided additional work-up is carried out.

Remarkably, IAP represented the second most common cause of AP in IBD patients. Drug-induced pancreatitis was the leading cause of AP in agreement with previous studies, while gallstones and alcohol represented 20% of all causes [6]. This distribution is notably different compared to what it is reported in the general population [3]. In our cohort three out of the ten patients with 5-ASA-related index AP developed azathioprine AP during follow-up, which has not been previously described. In 20.6% of our study population, the cause of AP remained unidentified after initial work-up and was labelled as idiopathic, a figure similar to the general population [4]. IAP occurred at a younger age in our cohort compared to previously reported in the general population, where it has been described to be over 40 years in more than 75% of patients [23].

Most AP episodes in IBD affect CD patients [5]. However, we found IAP to be independently associated with UC, even after excluding patients with an eventual diagnosis of autoimmune pancreatitis from the IAP group; this has not been earlier described even though previous research noticed pancreatic morphological changes in patients with UC. Autopsy studies conducted in the 50s showed macroscopic or microscopic pancreatic lesions in 53% of UC patients [24]. Moreover, in more recent series, up to 16% of UC patients with no previous history of alcohol consumption or prior episodes of AP showed pancreatic duct disorders on MRCP [25]. Pancreatic lesions have also been found in experimental colitis models in mice [26]. Even though no relation between IAP and the extent or the severity of IBD was found in our series, there were significant differences regarding timing of IAP presentation. Interestingly, AP preceded IBD diagnosis in 21% of IAP patients. IBD presenting after an episode of IAP has been previously reported to be more frequent among the pediatric population [27]. This may suggest that IAP, especially in young patients, might be considered as an early event in an as-yet undiagnosed IBD, particularly UC.

Pancreatitis in IBD patients has been reported to be generally mild [6,28]. In our cohort, the course of pancreatitis was favorable in all IAP patients without cases of severe pancreatitis. Azathioprine-

Table 2
Factors associated with idiopathic acute pancreatitis.

	IAP n = 38	Non-IAP n = 147	Univariate p value	Multivariate OR (95% CI); p value
BASELINE CHARACTERISTICS				
Male gender	22 (57.9%)	76 (51.7%)	0.50	
Age, years	41.1 (18.3)	42 (17.2)	0.78	
Comorbidity				
Active smoking	10 (26.3%)	64 (43.5%)	**0.02**	Excluded from final model
Diabetes mellitus	2 (5.2%)	2 (1.3%)	0.19	
Autoimmune diseases	1 (2.6%)	10 (6.8%)	0.47	
Charlson index	0 (0–2)	0 (0–2)	0.49	
ACUTE PANCREATITIS				
AP severity			**0.07**	Excluded from final model
Mild	32 (84.2%)	138 (93.8%)		
Moderate	6 (15.8%)	7 (4.8%)		
Severe	0	2 (1.4%)		
Number of patients with local complications[a]	5 (13.1%)	12 (8.1%)	0.35	
Acute fluid collections	5	7		
Acute necrotic collections	0	3		
Pseudocyst	2	2		
Walled-off necrosis	1	2		
Splanchnic vein thrombosis	1	0		
Hospital stay, days	10.2 (9.2)	7.6 (14.1)	0.29	
AP during a flare-up of the underlying IBD	11 (29%)	34 (23.1%)	0.49	
Time from AP to end of follow-up, years	5.8 (5.3)	7.2 (4.4)	0.21	
IBD				
IBD type			**<0.01**	
Crohn's disease	16 (42.2%)	111 (75.5%)		Reference
Ulcerative colitis	20 (52.6%)	34 (23.1%)		**3.61 (1.62–8.04), p = 0.002**
Unclassified colitis	2 (5.2%)	2 (1.4%)		4.22 (0.47–37.37), p = 0.19
Number of patients with extraintestinal manifestations	3 (7.9%)	33 (22.4%)	**0.04**	**0.26 (0.06–0.98), p = 0.005**
AP before IBD diagnosis	8 (21.1%)	5 (3.4%)	**<0.01**	**6.71 (1.77–25.35), p = 0.04**
Time from IBD diagnosis to end of follow-up, years	11 (10.4)	13.8 (10.1)	0.24	
Moderate/severe IBD flares within 12 months after AP	12 (31.5%)	44 (29.3%)	0.64	
IBD-related surgery 12 months after AP	1 (2.6%)	7 (4.7%)	0.25	
Moderate/severe IBD flares within 12 months before end of follow-up	9 (23.6%)	28 (19%)	0.73	
IBD-related surgery at end of follow-up	9 (23.6%)	50 (34%)	0.61	

[a] Patients had undergone the following abdominal imaging tests: ultrasound 164 patients (38 in IAP group; 126 in non-IAP), computerized tomography 66 patients (22 in IAP group; 44 in non-IAP), endoscopic ultrasound 14 patients (7 in IAP group; 7 in non-IAP), and magnetic resonance cholangiopancreatography 33 patients (13 in IAP group; 20 in non-IAP). Quantitative variables are provided as mean and standard deviation in brackets. Qualitative variables are provided as absolute values and percentages. Figures in bold indicate significance. IAP: idiopathic acute pancreatitis; OR: odds ratio; CI: confidence interval; AP: acute pancreatitis; IBD: inflammatory bowel disease.

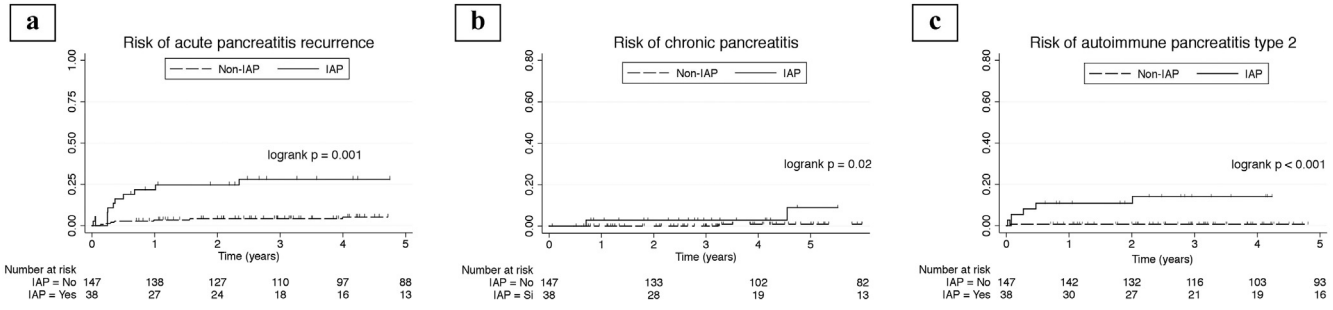

Fig. 1. Pancreatic follow-up: a) Five-year risk of acute pancreatitis recurrence; b) Five-year risk of chronic pancreatitis; c) Five-year risk of autoimmune pancreatitis diagnosis.
IAP: idiopathic acute pancreatitis.

induced AP was classified as moderate in four cases based on the presence of pancreatic fluid collections. Another important finding of our study is that additional diagnostic work-up (MRCP and/or EUS) after the first episode of IAP was performed in less than half of the patients, but a cause was found in 37.5% of them. Currently, there is no agreement regarding the need of additional work-up after a first episode of IAP in the general population. While the International Association of Pancreatology recommends EUS as the first step to assess for occult microlithiasis, neoplasms and chronic pancreatitis, the American College of Gastroenterology states that EUS in patients with IAP should be limited as the benefits of investigation are unclear [2,3]. Our data suggest that in IBD patients presenting with IAP extensive work-up with MRCP and/or EUS should be performed as it identifies a cause in more than one third. Therefore, recommendations of current guidelines regarding the etiological work-up that should be conducted after a first episode of AP that remains idiopathic after the initial work-up are likely to fall short, especially in the context of IBD. Fig. 2 represents a proposal for the etiological work-up study in IBD patients with a first episode of AP.

Diagnosis of autoimmune pancreatitis was significantly more common in the IAP group. Type 2 autoimmune pancreatitis is confined to the pancreas, is not associated with elevated IgG4 levels, occurs more often in younger patients, and it is frequently

Table 3
Factors associated with idiopathic acute pancreatitis after excluding patients diagnosed of autoimmune pancreatitis.

	IAP n = 33	Non-IAP n = 152	Multivariate OR (95% CI); p value
IBD type			
Crohn's disease	13 (39.4%)	114 (75%)	Reference
Ulcerative colitis	18 (54.6%)	36 (23.7%)	**3.22 (1.34–7.71), p = 0.008**
Unclassified colitis	2 (0.6%)	2 (1.3%)	5.31 (0.59–47.71), p = 0.13
Number of patients with extraintestinal manifestations	7 (21.2%)	35 (23%)	**5.32 (1.09–25.79), p = 0.03**
AP before IBD diagnosis	7 (21.2%)	6 (3.9%)	**0.14 (0.03–0.64), p = 0.01**
AP severity			
Mild	27 (81.8%)	143 (94%)	Reference
Moderate	6 (182%)	7 (4.7%)	3.07 (0.81–11.65), p = 0.09
Severe	0	2 (1.3%)	Not estimable

Quantitative variables are provided as mean and standard deviation in brackets. Qualitative variables are provided as absolute values and percentages. Figures in bold indicate significance. IAP: idiopathic acute pancreatitis; OR: odds ratio; CI: confidence interval; IBD: inflammatory bowel disease; AP: acute pancreatitis.

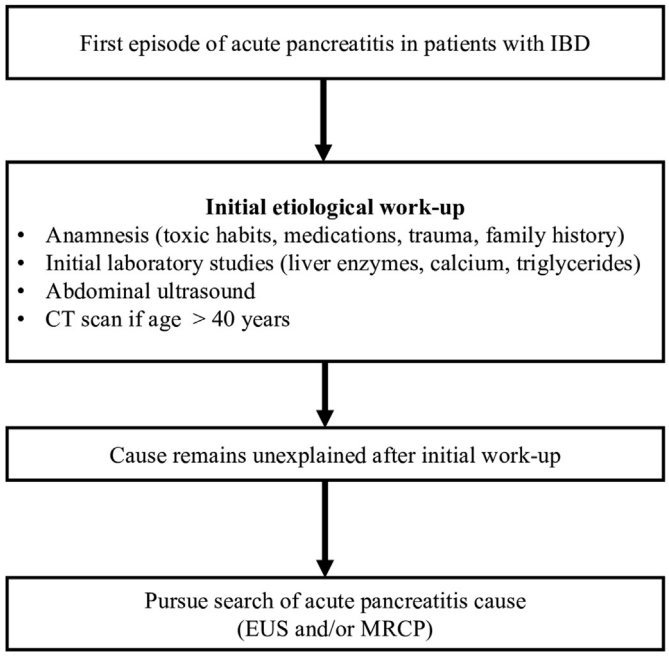

Fig. 2. Algorithm proposal for etiology investigation in patients with inflammatory bowel disease and a first episode of acute pancreatitis.
IBD: inflammatory bowel disease; CT: computerized tomography; EUS: endoscopic ultrasound; MRCP: magnetic resonance cholangiopancreatography.

associated with IBD, especially with UC. A recent study found that autoimmune pancreatitis in patients with IBD was associated with proctitis in patients with UC, and with fewer perianal lesions and an inflammatory behaviour in patients with CD [17]. Despite the low number of autoimmune pancreatitis in our cohort (six patients) we could not confirm those findings: 3/6 patients had UC, all left-sided, and the remaining three patients had CD of which 2/3 had inflammatory behavior and 1/3 had perianal disease. The same study found that patients with IBD and autoimmune pancreatitis have higher rates of colectomy than patients with just IBD, but none of the 6 patients in our cohort needed surgery. On the other hand, this study reported that in up to 80% of patients with autoimmune pancreatitis AP is the first manifestation of the disease. In our cohort, we observed that many patients with a first episode of AP labelled as idiopathic were eventually diagnosed of autoimmune pancreatitis during follow up (5/38, 13%), suggesting that some of these pancreatitis were not really idiopathic but the first manifestation of an underlying autoimmune pancreatitis. Therefore, in IBD patients with a first episode of IAP the possibility of underlying autoimmune pancreatitis as the cause of AP should be kept in mind, and additional imaging work-up in search of compatible pancreatic morphologic features should probably be carried out after the first episode without waiting for recurrences to occur, as it may lead to therapy adjustments that could prevent not only new episodes of pancreatitis but also the development of chronic irreversible changes.

Recurrence of AP was significantly more common in IAP patients. Furthermore, 54.5% of IAP patients in which AP reappeared presented more than one recurrence. The absence of an identifiable cause of AP has also been associated with a higher risk of AP recurrence in the general population [29]. Development of chronic pancreatitis was also significantly more frequent in IAP. Some reports have found pancreatic ductal changes in patients with IBD and PSC, suggesting that it may represent a 'pancreatic manifestation' of PSC. However, none of the patients diagnosed with chronic pancreatitis presented concomitant PSC in our cohort.

It is still controversial whether IAP can be considered as an extraintestinal manifestation of IBD, however most previous studies regarding this entity are case reports or series. The results of our study would go in a different direction since we found that both the absence of extraintestinal manifestations and IAP preceding IBD diagnosis were independently associated with IAP. Also, we found no differences regarding IBD activity and course in patients IAP compared to patients with other AP causes.

We believe that our results have relevant clinical implications for patients with IBD as they contribute with additional evidence regarding IAP in this specific group, and due to its multicenter and nationwide design our results may be extrapolated. However, we acknowledge that this study has limitations given its retrospective nature. We have not recorded in our data base the follow-up time of the 12,171 patients with IBD that are registered in the nine centers participating in the study, and therefore we could not calculate the cumulative incidence or the incidence rate. Also, due to the lack of consensus regarding additional work-up in IAP, further evaluation was not uniform and it was performed in a small percentage of patients. In addition, AP recurrence rate may be underrated, as we assumed that if there was no documented evidence of pancreatitis in medical records, then recurrence did not occur. Also, chronic pancreatitis may be underestimated as it was not systematically researched, and not all patients were screened.

In summary, IAP is significantly more frequent in patients with UC and it may appear before the diagnosis of IBD in up to 20%. Additional work-up, mainly with imaging studies, after a first episode of IAP in IBD patients identify a cause in more than one third. IBD course seems to be similar compared to non-IAP, but IAP patients present a higher risk of AP recurrence, chronic pancreatitis, and autoimmune pancreatitis.

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