

## Acute idiopathic pancreatitis in patients with inflammatory bowel disease: A retrospective case-series description

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### SUMMARY

**Background/aims:** To describe five patients who developed acute idiopathic pancreatitis either before (two patients) or after (three patients) the establishment of diagnosis of the underlying inflammatory bowel disease (IBD). **Results:** These patients represent an incidence for patient-years of 0.14% (3 cases with acute pancreatitis after the establishment of diagnosis of IBD per 2183 person-years, 95% CI 0.02-0.30%) and a frequency of 1.53 (5 patients with acute pancreatitis among 327 patients with IBD, 95% CI 0.20-2.86%). Extensive work-up aiming to identify an etiological factor, known to be involved in the pathogenesis of acute pancreatitis was negative. Four of these patients had Crohn's disease and one had ulcerative colitis. Three patients developed acute pancreatitis during a flare-up of the underlying IBD, while in two the appearance of acute pancreatitis preceded the clinical manifestations of IBD. The course of pancreatitis was favourable in the majority of cases. In one patient the administration of Infliximab resulted in prompt improvement of clinical and laboratory parameters. During the follow-up period, ranging from 14 months to 7 years, an exacerbation of pancreatitis was noted in one patient. **Conclusion:** This retrospective case-series suggests that acute idiopathic pancreatitis accompanies IBD, especially of Crohn's disease, either before or following the establishment of diagnosis of IBD. Large epidemiological studies are needed in order to further clarify the relationship between acute idiopathic pancreatitis and IBD.

**Key words:** Pancreatitis, idiopathic pancreatitis, inflammatory bowel disease, Crohn's disease, ulcerative colitis

### INTRODUCTION

During recent years, interest in the appearance of acute or chronic pancreatic during the course of inflammatory bowel disease (IBD), has increased considerably. A number of papers have been published relating to either case reports of acute pancreatitis in Crohn's disease,<sup>1-4</sup> or ulcerative colitis patients.<sup>5-9</sup>

The cases of acute pancreatitis complicating inflammatory bowel disease, described to date, are mainly related to drugs used in the treatment of IBD, namely sulfasalazine,<sup>10,11</sup> mesalazine,<sup>12-15</sup> azathioprine<sup>16,17</sup> 6-mercaptopurine,<sup>18,19</sup> and metronidazole.<sup>20</sup> Acute and chronic pancreatitis have also been linked with duodenal involvement from Crohn's disease,<sup>21-25</sup> and total parenteral nutrition.<sup>26,27</sup> Finally, acute pancreatitis has been described in children having either Crohn's disease,<sup>28-30</sup> or ulcerative colitis,<sup>31,32</sup> although there are patients with IBD who develop the so-called "idiopathic" pancreatitis, in which no responsible factor can be identified.<sup>33-36</sup>

The aim of this case-series is to describe 5 cases of acute idiopathic pancreatitis, appearing either before (two cases) or after (three cases) the establishment of diagnosis of IBD. The cases described here represent an incidence for patient-years of 0.14% (3 cases with acute pancreatitis after the establishment of diagnosis of IBD per 2183 person-years, 95% CI 0.02-0.30%) and a frequency of 1.53 (5 patients with acute pancreatitis among 327 patients with IBD, 95% CI 0.20-2.86%) diagnosed and followed-up in our department, a referral center for patients with IBD, during the last 15 years. An attempt to provide some information regarding the follow-up of these patients is also presented.

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## CASE REPORT

During the years 1990 to 2003, among 327 patients with newly diagnosed or already established inflammatory bowel disease, five developed acute pancreatitis, either before (two) or after (three patients) the establishment of diagnosis of IBD. Clinical details of these patients are as follows:

*Case 1:* A young male aged 20 was admitted to our department complaining of severe abdominal (mainly epigastric) pain. A tendency to vomiting and distress accompanied the clinical picture. Upper GI endoscopy performed immediately after admission revealed nothing important. Biopsy was not performed at that time as there were no significant findings. Abdominal ultrasound and CT disclosed an enlarged and edematous pancreas. Serum and urine amylase increased considerably (890 and 2800 IU respectively). Complete investigation aiming to identify a possible cause for acute pancreatitis including MRCP, serum triglycerides, serum calcium levels etc, was negative. The course of pancreatitis was uneventful and the patient was discharged after 7 days in good condition. Fifteen months later the patient started complaining of diarrhea (3-5 bowel movements per day), fatigue and loss of weight. Colonoscopy showed aphthous-like ulcers in the ileocecal area and a moderate degree of erythema and edema scattered throughout the large bowel. Histology revealed inflammatory infiltration of the lamina propria and granulomas in deep positions. Abdominal ultrasound and CT scan revealed a moderate degree of thickness of terminal ileum. With the diagnosis of Crohn's disease the patient started on metronidazole, mesalamine and prednisolone with favourable response. The patient's mother, aged 46, has also suffered from

extensive ulcerative colitis since the age of 34. After the establishment of diagnosis of Crohn's disease in her son, an abdominal ultrasound was performed in order to exclude possible cholelithiasis. The ultrasound was normal. During the 24 months of follow-up the patient has been in good condition, with no signs of recurrence of pancreatitis. Crohn's disease remains quiescent with only mesalamine (2g peros per day) (Table 1).

*Case 2.* A young girl, aged 17, developed an episode of acute pancreatitis at the age of 13. Diagnosis was based on the relevant clinical picture and the increased serum and urine amylase levels (Table 2). At that time, no drugs known to be involved in the causation of pancreatitis were taken by the patient. Diagnosis was also supported by the relevant abdominal ultrasound, MRI and CT scan. Small bowel follow-through was unremarkable. Upper and lower GI endoscopy were normal. Other causes of pancreatitis were excluded with appropriate investigation. The patient was discharged with no symptoms and normal serum and urine amylase. After more than one year, she started complaining of diarrhea, epigastric pain and vomiting. A diagnosis of small and large bowel Crohn's disease was made, based on the findings of upper and lower GI endoscopy. Histology of the large bowel showed inflammatory infiltration with granulomas. Since then, patient has managed with a combination of azathioprine and corticosteroids. A laparotomy was performed after two years because of several strictures in the small bowel. On operation a short resection with anastomosis and five stricturoplasties were performed. No laboratory or clinical signs of pancreatic inflammation were noticed. The patient, 6 years after the onset of pancreatitis and almost 5 years after the establishment of diagnosis of

**Table 1.** Clinicoepidemiological characteristics of patients with IBD, who developed acute pancreatitis.

Characteristic	Case				
	1	2	3	4	5
Age	20	17	36	53	42
Sex	Male	Female	Male	Male	Male
Crohn's disease	Yes	Yes	Yes	Yes	
Ulcerative colitis					Yes
Location of IBD					
<i>Small bowel</i>	Yes			Yes	
<i>Small &amp; large</i>		Yes	Yes		
<i>Extensive colitis</i>					Yes
Duration of IBD (years)	1	4	7	10	10
Family history of IBD	Positive (mother: ulcerative colitis)				

**Table 2.** Laboratory findings and course of acute pancreatitis

	Cases				
	1	2	3	4	5
Amylase: Serum (NV:<80IU)	890	680	2,200	1200	1150
Urine (NV: 200IU)	2,800	1,600	13,601	2300	2000
Complications (Pseudocyst)	-	-	-	Yes	-
Treatment of pancreatitis(Conservative)	Yes	Yes	Yes	Yes	Yes
Surgical intervention of IBD	No	Yes	No	Yes	No
Follow-up (Years after the onset of pancreatitis)	5	4	2	6	1
Outcome (Recurrence of pancreatitis)	No	No	Yes	No	No

Crohn's disease, does not show any clinical or laboratory signs of recurrence of acute pancreatitis. She is under maintenance treatment with azathioprine, while corticosteroids and antibiotics are used during flare-ups.

*Case 3.* This 36-yr-old male patient was diagnosed as having Crohn's disease at the age of 29. During this period he experienced four major flare-up of his disease. During the third severe recurrence of Crohn's disease, and while he was not receiving any kind of treatment, he developed severe epigastric pain and vomiting, accompanied with bloody diarrhea, fever and loss of weight. Physical examination revealed a thin man with tachycardia and abdominal tenderness. Colonoscopy revealed severe segmental Crohn's disease involving the left, transverse and ascending colon. Serum and urine amylase were 2,200 and 13,601 IU respectively. Abdominal US and CT scan revealed an enlarged edematous pancreas without peripancreatic collections. Upper GI endoscopy was negative. With the profound diagnoses of severe acute pancreatitis and severe relapse of Crohn's disease of the small and large bowel, the patient was started with parenteral fluids and electrolytes. Infliximab was administered in order to confront both the underlying Crohn's disease and the acute pancreatitis as well. The infusion (5 mg/Kg BW at 0, 2 and 6 week) was uneventful. Pancreatitis and Crohn's disease improved considerably over the next ten days. His general situation also improved markedly over the next weeks, although abnormal serum and urine amylase levels persisted for more than two months. The intermittent administration of Infliximab was continued over the next three years. An episode of acute pancreatitis, mild to moderate severity occurred 18 months after the first attack, which was settled promptly with conservative treatment. No other cause for the pancreatitis could be identified, including MRCP. During the follow-up period the patient received infliximab every two months (5 mg/Kg) and corticosteroids during flare-ups.

*Case 4.* A 53 yr-old man was diagnosed as suffering from Crohn's disease of the small bowel, at the age of 34. Since then, Crohn's disease has run with exacerbations and recurrences. At the age of 46, during a severe flare-up of the underlying Crohn's disease, the patient developed epigastric pain and vomiting. Upper GI endoscopy revealed only a mild degree of gastritis. Serum and urine amylase levels were indicative of acute pancreatitis (1200 and 2300 IU, respectively). The diagnosis of pancreatitis was also confirmed on the basis of the findings of CT scan and ultrasound of the abdomen, which showed an enlarged and edematous pancreas. No etiological factor responsible for the acute pancreatitis could be identified, including pharmaceutical agents. Two weeks later repeated abdominal ultrasound showed a pancreatic 6cm pseudocyst. Because of the development of clinical signs of incomplete bowel obstruction, the patient was operated-on. An enterectomy plus end-to-end anastomosis was performed. The recovery was uneventful. However, pseudocyst remained *in situ* over the next 3 months and gradually resolved. During the subsequent 5 years of follow-up, no signs of recurrence of pancreatitis were noted. Mesalamine, corticosteroids and antibiotics were administered during the follow-up period, according to the activity of the disease. Treatment with oral pancreatic enzymes was continued for more than one year.

*Case 5.* A 42 yr-old man was diagnosed as suffering from left-sided ulcerative colitis at the age of 32. Since then the disease has run with exacerbations of mild to moderate severity once every two or three years. In 2002, while he was not receiving maintenance treatment, he started having bloody diarrhea, accompanied by some degree of fatigue and loss of weight. Almost concurrently he started complaining of a moderate degree of epigastric pain and tendency to vomit. An upper GI endoscopy revealed a mild degree of antral gastritis. Colonoscopy showed a moderate to severe extensive colitis, involving

the ascending and transverse colon. An abdominal ultrasound showed enlargement of the pancreas, which appeared to be also quite edematous. Serum and urine amylase levels increased significantly (1150 and 2000 IU respectively). With the profound diagnoses of moderate flare-up of ulcerative colitis and acute pancreatitis, the patient was treated with systemic corticosteroids, and parenteral fluid and electrolytes. The recovery was prompt and he was discharged from hospital in a good condition. During the follow-up of 18 months after acute pancreatitis, no signs of recurrence of pancreatitis was observed. No maintenance treatment was applied.

Tables 1 and 2 summarize the clinicoepidemiological characteristics and outcome of these patients. No alcohol intake was described by any of the patients.

## DISCUSSION

Acute pancreatitis is a relatively common disease in the western world. Its incidence has been estimated in various studies to fluctuate between 35 and 45 new cases per 100,000 inhabitants per year.<sup>37-41</sup> The proportion of men to women is 2 to 1 and the mean age of first appearance is 59 years.

Patients with IBD are prone to develop acute pancreatitis. To date, many case reports referring to the development of acute pancreatitis in IBD patients have been published. In most cases acute pancreatitis is a consequence of drugs used in the treatment of IBD patients, while in others no association with known cause of pancreatitis can be identified. In the absence of drug use or duodenal involvement, pancreatitis appeared in approximately 1.2% of French IBD patients.<sup>42</sup> This frequency, as well as the frequency found in our study (1.53%), is more than 250 times higher than in a normal population sample. Unfortunately, there are no incidence rates of acute pancreatitis available in Greece and thus no more valid comparisons can be made. In a study of 852 patients with Crohn's disease, Weber et al<sup>1</sup> described 12 patients who developed clinically overt pancreatitis, (1.4%), in a follow-up period of 10 years. Only in two of them acute pancreatitis was probably a consequence of drugs. In the above-mentioned study, younger patients and those with active Crohn's disease seemed more at risk for developing acute pancreatitis. Niemela et al<sup>3</sup> described six patients among 513 patients with IBD, who developed acute pancreatitis during the course of the bowel disease, a frequency of 0.85%. Autopsy studies have shown macroscopic and histological lesions in 38% of Crohn's disease patients, who had no clinical history

compatible with pancreatic involvement.<sup>43</sup> In all these studies, acute pancreatitis was associated more often with Crohn's disease than ulcerative colitis. This is in agreement with what was found in our study.

Patients with IBD also have an elevated risk for developing chronic pancreatitis as well as pancreatic insufficiency. Prevalence of chronic pancreatitis in IBD patients also seems to be high, although the etiology of pancreatic duct changes or exocrine insufficiency, remain unclear. Most of cases of chronic pancreatitis remain clinically unapparent, although in some cases it may be accompanied by clinically relevant exocrine insufficiency.<sup>44</sup>

As far as the pathogenesis of pancreatitis is concerned in, most cases it is due to either side effects of drugs used for the treatment of these patients or local structural complications of IBD. The presence of duodenal-pancreatic duct fistulas or flow obstruction as well as reflux of duodenal content into the pancreatic duct have been implicated in the pathogenesis of acute pancreatitis developing in patients with duodenal involvement from Crohn's disease. In cases without duodenal involvement, and especially in cases with chronic pancreatitis complicating IBD, serum autoantibodies to acinar cells seem to play some role in the development of pancreatitis.<sup>45</sup> However, in a significant proportion of IBD patients, the cause of pancreatitis remains unexplained. It is possible that immunological mechanisms and production of various cytokines, including Tumour Necrosis Factor alpha, could be implicated.<sup>46</sup>

The clinical picture in most of the reported cases with idiopathic pancreatitis appearing in patients with IBD seems to be quite benign. No complications requiring surgical treatment has been described to date. However, in one of our cases the course of pancreatitis was quite severe. The symptoms persisted over a long period of time while the serum pancreatic enzymes persisted for more than eight weeks. Interestingly enough, the pancreatitis of this patient relapsed after 18 months. In another patient, a pseudocyst developed as a result of acute pancreatitis, which responded well to conservative treatment.

The estimation of serum and urine amylase and serum lipase, and the findings of the classical imaging techniques (abdominal ultrasound and CT scan) represent the most useful tests for the establishment of diagnosis in patients with suspected acute pancreatitis. However, mild increase of pancreatic enzymes can be found in up to 30% patients with quiescent IBD, probably related to

the extent of the disease.<sup>47,48</sup>

The exclusion of other factors predisposing to the development of pancreatitis must be done carefully in all patients. In our cases, an extensive work-up including Magnetic Resonance Cholangiopancreatography was done, in order to exclude other causes, including microlithiasis and pancreatic abnormalities, especially in the view of other extraintestinal manifestations of IBD (including primary sclerosing cholangitis).

The relation of extent and duration in pancreatitis is not well established. In our series of patients no clear relationship with these two parameters could be identified, as no specific site of involvement was found. On the other hand, duration of the disease seems not to play an important role as both short- and long-duration was deserved.

The management of a patient with IBD and acute idiopathic pancreatitis does not differ from the ordinary patients with acute pancreatitis. However, drugs with known harmful influence on the pancreas, such as mesalazine, azathioprine, may well have to be excluded - at least temporarily - from treatment, as relapses of pancreatitis after reintroduction of such drugs have been described. In our patients, we followed the classical treatment strategies including food restriction, liquid and electrolyte restoration, and close surveillance. It was necessary to administer analgesics to two patients. A nasogastric tube was placed in two patients. Infliximab was administered to one patient with a severe recurrence of Crohn's disease and severe acute pancreatitis as well. Relapse of acute pancreatitis in this patient 18 months after the first attack of pancreatitis, was settled with the same general measures, including administration of Infliximab. It must be stressed that idiopathic or overt hyperamylasemia must be distinguished and managed differently from symptomatic hyperamylasemia appearing during the course of acute or chronic pancreatitis in IBD. As was mentioned earlier, asymptomatic hyperamylasemia can be found in a significant proportion of patients with IBD, due or not to drugs used in the treatment of the underlying IBD. This asymptomatic amylase increase requires no treatment. It cannot be characterized as pancreatic inflammation.

As far as the follow-up of these patients is concerned, the available data are too few to draw firm conclusion. In a series of patients described by Weber et al, only two had a recurrence of pancreatitis.<sup>1</sup> Although the follow-up of our patients is relatively short, only one patient developed recurrence of pancreatitis, 18 months after the

first episode of acute pancreatitis. However, cases of evolution of pancreatic cystadenocarcinoma in patients with Crohn's disease and pancreatitis have been described.<sup>49</sup>

In conclusion, acute idiopathic pancreatitis accompanies IBD, especially Crohn's disease. Some cases of acute idiopathic pancreatitis in young patients might be considered as an early manifestation of an as-yet undiagnosed IBD. However large epidemiological studies are needed in order to answer the question about the true relationship between acute idiopathic pancreatitis and IBD.

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