MINIREVIEWS

Pancreatic disorders in inflammatory bowel disease

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Abstract

An increased incidence of pancreatic disorders either acute pancreatitis or chronic pancreatitis has been recorded in patients with inflammatory bowel disease (IBD) compared to the general population. Although most of the pancreatitis in patients with IBD seem to be related to biliary lithiasis or drug induced, in some cases pancreatitis were defined as idiopathic, suggesting a direct pancreatic damage in IBD. Pancreatitis and IBD may have similar presentation therefore a pancreatic disease could not be recognized in patients with Crohn's disease and ulcerative colitis. This review will discuss the most common pancreatic diseases seen in patients with IBD.

Key words: Pancreas; Pancreatitis; Extraintestinal manifestations; Exocrine pancreatic insufficiency; Ulcerative colitis; Crohn's disease; Inflammatory bowel disease

Core tip: Pancreatic disorders are not uncommon in patients with inflammatory bowel disease (IBD). The most frequent manifestation is acute pancreatitis (AP). Causes of AP are mainly a concomitant biliary lithiasis or drugs used in the treatment of IBD. However for some IBD-related pancreatitis, idiopathic by definition, where no relationship with lithiasis or drugs can be recognized, a direct pancreatic damage would be hypothesized.

INTRODUCTION

Crohn's disease and ulcerative colitis are the two major clinically defined forms of inflammatory bowel disease (IBD). Although they affect mainly the bowel, often present with systemic manifestations and involvement of organs other than the gastrointestinal tract. However distinguishing between proper extra-intestinal manifestations (EIMs), *i.e.*, systemic alterations directly

related to the disease, and extra-intestinal complications, *i.e.*, conditions secondary to metabolic disturbance, anatomic alterations or side effects of treatment, is not always straightforward. Although the most common EIMs are mucocutaneous, ophtalmologic, arthritic, hepato-biliary, pulmonary, an increased incidence of pancreatic disorders either acute pancreatitis (AP) or chronic pancreatitis (CP) has been recorded in patients with IBD compared to the general population[1]. The first report of association between IBD and pancreatitis dates back to 1950, when Ball *et al*[2] published a post-mortem study of 86 patients with ulcerative colitis where pancreatic lesions either macroscopic or microscopic were detected in 14% and 53% respectively. A similar autopsy study of 39 patients with Crohn's disease revealed pancreatic fibrosis in 38% of them[3]. No one of the cases in both studies had presented with symptoms or signs of pancreatitis, what suggests pancreatic disease had been subclinical or silent. Increasing number of cases of either acute or CP have been reported since[4-7].

In the pediatric population pancreatic disease is rare (0.7%-1.6%) but higher than in the general population. Incidence of AP is higher in females than in males with a greater occurrence in those with active and severe IBD. Children with IBD also have an increased risk of developing CP and asymptomatic hyperamylasemia[8].

However most of the pancreatitis in patients with IBD, both adults and children, seem to be related to biliary lithiasis or drug induced[9].

AP

Epidemiology
AP is the most common pancreatic disease associated with IBD; it is also the one associated with the highest morbidity. No definitive data are available regarding incidence of idiopathic AP in IBD. Figures obtained from small series estimate an incidence between 1.2% and 3.1%, higher in Crohn's disease than in ulcerative colitis[10,11]. The odd for AP seems to be as high as 4.3 and 2.1 times in Crohn's disease and in ulcerative respectively compared to the general population[12]. One study including patients with Crohn's disease after a 10 years follow up showed a significantly higher incidence of AP than in the general population (1.4% *vs* 0.007%)[13]. A large series of patients with Crohn's disease looked at etiology of AP: 21% and 15% of cases were due to biliary lithiasis and alcohol respectively; 12% and 13% of cases were associated with drugs or Crohn's disease to the duodenum; 8% of AP were defined as "idiopathic"[7]. In Seyrig's study idiopathic AP was only 1.5% (5 in 331 patients with IBD), but not all patients were investigated with ERCP[10]. In Heikius's study incidence of idiopathic AP was 3% in patients with IBD but 4% in the subgroup with Crohn's disease[13].

Diagnosis
The main issue in analyzing association between AP and IBD is the number of communal either clinical features either laboratory abnormalities. Two of following three criteria are required to make a diagnosis of AP: (1) typical abdominal pain; (2) threefold or more elevation of serum pancreatic enzymes; and (3) imaging confirming inflammation of the pancreatic gland[14]. However abdominal pain is also one of the cornerstone in the diagnosis of IBD and also typical symptoms of pancreatitis, like nausea, vomiting and diarrhea, may be present in Crohn's disease and ulcerative colitis. Moreover elevation of pancreatic enzymes may be found in patients with IBD with no clinical evidence of pancreatic disease[15]. Therefore an exacerbation of IBD might be mistaken for AP and *vice versa*.

Etiology
Biliary lithiasis: Incidence of biliary lithiasis increases in IBD compared to the general population, in particular in Crohn's disease with figures between 13% and 34%, where this variability depends either on study design either on selection criteria[16-19]. Nonetheless it seems also related to site and extension of intestinal disease (distal *vs* proximal ileum). Risk of biliary lithiasis is as high as three times in patients with extensive ilieal involvement, and this may be explained by a reduced enterohepatic circulation as a result of inflammation[18]. In fact, after surgery involving small bowel where the absorbing surface for biliary acids results reduced, incidence of biliary lithiasis is about 24%[20].

Drugs: Most of the drugs used to treat IBD may be associated with an increased risk of pancreatitis[21-23]. Azathioprine (AZA) and its active metabolite 6-mer-captopurine have AP as well-known side effect[24-27]. However other drugs as mesalamine, salazopyrin, metronidazole and steroids are reported to induce pancreatitis[28-35]. Toxic pancreatitis typically arises within the first weeks of treatment, presents with a mild clinical course and resolves quickly as soon as the drug is discontinued[21-23]. A prospective multicentric registration study has been recently carried out in 510 patients with IBD of which 338 with Crohn's disease, 117 with ulcerative colitis and 15 with unspecified colitis[36]. All patients were enrolled as soon as they started AZA; AP were diagnosed in accordance with international guidelines. AZA was stopped by 186 patients (36.5%). The most common cause of discontinuation was nausea (12.2%). Pancreatitis occurred in 37 patients (7.3%): 43% were admitted with a median inpatient length of stay of 5 d (10% had peripancreatic fluid collection, 24% had vomiting and 14% had fever). No patient underwent non-surgical or surgical interventions. At univariate and multivariate analysis smoking was found to be the strongest risk factor for AZA-induced AP[36]. However a meta-analysis showed that the risk of AZA-induced AP is very low[37].

However drug-induced pancreatitis could develop any time during the course of the treatment and it is not

always easy to establish a direct correlation between resolution of symptoms and drug withdrawal. Rechallenge test may be attempted in some cases of mild pancreatitis, as defined according to the CT severity index[38].

Duodenal obstruction: Finally, a cause of AP may be recognized in the duodenal involvement, found in 0.5%-4% of patients with Crohn's disease, often presenting with duodenal stenosis[39,40]. How a pancreatic obstruction can cause pancreatitis, it is not clear, but other conditions associated with similar anatomic alteration like stenosing cancer or annular pancreas can cause pancreatitis[41]. Overall, cases of pancreatitis associated with duodenal Crohn's disease are a small number in literature.

Natural history and management
No data are available regarding natural history of idiopathic AP in IBD but it has generally a benign course[9]. The youngest patient recorded is a 6 years old girl with underlying ulcerative colitis[42]. Whereas AP occurs in patients with Crohn's disease when they have an established diagnosis, in patients with ulcerative colitis it may either anticipate the diagnosis of colitis or arise later during the course of disease, or appear at the onset of the intestinal disease itself[43,44]. The record of a number of cases where an effective treatment of the underlying IBD produced improvement in the concomitant AP would support the theory of a direct pancreatic involvement in IBD, although it needs to be confirmed by longitudinal studies[45].

In most cases, AP in IBD patients are mild. The management should be the same of that in the general population, and involves supportive care with fluid therapy, electrolyte replacement, pain control, and nutritional support[46]. Treatment of active IBD in a patient with AP could be challenging because most of the drugs used for IBD (including total parenteral nutrition) can result in exacerbation of pancreatitis. A case of successful use of Infliximab for the treatment of idiopathic AP in a young male patient with a severe active Crohn's disease has been reported[47].

CP
IBD-related CP seems to be a different disease from calcific chronic pancreatitis (CCP) associated with alcohol abuse. First of all clinical presentation is different. In fact abdominal pain, the earliest and most common symptom in CCP (> 80%), is rarely present in IBD-related CP (16% in ulcerative colitis and 48% in Crohn's disease)[48]. Moreover CCP is more frequent in males whereas in IBD-CP ratio male/female is 3/10 in ulcerative colitis and 6/10 in Crohn's disease[48]. In addition, pseudocysts and pancreatic calcifications are typical in CCP but are almost absent in IBD-related CP[43]. Idiopathic CP in IBD is reported in 1.2%-1.5% of the cases, varying according

with the diagnostic technique[43].

Exocrine pancreatic insufficiency
Pancreatic insufficiency is reported in patients with IBD between 18 and 80% of the cases[15,43,44]. Maconi *et al*[49] showed reduced fecal elastase level in 18% of patients with IBD. Heikius *et al*[50] found that 19% of not selected patients with IBD had signs of pancreatic insufficiency either by paraminobenzoic acid (PABA) test either by secretin-cerulein test. During a secretin-cerulein test Angelini *et al*[51] observed a decrease in plasma bicarbonate and serum enzymes in 35% of patients with Crohn's disease and 50% of patients with ulcerative colitis whereas isolated decrease in lipase was noted in 58% of patients with Crohn's disease and in 80% with ulcerative colitis. In a larger series Hegnohj *et al*[52] confirmed that output of amylase and lipase can be proved significantly reduced by Lundh meal test. Pancreatic insufficiency seemed to be related to extension of Crohn's disease, mainly if with ileal location and in active phase.

Asymptomatic pancreatic hyperenzymemia
Serum pancreatic enzymes may be elevated, normal or reduced in CP. In patients with IBD, elevation in amylase and lipase has been noticed along with alterations in the pancreatic duct system, mainly in patients with concomitant primary sclerosing cholangitis (PSC)[50-52]. Katz *et al*[53] described hyperamylasemia with no pancreatitis in 8% of patients affected by Crohn's disease. Tromm *et al*[54] found asymptomatic hyperamylasemia and hyperlipasemia in 16% of patients with Crohn's disease and 21% of patients with ulcerative colitis, in absence of pancreatic morphological abnormalities on ultrasound and with no association with disease activity, duration or medication. On the other hand, in Heikius's study elevation in serum amylase and lipase (in 11% and 7% for Crohn's disease and ulcerative colitis respectively) linked to a more extensive and active disease as well as a concomitant PSC[13]. Whether slightly elevated serum pancreatic enzymes may be an early indicator of significant pancreatic damage, it should be evaluated by longitudinal studies and extended follow.

Moreover, it must be considered that in case of absent urinary amylase the source of elevated amylase could be the salivary glands. Even lipase, that is known to be pancreatitis-specific, sometimes can be found elevated without any symptoms.

Duct system abnormality in IBD
What the prevalence is of alterations within the duct system in IBD, it is controversial, however there does not always seem to be correlation with pancreatic insufficiency. Abnormalities may be like wall irregularity, short stenosis or dilation of the main pancreatic duct. Heikius *et al*[50] found duct abnormalities in 8.4% (20 in 237) of patients with IBD, investigated with ERCP (gold standard imaging). However ERCP has limitations, being an invasive study and causing pancreatitis itself: As a

Table 1 Cardinal features for differential diagnosis

Characteristics	Drug-induced pancreatitis	Idiopatic IBD-associated pancreatitis	Autoimmune pancreatitis
Epidemiology	Pediatric patients Elderly patients Females > males	Males >> females	Male-female 2:1 (type 1) Male-female: 1:1 (type 2)
Age at presentation of pancreatitis	Any ages	20-40 yr	60-65 yr (type 1) 45-50 yr (type 2)
Clinical presentation	Abdominal pain	Abdominal pain Exocrine pancreatic insufficiency	Jaundice Mild abdominal pain Diabetes
Sierology	Elevated pancreatic enzymes Normal IgG4	Elevated pancreatic enzymes Normal IgG4	Normal or slightly elevated pancreatic enzymes Elevated IgG4 (in type 1)
Imaging	Normal pancreas or oedematous pancreatitis	Normal pancreas or oedematous pancreatitis Diffuse pancreatic enlargement or long/multiple MPD narrowing No calcifications or pseudocysts	Diffuse pancreatic enlargement or long/multiple MPD narrowing No calcifications or pseudocysts
Key point	Direct correlation between resolution of symptoms and drug withdrawal Symptoms recurrence with re-challenge test	Exclusion of other causes of pancreatitis (drug, lithiasis, alcohol...)	Rapid response to steroid with radiologically demonstrable resolution or marked clinical improvement

MPD: Main pancreatic duct; IBD: Inflammatory bowel disease.

result it would be offered to a selected population, what may underestimate results. In two studies secretine-enhanced MR Cholangiopancreatography has been used: Toda *et al*[55] assessed 79 patients with ulcerative colitis, with no pancreatic symptoms and with or without alteration in pancreatic function tests: 16.4% had lesions suggestive of CP, half of them with normal amylase. On the other hand Barthet *et al*[44] found duct abnormality in 11% of 79 patients with IBD, but did recognize neither a link with history of pancreatitis nor pancreatic insufficiency.

PATHOPHYSIOLOGY

Pathogenesis of IBD-related pancreatitis is unknown. An immune pathogenesis has been proposed, but whether idiopathic pancreatitis in IBD is a type of autoimmune pancreatitis (AIP), this is still debatable[56] (Table 1).

AIP is a rare, distinct and increasingly recognized disorder of presumed autoimmune etiology and is classified into two types, which are mainly differentiated by clinical and histological features[57]. Type 1 AIP is the most common type worldwide, affects predominantly males in the sixth decade and pancreas is involved as part of a systemic IgG4-positive disease, often associated with involvement of other organs, accompanying conditions such as sclerosing cholangitis, sclerosing sialadenitis and retroperitoneal fibrosis. Treatment with steroids is usually effective and when a rapid clinico-radiological response occurs, this could be considered as a diagnostic criterion[58]. Type 2 AIP, on the contrary, is not characterized by elevated IgG4 levels, affects younger patients equally distributed between genders and is frequently associated with IBD. Both types of AIP may present with painless jaundice, weight loss, diabetes and mild abdominal pain[57]. Clinical presentation of AP

with high serum amylase is rare. Prevalence of IBD in patients with AIP seems to be higher than in the general population[59]. The relationship between IBD and AIP mainly involves ulcerative colitis and type 2 AIP. Specifically, the rate of ulcerative colitis in patients with AIP is up to 35%[60,61]. On the other hand, incidence of AIP in patients with IBD is low. A Japanese study conducted on 1751 patients with IBD found a 0.4% prevalence of AIP type 2 (n = 7)[62].

There is similarity between idiopathic pancreatitis in IBD (IBD-related pancreatitis) and AIP, either in imaging (alteration of duct system) either in pathology (when available). Duct system alteration with narrowing (segmental or diffuse) of the main pancreatic duct is a distinctive feature of AIP, nevertheless this is also a frequent finding in IBD-related pancreatitis[63,64]. Moreover in AIP as in IBD-related pancreatitis, calcifications and pseudocysts are absent. In a recent retrospective study of 71 patients with AIP, 4 (5.6%) had IBD (3 ulcerative colitis and 1 Crohn's disease) and IBD was diagnosed before or concomitantly to AIP[59]. In the intestinal specimen of one patient with ulcerative colitis IgG4 tissue infiltration was found, but was absent in the specimen of the only patient with Crohn's disease. In a French multicentric study as many as 38% of patients with AIP had a diagnosis of IBD[65]. These data suggest that AIP may be considered an EIM when found along with IBD. IgG4 elevation is considered typical of AIP: In 71%-92% of patients this tend to drop on steroids[63,64]. On the contrary in IBD-related pancreatitis IgG4 are almost always into the normal range. In the previously mentioned study of Barthet *et al*[44], 5 patients presented with diffuse narrowing of the duct system and 1 patient had pathology suggestive of AIP. Nevertheless all these patients had low level of IgG4, what may suggest that idiopathic pancreatitis found alongside IBD could be

considered a distinct but possibly closely related type of AIP. Moreover, in a recent retrospective study of 104 patients with AIP, 6 were founds to have ulcerative colitis, of which 2 showed colonic tissue with increased infiltration of IgG4-positive plasma cells whereas no infiltration was found in 24 patients with ulcerative colitis without AIP ($P = 0.006$): This suggests that ulcerative colitis may be an extra-pancreatic manifestation of AIP[66].

What also supports immune pathogenesis is the finding of antibodies anti-pancreas (PABs), mainly in Crohn's disease, where they are present in as many as 27%-39% of cases, whereas in ulcerative colitis they are rarely found (0%-5%)[9]. In IBD, PABS are usually found in about 20% of cases, but without association with pancreatic insufficiency or alteration of duct system[43,44]. Stöcker *et al*[67] described presence of PABs in 39% of patients with Crohn's disease and 4% with ulcerative colitis, whereas Seibold *et al*[68] found PABs in 27% of 212 patients with Crohn's disease. These antibodies are directed against exocrine pancreas and are located in the acinar lumen or in the acinar cells. However a clear pathogenetic role for PAB in IBD-related pancreatitis has not been proved yet and they don't seem to be connected with activity of disease neither with the onset of pancreatitis. Their presence may reflect immune deregulation caused by intestinal inflammation or cross reactivity, as well as for other auto-antibodies[69]. Another evidence supporting a direct association between IBD and pancreatic inflammation comes from a study conducted on animals, looking at MUC1, a transmembrane glyco-protein expressed on the apical surface of ductal epithelial cells in many organs and also present on colonic epithelium of humans with IBD[70]. MUC1 was abnormally expressed and hypoglycosylated and showed chemotactic properties for cells of the innate immune system thus promoting acute and chronic inflammation. In this paper, MUC1-specific T cells migrated not only to the colon, but also to the pancreas of mice with IBD, suggesting that pancreatic inflammation could be an EIM of IBD, characterized by pro-inflammatory, abnormal MUC1 expression[70].

Why pancreatic secretion is reduced in IBD, it is not clear. In Crohn's disease, one reason may be malnutrition, common in many patients, or a reduced hormone secretion by the intestinal wall, because of inflammation or consequences of scarring[13]. An important issue is whether increase of serum pancreatic enzymes is due to direct pancreatic damage or other causes as, for example, increased intestinal passage of intraluminal enzymes. Hyperenzymemia during more extensive and more severe intestinal disease supports the latter, as for analogy with hyperamylasemia found during other intestinal inflammatory conditions like ischemic colitis[13].

Other mechanisms have been speculated to explain a direct pancreatic damage in IBD. A single case was reported of a patient with Crohn's disease, found with a pancreatic granuloma on pathology: This may be the first case of histologically proved extra-intestinal localization

of disease[71].

Finally, a possible coexistence of IBD with other autoimmune condition, like lupus mesenteric vasculitis, should be considered in case of pancreatitis, since IBD predominantly affects gastrointestinal tract, while lupus mesenteric vasculitis may also present extraintestinal involvement such as pancreatitis[72].

CONCLUSION

Patients with diagnosis of IBD have increased risk of either acute or CP. Causes are mainly a concomitant biliary lithiasis or drugs used in the treatment of IBD. However a number of pancreatitis, "idiopathic" by definition, should be considered EIM. Pancreatitis and IBD may have similar presentation therefore a pancreatic disease could not be recognized in patients with Crohn's disease and ulcerative colitis. However elevation of pancreatic enzymes only, without symptoms nor imaging suggestive of pancr-eatitis, is not an indication to start a treatment but should recommend follow up in first instance. On the other hand patients with IBD presenting with pancreatitis-like abdominal pain should be investigated to rule out a concomitant pancreatic disease.

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