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Current View

Pancreatic Involvement in Patients with Inflammatory Bowel Disease

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SUMMARY

In this paper we review the existing data concerning the incidence, pathogenesis, clinical picture, management and long-term outcome of patients with IBD who developed acute or chronic pancreatitis before or during the course of their underlying bowel disease. It seems certain that patients with IBD are considered to be at increased risk for developing acute pancreatitis, although large epidemiological studies are scattered. They have also an elevated risk for developing chronic pancreatitis and/or pancreatic insufficiency. Increased levels of amylase and lipase can occur in up to 11% of asymptomatic IBD patients. Drugs could be a definite cause of acute pancreatitis in patients with IBD, immunosuppressives and mesalamine being the most frequently encountered. Some of the factors possibly involved are related to the secretory acinar cells, the protease-activated receptor-2, the pro-inflammatory cytokines IL-1 and TNF-α, the pancreatitis-associated protein, the pancreatic autoantibodies and prolonged stress. In most cases chronic pancreatitis is clinically unapparent, although it may be accompanied by clinically relevant exocrine insufficiency. The course of pancreatitis after cessation of the acute flare is quite benign. The management does not differ from ordinary patients with acute pancreatitis.

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1. INTRODUCTION

During the last years, a considerable increase in interest concerning the relationship between IBD and pancreatic involvement has been noticed. A number of papers have been published referring to either concurrent appearance of acute pancreatitis and CD or UC patients, and/or to case series description. Although most of the cases were the consequence of the drugs used in the treatment of IBD in others no association with known cause of pancreatitis could be identified.

The aim of this review is to describe the existing data concerning the incidence, pathogenesis, clinical picture, management and long-term outcome of patients with either CD or UC, who developed acute or chronic pancreatitis the later accompanied or not by pancreatic insufficiency, before or during the course of their disease.

2. INCIDENCE OF PANCREATITIS IN IBD

2.1 Acute pancreatitis

Patients with IBD are considered to be at increased risk for developing of acute pancreatitis,[1] although large epidemiological studies are scattered. In Denmark, the SIR for acute pancreatitis was found to be increased both in patients with CD (SIR = 4.3) and in those with UC (SIR= 2.1).[2] Weber et al described an incidence of 1.4% among 852 patients with CD in a follow-up period of 10 years.[3]

Abbreviations:

IBD=Inflammatory Bowel Disease
CD=Crohn's Disease
UC=Ulcerative Colitis
SIR=Standardised Incidence Rate

Bermejo et al[4] described an incidence of acute pancreatitis of 1.5% an incidence similar to that described by Triantafillidis et al who reported an incidence of 1.53% among all patients with IBD seen and followed up for 15 years in their institution.[5] This incidence is more than 250 times higher compared to that expected in the normal population. Niemela et al described 6 patients among 513 patients with IBD who developed acute pancreatitis during the course of IBD, a frequency of 0.85%.[6] Finally, a nearly four-fold increased risk of acute pancreatitis in patients with CD and a 1.5-fold increased risk for UC were noticed in Denmark.[7]

It is of interest that autopsy studies have shown macroscopic and histological lesions in the pancreas of 38% of CD patients, who had no clinical history compatible with pancreatic involvement.[8]

2.2 Chronic pancreatitis

Patients with IBD also have an elevated risk for developing chronic pancreatitis and/or pancreatic insufficiency. Prevalence of chronic pancreatitis in IBD patients seems to be high, although the exact etiology of pancreatic duct changes and/or exocrine insufficiency remains unclear.[9]

2.3 Autoimmune pancreatitis

Almost 6% of patients with proven autoimmune pancreatitis have a diagnosis of IBD compared to a prevalence of approximately 0.4%-0.5% in the general population, potentially implying a 12-15-fold increase in risk.[10]

2.4 Coexistence with other situations

Idiopathic fibrosing pancreatitis is an uncommon condition in children and adolescents of unknown aetiology. However coexistence of this situation with CD of the large bowel appearing 5 years after the establishment of diagnosis of pancreatic disease has been described.[11]

Finally, concurrent development of parotitis and acute pancreatitis in a child with UC has also recently been described.[12]

3. INCIDENCE OF ABDORMAL BIOCHEMICAL FINDINGS

Increased levels of amylase and lipase can occur in up to 11% of asymptomatic IBD patients, being significantly higher in patients with a positive previous history for acute pancreatitis.[13] On the other hand, low fecal elastase (reflecting impaired exocrine function) could be identified in up to 30% of patients and again in a significantly greater proportion in patients with a positive history for acute pancreatitis compared with patients with not such a history (50% vs 17%).[13] In the same study the frequency of elevated enzyme values varied from 12% for amylase and lipase to 18% for pancreatic associated protein, 20% for pancreatic autoantibodies and 45% for CRP.[13]

Bokemeyer et al found an elevation of serum lipase and amylase without symptoms of pancreatitis in 14% of IBD patients.[14] Heikius et al[15] described the presence of hyperamylasemia in 11% and hyperlipasemia in 7% of the total number of 237 patients with IBD. The corresponding prevalence was 17% and 9% in patients with CD, 9% and 7% in patients with UC and 10% and 5% in patients with indeterminate colitis, respectively. [15]

The finding that high levels of serum amylase and pancreatic isoamylase are associated with extensive involvement of the colon accompanied by high histological activity is of clinical significance.[15] Amylase, but not lipase, was significantly elevated in patients with primary sclerosing cholangitis. Smokers showed higher urinary amylase levels than non- and ex-smokers.[15]

Patients with both autoimmune pancreatitis and IBD may have increased extent and severity of IBD.[10]

In all these studies, acute pancreatitis was associated more often with CD, than UC.

4. INCIDENCE OF DRUG-INDUCED PANCREATITIS IN IBD

Generally, drugs could be a definite cause of acute pancreatitis, in an incidence of 0.1-2%.[16] In patients with IBD, responsible drugs include mainly immunosuppressives (azathioprine/merkaptopurine) and mesalamine,[4] although cases due to corticosteroids[17,18] and metronidazole[19] have also been described.

In a recent study it was found that most of cases with acute pancreatitis were a consequence of drug exposure namely azathioprine/ mercaptopurine and mesalazine.[4] Of the remaining, 20.7% were idiopathic, and 12.2% were biliary. The incidence of acute pancreatitis in patients treated with AZA/MP was 3.1%. Female gender and the existence of CD were risk factors for AZA/MP-associated acute pancreatitis.[4]

In a series of patients with CD, the aetiology of pancreatitis was found to be gallstones (21%), significant alcohol intake (15%), use of purine analogs (13%), duodenal involvement by CD (12%), postendoscopic complications of retrograde cholangiopancreatography (10%), postoperative complications (12%), use of other medications (4%) and idiopathic (8%).[20]

In the study of Floyd et al, the incidence rate for acute pancreatitis among all users of azathioprine was one per 659 treatment years.[21] The crude OR of having redeemed prescriptions for azathioprine within 90 days before admission for acute pancreatitis was 7.5. After adjustment for the presence of gallstones, alcohol abuse, IBD, and use of glucocorticoids, the OR increased to 8.4.

In a recent meta-analysis which included 8 randomized placebo-controlled trials of azathioprine and 6-mercaptopurine therapy in adult patients it was found that adverse events requiring withdrawal from a trial, principally allergy, leukopenia, pancreatitis, and nausea, increased with active therapy (OR 3.44).[22] In up to 23% of patients with IBD, azathioprine is withdrawn due to these side effects. It is increasingly more apparent that side effects occur more often in IBD than in other autoimmune diseases.[23,24]

Concerning the relationship between mesalamine use and appearance of acute pancreatitis there is an abundance of case-reports linking the use of this drug with the appearance of acute pancreatitis. However, there are opposite views. In a large epidemiological study conducted in Denmark it was found that although patients treated with 5-ASA and sulfasalazine had adjusted odds ratios for acute pancreatitis of 0.7 and 1.5 respectively, restricted to patients with IBD only, the corresponding adjusted odds ratios were 0.7 and 0.6 respectively. So, in the above study the use of 5-aminosalicylic acid or sulfasalazine was not associated with increased risk of acute pancreatitis. [25]

Nevertheless, the link between mesalamine and acute pancreatitis in case series reports is further emphasized by the appearance of acute pancreatitis in two out of 434 MMX mesalamine (the new form of mesalamine) recipients. [26]

5. PATHOGENESIS OF PANCREATIC INVOLVEMENT

The frequency of idiopathic acute pancreatitis is higher than expected, suggesting that part of these cases could be extraintestinal manifestations of IBD. However, few data exist on the mechanisms of acute pancreatitis development on the ground of IBD. Some of the possibly involved factors are analyzed below.

The secretory acinar cells

It is widely accepted that the acinar cells play a central role in the development of acute pancreatitis because they contain abundance of zymogen precursors. The intra-acinar activation of digestive enzymes is considered to be a critical event in the pathogenesis of acute pancreatitis. However, the molecular mechanism by which zymogen fails to leave the secretory acinar cells in patients with acute pancreatitis remains unknown. However, loss of the terminal actin web or a displacement of one of the membrane proteins, which regulate exocytosis has been proposed as a possible mechanism.[27]

The inflammatory response could be a consequence of release of chemokines from secretory acinar cells, following by recruitment of T helper lymphocytes and macrophages being responsible for inflammation of the pancreas. The systemic release of cytokines could be the cause of the systemic response. [28] The acute inflammatory process results in interstitial edema. Following this, some cases (10-15%) progress to necrosis of parts of the pancreas and possible bacterial infection.

Protease-activated receptor-2 (PAR-2)

PAR-2 activation can participate in inflammatory reactions, be protective to mucosal surfaces, modify gut motility or secretory functions, and stimulate cell proliferation and motility. Proteinases could act as signalling molecules that actively participate in the spectrum of pathophysiology of pancreatitis.[29]

Proinflammatory cytokines (TNF-α & IL-1)

Experimental evidence suggests involvement of proinflammatory cytokines in the eventual development of pancreatic lesions associated with IBD. The concomitant pancreatic over-expression of IL-1 and TNF-α, two important proinflammatory cytokines, in patients with acute pancreatitis is in favour of the existence of a pancreatic inflammatory mechanism mediated by proinflammatory cytokines.[30] Polymorphisms of TNF-α genes may increase susceptibility in acute pancreatitis.[31]

During acute pancreatitis the serum levels of TNF-α are usually elevated. It is well established that the synthesis and release of TNF-α take place in the macrophages of the pancreas. Secretory acinar cells also release TNF-α and express TNF-α receptors during acute pancreatitis.[32,33]

The plasma concentrations of soluble TNF receptors are useful predictors of the development of multiple organ failure in patients with acute pancreatitis. These data led to the hypothesis that the chimeric anti TNF antibody could be of value in patients with acute pancreatitis. Blocking the TNF-α mediated inflammation with anti-TNF-α antibodies seems to have a beneficial effect on histology score and mortality in experimental animal models.[34-37]

However, no data on humans has hitherto been published apart from a single case-report concerning a patient with interstitial pancreatitis. In this case, a young man with severe bloody diarrhoea due to segmental CD also showed

signs of acute pancreatitis. Serum amylase was high and ultrasound and abdominal computer tomography scans revealed an edematous pancreas. Treatment with steroids and azathioprine was abandoned and a single infusion with infliximab 5 mg/kg was administered without complications. The patient's overall condition improved and serum amylase levels normalized.[38-40]

So far, the complete regulatory role of TNF-α in modulating the inflammatory cascade in acute and chronic pancreatitis has not been fully elucidated. Consequently, the role of TNF-α blockade in acute pancreatitis accompanying IBD or not needs further investigation. At the moment, we cannot conclude whether anti-TNF treatment is beneficial or harmful in patients with either acute (idiopathic or secondary) pancreatitis or chronic recurrent pancreatitis.

Pancreatitis-Associated Protein 1 (PAP-1)

PAP-1 is a protein synthesized by Paneth cells and secreted upon induction of acute pancreatitis. It inhibits NFkB activation and down-regulates cytokine production and adhesion molecule expression in inflamed tissue.[41] Increased PAP mRNA has been reported in active IBD. So, patients with active IBD have increased serum PAP levels compared with controls, and these levels are correlated with clinical and endoscopic disease severity. PAP is also over-expressed in colonic tissue of active IBD. There are experimental data suggesting that the over-expression of PAP in the pancreas during the course of TNBS-induced colitis in rats is a consequence of inflammatory stress occurring in the mouse pancreas during experimental colitis. PAP-1 may be a defensive gene for oxidative stress-induced cell death of pancreatic acinar cells.[42]

The patchy distribution of PAP-expressing acini is very similar to that of pancreatic lesions observed in IBD-associated pancreatitis in humans. It is noteworthy that intrarectal instillation of 50% ethanol already triggered pancreatic stress response, suggesting that mucosal alteration rather than colitis itself is responsible for pancreatic response.

Pancreatic Autoantibodies (PAAs)

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 cause of pancreatitis.[43-46] Circulating PABs are found in approximately 30% of patients with CD. PABs are not found in healthy controls, in patients with other gastrointestinal diseases or in patients with various autoimmune disorders. Since PABs and azathioprine-induced pancreatitis are specific for CD, an association or a pathogenic role of PABs in azathioprine-induced pancreatitis could be expected. One pathogenic mechanism could be that azathioprine aggravates the inflammation in an already inflamed pancreas in CD in PAB-positive patients.

Prolonged stress

Mild histological lesions in the pancreas might eventually develop upon exposure to a prolonged stress associated with chronic colitis. Induction by colitis of a mild pancreatic stress would explain why IBD-associated pancreatitis is clinically silent.

Autoimmune pancreatitis

Concerning autoimmune pancreatitis and IBD, the finding of IgG4-positive cells on the large bowel mucosa of these patients suggests that IBD may represent an extra-pancreatic manifestation of autoimmune pancreatitis.[10]

Drug-induced acute pancreatitis

It is possible that the likelihood and type of adverse effect of azathioprine could be related to thiopurine methyltransferase enzyme (TPMT) activity and genotype. Polymorphisms in the gene encoding for TPMT have been suggested to be associated with the development of dose-dependent side effects (myelosuppression) but not with azathioprine-induced pancreatitis.[47] However in a relevant study a slight trend for more frequent TPMT mutations in the patients with adverse reactions was noticed. Most patients with reactions did not have gene mutations.[48]

Another possible mechanism for the occurrence of side effects in azathioprine therapy might be an inosine triphosphate pyrophospatase (ITP-ase) deficiency. In one study, flu-like symptoms, rash and acute pancreatitis were associated with a missense mutation in the gene encoding for ITP-ase,[49] although subsequent studies failed to confirm this association.[50,51]

Prevention of drug-induced pancreatitis requires an up-to-date knowledge of drugs that have the strongest evidence linking their use to the development of pancreatitis as well as the proposed mechanisms through which they may cause the reaction.[16]

Asymptomatic increase of pancreatic enzymes

Possible reasons for an asymptomatic increase of lipase/amylase in IBD patients include latent extra-intestinal involvement of the pancreas in IBD with pancreatitis, extra-pancreatic release of lipase/amylase from the inflamed bowel, and intestinal re-absorption of released lipase/amylase in the inflamed bowel. [14]

Duodenal Crohn's Disease

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 CD.

It can be concluded that in cases of acute pancreatitis without any firm explanation concerning the cause, it is possible that immunological mechanisms and production of various cytokines play a very significant role.[52]

5. CLINICAL PICTURE AND DIAGNOSIS

5.1 Acute pancreatitis

Clinical symptoms of IBD-associated acute pancreatitis are found in approximately 2% of patients. However, the frequency of pancreatitis could be much higher since IBD-associated pancreatitis could be a silent disease.

The majority of cases are mild, but severe and even fatal cases may occur, thus making identification of the offending agent critical. In the study of Bermejo et al, among 82 acute pancreatitis episodes 98% were of mild severity.[4] In the study of Triantafillidis et al[5] the clinical picture in most of their cases was also quite benign. In the above study no complications requiring surgical treatment were noticed. However, in one patient the course of pancreatitis was quite severe. The symptoms persisted over a long period of time and the serum pancreatic enzymes persisted for more than eight weeks. Pancreatitis of this patient relapsed after 18 months. In another patient, a pseudocyst developed as a consequence of acute pancreatitis, which responded well to conservative treatment.

We must bear in mind however, that episodes of mild acute pancreatitis observed in patients with IBD are not always due to adverse effects of treatment and can be acute manifestations of the chronic disease.[8]

The appearance of acute pancreatitis may precede the diagnosis of IBD both in CD[53] and UC.[54,55]

Diagnosis can be facilitated by the estimation of serum and urine amylase and serum lipase. Classical imaging techniques such as abdominal ultrasound, CT scan, and MRCP represent the most useful tests for the establishment of diagnosis in patients with suspected acute pancreatitis. The exclusion of other factors predisposing to the development of pancreatitis must be carefully done in all patients by performing an extensive work-up including magnetic resonance cholangiopancreatography.[56] The diagnosis of drug-induced pancreatitis is often challenging because there are no unique clinical characteristics to distinguish drugs from other causes of pancreatitis.

5.2 Chronic pancreatitis

In most cases chronic pancreatitis is clinically unapparent, although in some patients it may be accompanied by clinically relevant exocrine insufficiency.[9] Silent exocrinopathy of the pancreas could be observed in both patients with a history of pancreatitis and patients with no such history, pancreatic autoantibodies and pancreatic duct alterations reaching the level of 20% and 11% of patients, respectively.[13]

In a study of 79 patients with UC using MRCP, the prevalence of pancreatic duct abnormalities was 16.4%. Abnormalities compatible with chronic pancreatitis such as coexisting dilatation and narrowing of the main pancreatic duct, diffuse narrowing of pancreatic ducts, and dilatation of pancreatic ductal branches were found in 5%, 5%, and 3% respectively. Among the controls, no pancreatic duct abnormality was found. So, changes in the pancreatic duct were noticed in approximately one-sixth of patients with UC, none of whom had a history of overt pancreatitis. These pancreatic duct abnormalities are likely to be specific to patients with UC.[57]

Chronic idiopathic pancreatitis can be diagnosed on the basis of abnormal pancreatograms suggestive of chronic pancreatitis associated with or without impaired exocrine pancreatic function, or on the basis of pathological examination in patients undergoing pancreatic resection. According to the report of Barthet et al, who reviewed the available literature, they were able to identify 6 cases of chronic pancreatitis associated with UC and 14 cases of chronic pancreatitis associated with CD. Hyperamylasemia was not a sensitive test since it was present in 44% and 64% of patients with UC or CD respectively. Pathological specimens were analyzed in 5 patients and demonstrated the presence of inter- and intralobular fibrosis with marked acinar regression in 3 patients and the presence of granulomas in 2 patients, both with CD.[8]

In two studies, the pancreatic exocrine function assessed by the secretin-cerulein test, a Lundh meal test or the PABA test was found to be altered in 21% to 80% of patients, without systematic association with pancreatic ductal changes.[58,59]

An important clinical question concerns the possible differences in the IBD-associated chronic pancreatitis between UC and CD patients. It has been suggested that chronic pancreatitis associated with UC differs from that observed in CD by the presence of more frequent bile duct involvement, weight loss, and main pancreatic duct stenosis. Pancreatitis has a lesser frequency of pancreatic stones. There has also been a trend toward more severe bowel disease.[8]

However, these differences have no influence on the long-term consequences of pancreatic involvement. Even though in the majority of cases the diagnosis of pancreatitis precedes that of UC, pancreatitis can follow or coincide with the occurrence of UC. It is important to ascertain the cause of loose stools in each episode of exacerbation of UC as both IBD and pancreatic insufficiency due to chronic pancreatitis can involve similar symptoms.

5.3 Follow-up after cessation of acute pancreatitis

The course of pancreatitis after cessation of the acute flare is quite benign. The rate of recurrence of acute pancreatitis fluctuates between 13%[4] and 21%[20] of patients. In a series of patients described by Weber et al, only two developed recurrence of pancreatitis.[3] Triantafillidis et al also suggested that the course after resolution of pancreatitis might be quite benign, as only one patient developed recurrence of pancreatitis 18 months after the first episode of acute pancreatitis.[5] It must be emphasized however, that there is a possibility of appearance of malignancy after a certain period of time. Gotian et al described a 74-yr-old woman with CD and acute pancreatitis who 3 years after resolution of the latter developed cystadenocarci-noma of the pancreas.[60] They wonder if Crohn's-associated pancreatitis might be a premalignant state for cystadenocarcinoma of the pancreas. Furthermore, in a series of patients with acute pancreatitis and IBD, Moolsington et al noticed that three patients (6%) were subsequently diagnosed with pancreatic cancer.[20] The possibility of appearance of malignancy must always be kept in mind by clinicians.

6. TREATMENT

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 and azathioprine may well have to be excluded -at least temporarily- from treatment.

Concerning the use of biologic agents, infliximab was administered in one patient who developed severe acute pancreatitis on the course of severe recurrence of CD. The response was quite favorable although pancreatitis lasted for more than 3 weeks. A relapse of acute pancreatitis after 18 months was settled with the usual therapeutic measures including administration of infliximab.[38-40]

Management of drug-induced acute pancreatitis requires withdrawal of the offending agent and supportive care. In a case of appearance of acute pancreatitis after administration of mesalamine, 4-aminosalicilic acid (4-ASA) could be tried instead of 5-ASA. 4-ASA differs from its 5-ASA counterpart by the position of the NH2 group. In a relevant study, 4-ASA enemas were found to be a safe and well-tolerated therapeutic alternative whenever 5-ASA-induced pancreatitis occurs.[61]

The increase of lipase or amylase, without typical symptoms, makes pancreatitis with a required therapy unlikely. A specific pancreatitis therapy is not necessary in these cases. Treatment should be guided by the requirements of the IBD therapy.[14,62]

Dietary polyphenols are a major source of antioxidants consumed by humans. Polyphenols possess not only antioxidant properties but also antiviral, antibacterial, anti-inflammatory and anticarcinogenic ones. Moreover, they have the ability to modulate certain signalling pathways such as nuclear factor-kappaB activation. Substantial *in-vitro* and animal studies support the beneficial effects of polyphenols in many gastrointestinal diseases including acute pancreatitis.[63,64] More studies are needed in order to further clarify the role of polyphenols in patients with acute pancreatitis and IBD.

Weekly measurement of serum amylase has been proposed as a useful method to predict the appearance of acute pancreatitis in patients with active IBD.[65]

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