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Lecture

Pancreas and Inflammatory Bowel Diseases

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SUMMARY

Pancreatic involvement is an important extraintestinal manifestation of Crohn's disease and ulcerative colitis. Though not especially common from a symptomatic standpoint, a quite significant percentage of patients exhibit asymptomatic involvement, either in the form of elevated pancreatic enzymes or as abnormal pancreatic imaging in ERCP or MRCP studies. Still, it remains unclear how pancreatic involvement correlates with the long-term prognosis of IBD. Moreover, further research is needed to ascertain the mechanisms of injury. It is worth noting that in a handful of reports pancreatic involvement precedes the diagnosis of IBD. Lately the evidence that support more than an accidental association of pancreatitis and pancreatic insufficiency in patients with IBD is growing. According to present data, pancreatic disease seems to be one of the extraintestinal manifestations in IBD patients, especially in those with primary sclerosing cholangitis, so that increased awareness of the possible pancreatic involvement in IBD is recommended.

INTRODUCTION

Inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are systemic diseases characterized by chronic intestinal inflammation of an unknown origin, and similar to other systemic disorders are not only restricted to their intestinal tract manifestations.

The importance of extraintestinal involvement is underlined by the fact that such complications can be more prominent and even more difficult to control than the actual intestinal disease itself.

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Pancreatic involvement associated with IBD is rare compared to other extraintestinal manifestations, such as skin, eyes, liver or joint involvement.[1,2] A variety of pancreatic abnormalities have been described in IBD; CD and UC have both been implicated with CD being more frequent in the majority of cases.[3] Most of the relevant data has been gathered by clinical observation, but documentation of pancreatic morphology in histological studies has only rarely been described.

The first observation of the association between IBD and changes in pancreatic histology was reported in 1950. Post mortem autopsy findings in UC, by Ball et al,[4] showed the presence of macroscopic and microscopic pancreatic lesions in 14% and 53% respectively in 86 cases, although none of those cases have had any clinical evidence of pancreatic disease. The most common findings in these autopsy studies were chronic interstitial pancreatitis and pancreatic fibrosis, whereas no significant abnormalities of the pancreatic duct were noted. Some years later in 1956, Chapin et al. found mild-to-moderate fibrosis in autopsies in 38% of 39 patients with CD compared to 3% of healthy controls. In another study by Axon et al. on a consecutive series of 59 abnormal pancreatograms by ERCP, 5 patients were reported to have IBD, suggesting a possible association between chronic pancreatitis and IBD.[5] However none of the patients had pancreatic insufficiency.

The pancreas may be presented with two symptomatic clinical manifestations in IBD, namely acute pancreatitis and exocrine pancreatic insufficiency, although asymptomatic elevation of pancreatic enzymes, pancreatic autoantibodies, pancreatic duct abnormalities or macroamylasemia may be observed. Reports on pancreatic calcification in conjunction with IBD, in this case ulcerative colitis, are extraordinarily rare[6] whether this is a true causative linkage or attributable to the medication (azulfidine and corticosteroids) remains undetermined.

This review will focus on pancreatic alterations which have been described in association with IBD, although reports on this association are very rare in general[7,8], and will give possible explanations for the pancreatic involvement in this setting. The connection between IBD and the pancreas may be seen from a different angle in the future, since autoimmune pancreatitis emerging as a new entity, may represent a distinct form of pancreatitis to be found either on its own or linked to other autoimmune syndromes including CD.[9]

Etiopathogenesis of IBD- associated pancreatic diseases

The following etiopathogenetic conditions have been proposed as contributing factors to pancreatic involvement in IBD, by several authors:

1. Treatment with drugs, such as 5-ASA, sulfasalazine, azathioprine and 6-mercaptopourine.
2. Duodenal reflux into pancreatic ducts via an inflamed, incompetent and stenotic ampulla of Vater as a possible mechanism in CD-associated pancreatitis. Direct ampullary involvement by CD may also cause intermittent obstruction of pancreatic flow.
3. Small gallstones or sludge as a responsible trigger factor for at least some cases of pancreatitis in IBD.
4. Presence of autoantibodies against the exocrine pancreas suggesting an immunologic basis for etiology as they have been reported in 31-39% of patients with CD.
5. IBD, PSC and pancreatitis existing in combination, are seen as manifestations of an autoimmune disease on a genetic disposition basis, as it has been hypothesized. Both PSC and pancreatitis may precede the onset of clinical IBD.
6. Immunological mechanisms and production of various cytokines, including Tumor Necrosis Factor a, may also play some role in the pathogenesis of IBD associated acute pancreatitis.[10,11]

ACUTE PANCREATITIS

Acute pancreatitis (AP) as a complication of IBD has been well established in epidemiological studies. A nationwide Danish cohort study detected an increased risk of acute pancreatitis in patients with IBD compared with the general population. Patients with CD were found to have a fourfold increase in risk of developing acute pancreatitis and patients with UC a twofold increase in risk compared with the general population. The highest risk was found in middle aged women with CD.[12] Moreover, a multiregional study from Sweden estimated that patients with IBD had at lest a threefold increase in risk. In addition, a case control study from Denmark found an AP prevalence of 0.9% for CD and 0,4% for UC among 1,590 AP cases versus a prevalence of 0.2% among 15,913 controls, suggesting a fourfold increase in risk for AP in CD and a 1.5-fold increased risk in UC patients. Interestingly, in this study, the use of 5-aminosalicylic acid or sulfasalazine was not associated with increased risk of AP in patients with IBD.[13]

Concerning the etiopathogenesis, pancreatitis in IBD may be induced by disease-associated morphologic abnormalities in the upper gastrointestinal tract-duodenal or papilla area involvement causing duodenal reflux or papilla obstruction- or by medical treatment (azathioprine and its metabolite 6-mercaptopourine,[14] 5-aminosalicylic acid,[15] metronidazole[16]), or finally by the classical causes of pancreatitis such as alcohol and bile duct stones.

Patients with CD have an increased risk of developing gallstones, regarding that the prevalence of gallstone disease in CD has been reported to be 26% in a population-based cohort study from Stockholm. In contrast the prevalence of gallstones in the normal population is only about 10%. Gallstone formation is considered to be multifactorial. A potential risk factor may be high bilirubin concentrations in the bile, which can be found in patients with resection or severe inflammation of the terminal ileum.[17] Successful prophylactic strategies to avoid gallstone development in CD are not available.

Most of the cases (two-thirds) of acute pancreatitis in IBD patients reported in the literature have been considered as the result of adverse effect of medical treatment for IBD, and the remaining cases have no established cause for pancreatitis other than the IBD itself. In only one case of pancreatitis in CD, CD was proved to directly affect the pancreas based on the histological examination that demonstrated granulomatous inflammation of the pancreas head. This finding shows clearly that the pancreas may also be a primary site of localization of CD.[18]

Acute pancreatitis may occur as a rare adverse event after drug treatment of IBD. In patients with acute pancreatitis, medications are though to be the etiological factor in approximately 5% of the cases, although the determination of medication causing pancreatitis can be difficult. Clinical improvement after the withdrawal of

the drug and recurrence with the rechallenge, constitutes the gold standard for establishing a definitive association. However a causal relationship between some drugs and acute pancreatitis remains largely unproved, as in the case of corticosteroids. Finally the role of the chimeric antibody against TNFa (infliximab) in inducing acute pancreatitis remains obscure since controversial reports on its use in such cases exists.

According to the few reports available, the incidence of acute pancreatitis in IBD may vary between 1.5%-5%.[19,-22] Patients with CD have a four times higher risk of acute pancreatitis than control patients without CD and patients with UC have a twofold increase of risk. Usually, these episodes of acute pancreatitis are mild and recurrent attacks are rare.[23,24]

EXOCRINE PANCREATIC INSUFFICIENCY

Pancreatic exocrine impairment is a far more frequent occurrence than is generally recognized in clinical practice and seems to be the most frequent manifestation of pancreatic involvement in IBD.

By using the secretin-cerulein test, Angelini et al[25] found a decrease in bicarbonate and enzyme output in 11 of 27 patients (35% with CD and 50% with UC) and isolated decrease of lipase output in 18 of 27 patients (58% with CD and 80% with UC) in a series of 17 patients with CD and 10 patients with UC. Hegnohj et al[26] confirmed a significant decrease of amylase and lipase output as compared to 115 controls using the Lundh meal test and duodenal aspirates analysis. This exocrine pancreatic insufficiency appeared to correlate with the extension of the lesions of CD, especially with ileal location and with disease activity in case of predominant lesions to the ileum. Heikius et al., in a series of 170 patients with UC and 46 with CD, found abnormal paraaminobezoic acid test results in 21.8% and 26% of these cases.[27] This exocrine pancreatic insufficiency does not seem to be always associated with pancreatic ductal changes. As Heikius et al. demonstrated, only 5 of 10 patients with abnormal secretin test had pancreatic ductal alterations.

Since the detection of autoantibodies in pancreatic acini and pancreatic juice proteins there has been some debate about a distinct defect in the secretory capacity of the pancreas in patient with CD. Some recently published data suggest that malnutrition may also play a significant role in the impairment of pancreatic exocrine secretion in CD patients.

In earlier studies of the pancreatic response to intravenous secretin[28], abnormalities were demonstrated in up to 31% of patients with CD without symptoms of pancreatic dysfunction. The most consistent defect observed was in enzyme secretion. However, its nature still remains undetermined. With the use of faecal elastase-1 pancreatic function test[29], a non-invasive powerful tool is available for routine screening for exocrine pancreatic insufficiency despite some draw-backs for mild disease.[30,31] This test needs to be explored in CD in order to screen patients on a routine basis.

ASYMPTOMATIC ELEVATION OF PANCREATIC ENZYMES

Elevated serum levels of amylase along with lipase are usually markers of pancreatitis. However these enzymes are elevated in some patients with IBD without clinical symptoms of pancreatitis. The possible mechanisms for an asymptomatic increase of pancreatic enzymes in IBD are:

1) Latent extra-intestinal involvement of the pancreas in IBD

2) Extra-pancreatic release of amylase/lipase from the inflammatory bowel

3) Intestinal reabsorption of released amylase/lipase in the inflammatory bowel.

Katz et al[32] reported hyperamylasemia without clinical evidence of pancreatitis in 8% of patients with CD. Tromm et al[7] found painless hyperamylasemia or hyperlipasemia in 16% of patients with CD and in 21% in patients with UC in a prospective study of selected patients. They found no relation with the activity or the duration of the disease or the drug treatment except for a higher frequency of pancreatic hyperenzynemia in Crohn's colitis compared to ileitis or ileocolitis. Another group, performed a cross-sectional study on pancreatic enzymes in an unselected population of 237 IBD patients, and found hyperamylasemia in 17% and hyperlipasemia in 9% of the patients with CD, whereas the corresponding findings in UC were 9% and 7%. In contrast to the results of the two first studies, the latter authors reported elevated enzymes to be related to extent and activity of the disease process.[33] Oishi et al[34] found the prevalence of hyperamylasemia in patients with CD to be 16%. All hyperamylasemic patients then underwent pancreatic imaging, mostly via transabdominal US, but some were further evaluated with ERCP, CT and MRCP. The cumulative incidence of abnormal pancreatic imaging among the entire population was estimated to be 5.2% at 5 years and

6.3% at 10 years following diagnosis of CD. Whereas there was no characteristic pattern of imaging abnormalities, 69% displayed intrapancreatic coarness on US and 81% displayed pancreatic deformity with irregular contour on CT and US. A substantial number of patients displayed ductal abnormalities on ERCP and MRCP, as well.

Whether asymptomatic increase of pancreatic enzymes represents true pancreatic involvement of the underlying IBD or whether it is merely an effect of the medication remains to be clarified, but in the absence of appropriate indications in IBD patients it requires no further diagnostic investigation. In this setting, the decision to initiate treatment for pancreatitis should not be based on the serum markers alone and the clinical presentation and examination should be encompassed in the decision making process.

PANCREATIC AUTOANTIBODIES

An immunologic basis for pancreatic involvement in IBD might be suggested by the demonstration of increased titers of serum autoantibodies to the exocrine pancreas among patients with CD, described by Stöcker et al.[35] He theorized that the reason that pancreatitis is not as prominent as other extraintestinal manifestations is because the bulk of autoantigens comes into contact with the immune system only outside the pancreas.

Published reports have identified PABs (antibodies to exocrine pancreatic tissue) in 15-40%[36] of CD patients, but only 0-4% of UC patients and 0-4% of normal controls.[37] CD patients with PABs have not been found to have pancreatitis more often than those without these antibodies.

Pancreatic autoantibodies are considered to represent a specific marker for CD. However, in contrast to other autoimmunity mediated disorders; determination of autoantibodies in CD does not play an important role, so far, in the clinical diagnosis. In the setting of the two clinical pancreatic conditions which are associated with CD, that is acute pancreatitis and exocrine pancreatic insufficiency, it is mandatory to re-evaluate the role of autoantibodies although there is still no conclusive evidence of a direct pathogenic role for these autoantibodies in CD[38] and they do not correlate with the activity of the intestinal disease or the incidence of acute pancreatitis. To our present knowledge, there is only one study by Sebold et al[39] that was conducted to evaluate a possible correlation between PAB and pancreatic function in CD. In this study exocrine pancreatic function was significantly more often impaired in PAB positive patients (27%) than in PAB negative patients (8%).

Although the prospect of building a link between two epithelial linings is intriguing, that is the gut mucosa and the pancreatic epithelial cell in CD, overall evidence for crossover autoimmunity or a causative relationship between CD and pancreatitis or exocrine pancreatic insufficiency is still rather sparse and these serologic findings do not establish a direct cause-effect relationship for pancreatic disease.

AUTOIMMUNE PANCREATITIS

Autoimmune pancreatitis (AIP) is a distinctive type of chronic pancreatitis which has been described particularly in Japan but has also been observed in Western countries. This disease is characterized by associated autoimmune markers, occasional coexistence with other autoimmune diseases and is clinically distinguished in particular by good response to treatment with corticosteroids. AIP is defined histologically by periductal and interacinar lymphocytic infiltration. The characteristic findings in most cases of AIP are summarized in table I. Both primary (with no association to other autoimmune diseases) AIP and secondary (associated with other autoimmune diseases).[40] AIP are now included in the recent etiology-risk-based chronic pancreatitis classification system TIGAR-O.

A patient with PSC and AIP has first reported in 1997 by Ectors et al.[9] The pancreatic pathology showed a dense lymphocytic periductular infiltration with destruction of the pancreatic ducts. In this paper, 2/12 patients had CD and UC respectively, 1/12 had Sjögren's syndrome and 1/12 had PSC[5]. Since PSC is known to be commonly associated with UC, the concomitant occurrence of UC, PSC and chronic pancreatitis may be more frequent than

Table 1. Characteristic findings of AIP

1. Middle-old age
2. Increased levels of serum gammaglobulin, IgG, or IgG4
3. Presence of autoantibodies
4. Diffuse enlargement of the pancreas
5. Diffusely irregular narrowing of the main pancreatic duct and occasionally stenosis
6. Fibrotic changes with lymphocyte infiltration
7. No symptoms or only mild symptoms, usually without acute attacks of pancreatitis
8. Rare pancreatic calcification or cysts
9. Occasional association with other autoimmune diseases
10. Effective steroid therapy

is so far recognized. This assumption is supported by the early report by Ball el al[4] who found in post mortem studies of patients with UC some pancreatic changes in more than half of the cases. Similar results might also be expected in patients with CD. These histological features had been noted already in 2/53 patients with hereditary pancreatitis,[41] then called acute interstitial pancreatitis.[42] The serological evidence may derive also from the fact that, in another study in patients with idiopathic chronic pancreatitis and Sjögren's syndrome, antibodies against the lead enzyme of pancreatic duct cell, carbonic anhydrase type II, have been described.[43] A valuable study, yet to be conducted, would be to determine those antibodies in patients with IBD suspected to suffer from pancreatic involvement in order to assess the frequency of an autoimmune component in this disease.

Barthet et al,[44] after histological examination of pancreatic tissue of patients with simultaneous pancreatitis and IBD, suspected that pancreatitis associated with IBD was an autoimmune disease. In this study, 5 patients showed diffuse narrowing of pancreatic ducts that resembled the changes in autoimmune pancreatitis, and a biopsy sample taken from one patient was histologically compatible. However, serum IgG subclass 4 concentrations, reported to be a highly sensitive and specific marker of autoimmune pancreatitis, was low in all patients tested.

In one MRCP study in patients with UC, without history of pancreatitis, pancreatic duct changes were found in 16.4%.[45] Interestingly 30% of patients with abnormal MRCP findings had pancreatic duct changes compatible with AIP, namely diffuse narrowing of the main pancreatic duct but none of them had elevated serum IgG subclass 4 concentrations. Thus, the chronic pancreatitis seen in patients with IBD is probably a distinct form, although it is possibly related to autoimmune pancreatitis.

PANCREATIC DISEASES IN PATIENTS WITH CONCOMMITANT PSC AND IBD

The commonest hepatobiliary disorder in IBD patients is primary sclerosing cholangitis (PSC), a chronic cholestatic syndrome of unknown origin characterized by chronic fibrosing inflammation of both intrahepatic and extrahepatic bile ducts. The course of PSC is unpredictable but tends to be progressive and leads to cirrhosis and portal hypertension, 4-10% of patients develop cholangiocarcinoma. There are no specific markers to predict development of cholangiocarcinoma in PSC.[17] CD and UC are associated in up to 10% with PSC and approximately 70% of all patients with PSC suffer from coexisting UC. This high degree of association suggests a common mechanism in pathogenesis. However, no causal relationship has yet been established.

The prevalence of coexisting pancreatic duct abnormalities in patients with PSC associated with IBD is 48% in the study of Heikius et al.[46] In the study by Lindstöm et al[47] pancreatic ductografic changes were seen in 20% of patients with IBD and concomitant PSC. The mechanisms causing pancreatic involvement in PSC associated with IBD are not clearly understood. It is possible than in some instances the changes in the pancreatic ducts represent extensions of the same disease process that affect the bile ducts. In some cases the pancreatic ductal changes have been seen to disappear spontaneously[48] or after treatment with ursodeoxycholic acid. However, the question remains open as to whether these concomitant pancreatic duct changes in PSC have any relevant clinical or prognostic implication, and therefore follow-up studies are needed.

PANCREATIC CANCER, CROHN'S DISEASE AND PANCREATITIS

Pancreatic cancer associated with pancreatitis is well recognized and it has been described only in the setting of chronic pancreatitis.[49] Interestingly in the study of Moolsintong et al,[20] 2 patients who were found to have unexplained acute pancreatitis and CD later developed pancreatic cancer, both within 4 years of diagnosis of pancreatitis. To our knowledge there is only one other case report of pancreatic cystadenocarcinoma developing in a patient with pancreatitis and CD.[50] In this unusual case of pancreatic cancer which developed in a 74 year-old woman 3 years after a single episode of acute pancreatitis that completly resolved. In these cases a causal relationship between CD, pancreatitis and pancreatic cancer is difficult to establish, thus it is not know if Crohn's-associated pancreatitis may be a premalignant status for pancreatic cancer. Moreover the pancreatic duct abnormalities, seen in patients with PSC and IBD, are not known to predispose to pancreatic ductal adenocarcinoma.

CONCLUSIONS

According to the present data, pancreatic diseases seem to be extraintestinal manifestations of IBD, suggesting that increased awareness of possible pancreatic disease in IBD patients is recommended.

Pancreatic duct abnormalities and pancreatic exo-

crine dysfunction occurs in some patients with IBD. Acute idiopathic pancreatitis may complicate IBD and pancreatic enzyme levels are elevated in a significant proportion of these patients without any clinical signs of pancreatitis. This late condition is not related to medications but probably the enzyme increase is associated with a more extensive and active IBD.

A direct role for PAB, in the pathogenesis of IBD-associated pancreatitis, is not yet established but these autoantibodies may either reflect an immune deregulation triggered by the bowel mucosal ulcerations or they may be attributed to cross-reactivity, as has been shown for other autoantibodies in some autoimmune diseases.

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