Idiopathic pancreatitis in inflammatory bowel disease

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Abstract

Background and aims: The incidence of pancreatitis is increased in inflammatory bowel disease. However, pancreatitis as an extraintestinal manifestation of the intestinal disease is exceedingly rare. We have retrospectively analyzed the prevalence of pancreatitis in a combined hospital cohort, and specifically studied cases in which no other cause than the intestinal disease itself could be found.

Methods: The prevalence of pancreatitis in 1057 inflammatory bowel disease patients from two hospitals in the Community of Madrid, Spain, was determined by means of database examination.

Results: The prevalence of pancreatitis was 2.74% (29 cases); only in four patients (0.38%) it was considered idiopathic and thus a possible extraintestinal manifestation. Underlying chronic pancreatitis was identified in three of these four patients.

Conclusions: In inflammatory bowel disease patients, pancreatitis is more often due to a nonrelated cause, and cases that can be ascribed to extraintestinal manifestation of the intestinal disease are comparatively rare.

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KEYWORDS
Chronic pancreatitis; Inflammatory bowel disease; Crohn’s disease; Ulcerative colitis; Extraintestinal manifestation

1. Introduction

Pancreatic involvement in patients with inflammatory bowel disease (IBD) ranges from asymptomatic elevation of pancreatic enzymes, to chronic pancreatitis with repeat bouts of superimposed acute inflammation. As in any other patient, pancreatitis can be caused by multiple etiologies, but in a fraction of cases, no apparent cause is found after extensive examination. These idiopathic cases can be ascribed to extraintestinal manifestations of the underlying disease, and are sometimes associated to overt chronic pancreatitis changes.

Chronic pancreatitis (CP) is characterized by a permanent damage of the pancreatic gland, including inflammation and fibrosis, that eventually lead to destruction of both exocrine and endocrine parenchyma. Histology is not a useful diagnostic tool, and the observation of the typical morphologic changes in diverse imaging techniques is currently the preferred diagnostic method. However, normal imaging does not

Abbreviations: IBD, inflammatory bowel disease; CP, chronic pancreatitis.

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exclude CP. In developed countries, the main cause of CP is alcohol, followed by metabolic diseases, pancreatic duct obstruction and congenital causes. Rarely, immune activation processes can encompass pancreatic inflammation, and gradually lead to an established CP. One of these immune activation processes is inflammatory bowel disease (IBD), and CP in this setting is considered an extraintestinal manifestation, if no alternative explanation can be found.

This entity is either infrequent or poorly recognized: a literature search revealed 33 cases of IBD-associated CP. Twenty patients had been diagnosed with Crohn’s disease (CD), and 13 with ulcerative colitis (UC).

We have reviewed the joint databases of two hospitals in the Community of Madrid, Spain, (Hospital Universitario “Ramón y Cajal” and Hospital Universitario de Fuenlabrada), identifying four cases of recurrent pancreatitis with suspected CP (three UC, one CD). The absence of alternative causes, made us identify these cases as extraintestinal manifestations of IBD.

2. Case report

The joint databases of our hospitals included, at the time of reviewing (July 2007) 1057 patients with IBD. These databases are prospectively maintained by the two physicians in charge (ALSR and FB), and any event that affects the patients is immediately entered into the database. Thus, a good degree of accuracy is expected. Additionally, for the purposes of this work, the general hospital databases were searched for patients discharged with the joint diagnoses of pancreatitis, IBD or UC.

At least one episode of pancreatitis was registered in 29 patients (2.74%). In four of these patients, pancreatitis could not be ascribed to any identifiable cause, and was labelled as an extraintestinal participation of the underlying IBD. This corresponds, in turn, to 13.79% of all pancreatitis episodes observed in our patients, a prevalence of 0.38%.

The diagnosis of acute pancreatitis was based on the combination of abdominal pain with a level of amylase, lipase or both reaching at least three times the upper normal value. Chronic pancreatitis was defined as compatible clinical presentation associated to typical morphological changes in one or more imaging procedures (ERCP, endoscopic ultrasonography, abdominal computed tomography — CT). The diagnosis of IBD was done according to the usual criteria.

In every patient with pancreatitis, usual causes (alcohol abuse, gallstones, drugs) were ruled out.

2.1. Case 1

A 27-year old woman, was diagnosed with ulcerative proctitis in 2003. She additionally suffered two different episodes of brisk abdominal pain. The first coincided with the onset of proctitis, before mesalazine was started, and the second appeared three years later, with the patient on mesalazine. In both occasions, amylase and lipase increased to over 1000 UI/L and hospital admission was necessary. During the second episode, an abdominal ultrasound failed to detect the presence of gallstones. Once the acute episodes were over, the presence of possible causes of recurrent pancreatitis was ruled out (normal or negative triglycerides, aminotransferases, immunoglobulins, antinuclear antibodies, anti smooth muscle antibodies, calcium, parathormone, and fecal elastase). Abdominal CT scan was also normal. Endoscopic ultrasonography showed slightly irregular pancreatic parenchyma, with hyperechoic tracts and lobulations. These findings, though characteristic of CP, are insufficient for its diagnosis.

2.2. Case 2

A 46-year old male was diagnosed in 1998 with ulcerative pancolitis. Also, during the first admission, and while on prednisone, he developed a crisis of abdominal pain with tenfold elevation of lipase and amylase levels. Abdominal US and abdominal CT were normal, except for a slight pancreatic enlargement. Five months later, while on oral mesalazine, he suffered a new episode of abdominal pain, with normal amylase and lipase levels, but with an enlarged, hypodense and poorly demarcated pancreas, together with a small amount of intraperitoneal fluid. An ERCP was performed, that showed a diffusely stenosed Wirsung’s duct, with a small cyst in the union of pancreatic head and body and dilatation of secondary pancreatic duct branches. All these were interpreted as suggestive of CP.

2.3. Case 3

A 32-year old male with a previous diagnosis with UC, presented three years later with a clinical picture suggestive of acute pancreatitis (epigastric pain with more than tenfold elevation of amylase and lipase). He had been all three years on mesalazine, but the drug was now withdrawn as a precaution. In spite of this, a similar episode appeared four months later, while on prednisone. The following analyses were performed, with normal results: parathormone, calcium, triglycerides, antinuclear and anti smooth muscle antibodies, total immunoglobulines and IgG4 fraction. An abdominal CT scan was considered indicative of acute pancreatitis (Fig. 1). Two more episodes followed within six months. An endoscopic US showed a slightly dilated pancreatic duct with dilatation of secondary pancreatic ducts, and a lobular parenchyma with hyperechoic foci and fibrous tracts. All these, together with a fecal elastase level of 26 µg/g (normal > 200 µg/g), confirmed the diagnosis of CP.

Figure 1 Abdominal CT image with oral and intravenous contrast, which shows an increase pancreatic head’s size and peri-pancreatic fat inflammation, compatible with acute pancreatitis degree C of Balthazar’s score.
2.4. Case 4

A 49-year old male suffered five bouts of acute pancreatitis between 2004 and 2007. He denied ethanol abuse, and neither cholelithiasis nor biochemical alterations explaining the recurrent pancreatitis were found. An ERCP showed a normal pancreatic duct, but an endoscopic sphincterotomy was performed, as indicated by the recurrent acute pancreatitis. In 2007, ileocecal Crohn’s disease was diagnosed, and the previous episodes interpreted as acute bouts on an underlying CP.

3. Discussion

Patients with IBD have an increased incidence of both acute and chronic pancreatitis, as shown by a prospective 10-year follow-up study, that identified an incidence of pancreatitis of 1.4% in 852 patients. The most frequent causes of AP in patients with IBD are cholelithiasis (whose incidence is increased in CD23), and drug-induced pancreatic injury (mesalazine, sulphasalazine, azathioprine, mercaptopurine, glucocorticoids and metronidazole). This can explain up to 3/4 of cases, even after prolonged administration of the drug. A third characteristic cause is the pancreatic duct obstruction that can be induced by periamillary mucosal lesions in CD.

In western countries, the first cause of CP is alcohol abuse, followed by metabolic causes, pancreatic duct obstruction and hereditary diseases. Infrequently, some autoimmune disorders can induce CP. Histology is the golden standard for CP diagnosis, but its invasivity limits its applicability. The use of imaging techniques is accepted as the alternative option, although normal studies do not rule out CP.

The pancreatitis is labelled idiopathic when all usual etiologic factors are ruled out. In the setting of IBD, many authors consider that such cases could represent a form of extraintestinal manifestation; this presentation, however, is rare.

A review of the literature allowed us to identify 33 cases of IBD-associated CP. Twenty affected Crohn’s disease patients, and the rest were associated to UC.

The frequency of necropsy macro- or microscopic pancreatic injury in IBD patients can go up to 50% of cases, a figure much higher than what one could deduce from the small number of pancreatitis diagnosed during lifetime; this suggests the possibility of silent subclinical chronic pancreatitis being present in a high proportion of patients.

To estimate the real prevalence of IBD-associated pancreatitis, a number of studies have been performed, either determining amylase and lipase levels, studying exocrine function or studying the presence of morphological change of the pancreatic gland through different diagnostic methods. The finding of elevated levels of serum lipase, amylase or both can be present in 5.8–15.8% of patients with IBD, but this does not necessarily imply a pancreatic injury; alternative explanations include elevation of intestinal amylase, increased amylase absorption in the inflamed gut, or macroamylasemia. Exocrine pancreatic insufficiency, as measured by pancreatic stimulation tests, can be present in 4–80% of patients; this dysfunction is not always accompanied by pancreatic duct alterations. Finally, alterations in endoscopic pancreatography (ERCP) have been described in 8–20% of IBD patients.

Some authors have described a different behaviour of CP, depending on its association to Crohn’s disease or to ulcerative colitis. CP often follows the diagnosis of Crohn’s disease, although it can be its first manifestation. In UC, pancreatitis seems to antedate IBD in more than half of cases, and is more frequently associated to a severe pancolitis and thus to the need for surgery. IBD-related CP has been described in association to both primary sclerosing cholangitis and primary biliary cirrhosis.

The pathogenesis of IBD-associated pancreatitis is not well understood. Classically, Crohn’s disease-associated pancreatitis was linked to the presence of duodenopancreatic reflux or papillary obstruction due to duodenal inflammation. The presence of pancreatic autoantibodies in IBD, more specially in Crohn’s disease, could account for pancreatic exocrine lesion, according to some authors. These autoantibodies appear in one third of Crohn’s disease patients, but with a similar prevalence in patients who do and who do not develop pancreatic injury. Its presence is thus not necessary for the production of pancreatic injury, and their pathogenetic relevance has been questioned. Other mechanisms invoked as determinants of pancreatic injury are the formation of microthrombi by platelet aggregation, or the development of pancreatic granulomas, together with nonspecific pancreatic changes (interlobar and interacinar fibrosis, acinar regression, intense inflammatory infiltrate).

IBD-related pancreatitis tends to be less painful and less frequently severe, than other causes of pancreatitis. They are sometimes but not always associated to a flare up of intestinal disease, though some studies have shown that the extension and activity of ileal lesions could be directly related to the intensity of exocrine pancreatic insufficiency.

Diagnosis of CP is sometimes made more difficult by the overlap of its manifestations (weight loss, abdominal pain, and diarrhea) with IBD signs and symptoms. IBD-associated CP is seldom calcified.

In summary, it seems important to rule out the presence of acute pancreatitis in IBD patients presenting with brisk abdominal pain, though this can be difficult, due to the frequent elevation of serum lipase and amylase in such patients. The presence of pancreatitis recurrence should, as always, prompt the exclusion of usual causes of CP. However, true IBD-related pancreatitis seems to be prone to progress to chronicity, and it has not yet been described if a better control of the intestinal disease could prevent such progression.

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