

## Inflammatory bowel disease and pancreatitis

### A fortuitous association or a causal relationship?

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Pancreatic involvement on gross pathology and histology was documented in early reports on autopsy material in patients with ulcerative colitis.<sup>1</sup> At first sight this is not surprising, taking into account the systemic nature of inflammatory bowel disease (IBD) and the effect on various organ systems. Subsequent clinical observations, mainly in case reports, indicated an association of acute pancreatitis or hyperamylasemia in IBD. These reports were focused primarily on the possible etiological factors of drug treatment in patients with IBD, namely azathioprine, salicylazosulfapyridine, 5-aminosalicylic acid, mesalamine, 6-mercaptopurine, metronidazole and corticosteroids.

Azathioprine is the most common offender among these agents. A substantially increased relative risk of pancreatitis has been reported in users of azathioprine in a study from Denmark<sup>2</sup>. In another study, Weersma et al<sup>3</sup>, reported an increased incidence of azathioprine induced pancreatitis in patients with Crohn's disease compared with other diseases, namely auto-immune hepatitis, systemic lupus erythematosus, and post liver and kidney transplantation. Azathioprine toxicity and the necessity of withdrawal was more common in inflammatory bowel disease, and Crohn's disease in particular, compared with other diseases.

Acute pancreatitis was also reported in patients with Crohn's disease of the duodenum, implicating the inflam-

matory process and fibrosis affecting pancreatic secretion or reflux of duodenal contents to the pancreatic duct, which predisposes to attacks of pancreatitis.

What is intriguing, however, is the development of idiopathic pancreatitis in patients with IBD, not attributed to exogenous factors (drugs), or structural defects of the duodenum. In this context, the vexing question is whether pancreatitis in IBD is a fortuitous association or there is a causal relationship emanating from the pathogenesis of autoimmune diseases. In this regard, little is known and even less is well-documented.

In this issue of the ANNALS, Triantafillidis et al,<sup>4</sup> in a retrospective case-series study, describe 5 patients out of 327 with IBD who developed acute idiopathic pancreatitis, which represents an incidence of 0,14% patients – years and frequency of 1,53%. It is of interest that two patients developed pancreatitis before and 3 patients after the diagnosis of IBD was made. The authors conclude that acute idiopathic pancreatitis is associated with IBD especially Crohn's disease. In the same issue of the ANNALS in another article Katsanos et al<sup>5</sup> report a case of IBD with persistent hypamylasemia without clinical expression of pancreatitis, which is different from the cases of pancreatitis described by Triantafillidis et al. Asymptomatic hyperamylasemia may be attributed to a number of causes and does not necessarily imply clinical disease.

Pancreatitis has also been reported in children with IBD. In a large series of 124 patients, Le Large-Guiheneuf et al,<sup>6</sup> reported 25 patients (20%) with pancreatitis and asymptomatic hyperamylasemia. This high frequency of pancreatitis was attributed to several factors, including drugs (azathioprine, 5-aminosalicylic acid) and duodenal involvement and not solely to the disease per se. It emphasizes, however, the need to monitor the possibility of pancreatitis or asymptomatic hyperamylasemia

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in this group of patients, in order to modify drug treatment implicated in pancreatitis, mainly azathioprine and to a lesser frequency 5-aminosalicylic acid to prevent recurrence of pancreatitis.

The clinical significance of pancreatitis in adult patients with IBD is rather limited due to low incidence and does not justify monitoring these patients for pancreatic disease by imaging studies of the pancreas. When the problem arises, diagnostic evaluation of pancreatitis is indicated in order to exclude other causes. Asymptomatic hyperamylasemia is also an indication for initial evaluation, but not on a regular follow-up basis. A careful history should be recorded in these cases to exclude the possibility of drug related pancreatitis or other causes of pancreatitis.

The challenge in exploring the manifestation of pancreatitis in IBD lies in the potential causal relationship emanating from the biology of the diseases. To start with taking into account the concept of auto-immune process, several auto-immune diseases have been reported in pancreatitis, namely rheumatoid arthritis, systemic lupus erythematosus, primary sclerosing cholangitis, sarcoidosis and inflammatory bowel disease.<sup>7,8</sup>

Several issues regarding the pathogenesis of IBD vis-à-vis pancreatitis need to be addressed. The inflammatory process per se and the release of cytokines in IBD, particularly of tumor necrosis factor- $\alpha$  and its effect on pancreas may have a role in the development of pancreatitis. It is relevant, but by no means conclusive, that infliximab was associated with a favorable response in acute pancreatitis in patients with Crohn's disease<sup>9</sup> and in cerulein-induced pancreatitis in the rat<sup>10</sup> with a decrease of serum amylase and histopathological score of inflammation and pancreatic necrosis.

Another line of implication of the auto-immune mechanisms is the presence of autoantibodies to the pancreas (PAB) characterized by high specificity in patients with Crohn's disease.<sup>11</sup> This observation, however, may not fully explain the development of pancreatitis in patients with IBD. The presence of antibodies in IBD may be an epiphenomenon, caused by cross reactivity with other antigens of bacterial origin generated in the colon.

The role of gut in acute pancreatitis is well recognized in regard to the defect of mucosal barrier and increased intestinal permeability, which correlates with bacteremia attributed to translocation of enteric pathogens.<sup>12</sup>

The role of bacterial component is not directly related to the pathogenesis in IBD but the development of antigens generated by the gut may affect other organs via the immune process.

The gut is a rich source of cytokines and the site of neutrophil priming. Overproduction of interleukin-6 and activation of phospholipase-A2 which affects cell membrane phospholipids, play an important role in the sequestration of neutrophils in other organs, i.e. pancreas, to cause microvascular injury, which occurs in acute pancreatitis.<sup>13</sup>

Another link between IBD and pancreatic function is malnutrition and malabsorption, which characterize chronic IBD causing a decrease of pancreatic secretion in patients with Crohn's disease.<sup>14</sup> Patients with Crohn's disease present with significant impairment of pancreatic enzymes synthesis and reduction of zymogen stores. The interaction between luminal factors of the gut and exocrine pancreatic secretion is well documented in malabsorptive states.

The emergence of the entity of auto-immune chronic pancreatitis, may shed some light in regard to the association of pancreatitis with other auto-immune diseases.<sup>15</sup> These include Sjogren syndrome, primary sclerosing cholangitis, ulcerative colitis, primary biliary cirrhosis and systemic lupus erythematosus. The characteristics of autoimmune pancreatitis are the following<sup>16</sup>:

1. Enlargement of the pancreas and narrowing of the pancreatic duct
2. Hypergammaglobulinemia and presence of auto-antibodies
3. Histological changes of the pancreas with fibrosis and infiltration with lymphocytes and plasma cells
4. Response to steroids.

It is evident that IBD, as an auto-immune disease, shares similar characteristics with auto-immune pancreatitis.

The current concept that autoimmune pancreatitis is classified as primary (no association with other auto-immune diseases) or secondary (associated with other auto-immune diseases, among them IBD) lends support to the notion that there may be a link between IBD and pancreatitis, sharing a common pathogenetic immune mechanism. At this stage it is not clear whether the mechanism of primary or secondary auto-immune pancreatitis differs or whether patients with primary auto-immune pan-

creatitis will develop in the course other auto-immune disease.<sup>17</sup>

The road to unlock the mysteries between these two fascinating and enigmatic entities IBD and pancreatitis is a long one, as we are still in the beginning. Excluding the cases of pancreatitis in IBD, which are drug induced, or due to duodenal involvement, the idiopathic acute pancreatitis in IBD may prove to be yet another extra intestinal manifestation which may precede the diagnosis of IBD, similar to the arthropathy in IBD. The spectrum of pancreatic involvement from asymptomatic hyperamylasemia to overt disease is obviously influenced by other underlying factors. These are pancreatic enzyme synthesis, cytokines, microcirculation, the effect of endothelin on pancreatic capillary permeability and the process of ischemia – reperfusion, which sets the stage for pancreatitis.

Obviously, the plot thickens and the puzzle becomes more complex. After all this is the mystic of research in human disease.

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