Review

Acute Pancreatitis: An Emerging Presentation for Autoimmune Pancreatitis in Patients With Inflammatory Bowel Disease

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Halabi reported a case of acute pancreatitis with concomitant ulcerative colitis in a 6-year-old girl.[1] The specific type of acute pancreatitis is called idiopathic pancreatitis, but it is likely a case of autoimmune pancreatitis (AIP) because of the frequency of the association of AIP with ulcerative colitis. The very young age of the patient (6 years) is striking; in fact, she is the youngest patient with pancreatitis and ulcerative colitis reported in the literature to date to our knowledge. The mean age of AIP cases reported in the literature is 45 years (range, 15–77 years).[2-5] The author noted that concomitant presentation of the two conditions is rare, but, in fact, simultaneous presentation of both inflammatory bowel disease and AIP is not so uncommon. In addition, pancreatitis may precede inflammatory bowel disease–related manifestations in 58% of cases.[6,7]

Numerous cases of pancreatitis occurring during the course of Crohn's disease or ulcerative colitis have been described in the literature. Many of them can be attributed to biliary lithiasis or intake of either 5-aminosalicylic acid, sulfasalazine, corticosteroids, azathioprine, or 6-mercaptopurine.[8,9] Duodenal reflux or papillary obstruction was also potentially considered responsible for pancreatitis observed during inflammatory bowel disease.[10-12] A large recent series has evaluated the etiology and outcome of acute pancreatitis occurring during the course of Crohn's disease.[13] Gallstones and alcohol intake were found in only 21% and 15% of the cases, whereas drug-induced pancreatitis or duodenal Crohn's disease involvement was found in 12% and 13% of cases, respectively. The final rate of idiopathic pancreatitis was 8% in this series.[13] Whether so-called idiopathic pancreatitis is coincidental or can be considered a rare extraintestinal manifestation of inflammatory bowel disease remains a matter of debate. Seyrig and associates have reported the frequency of idiopathic pancreatitis associated with Crohn's disease to be only 1.5%.[14] In a series from our institution, the incidence of these two conditions was close to the rate found by Seyrig and colleagues, but no prospective data have been available until now.[6,7] AIP could represent approximately 2% of chronic pancreatitis and up to one third of idiopathic pancreatitis based upon pathologic examination.

The question of whether inflammatory bowel disease–related pancreatitis may be a special form of AIP is still being debated.[15] AIP and inflammatory bowel disease–related pancreatitis have similar pancreatic duct changes and histologic findings, when specimens are available. Ductal changes with mainly a diffuse irregular narrowing of the pancreatic duct, as reported in previous series, are considered to be characteristic of AIP in the European and Japanese literatures.[16-21] Histologic changes demonstrated in patients with AIP or inflammatory bowel disease–related patients who underwent surgical resection or biopsy because of pseudotumorous presentation were similar.[6,15,22-24] The pathogenesis of inflammatory bowel disease–related pancreatitis remains unknown. In the series conducted at our institution, pancreatic antibodies were found in 20.2% of patients but did not correlate with pancreatic insufficiency or pancreatic duct changes.[6,7] Stocker and coworkers demonstrated the presence of pancreatic antibodies in the sera of 4–39% of patients with inflammatory bowel disease.[25] The Crohn's disease–related autoantigen was demonstrated to be a component of normal pancreatic juice. Seibold and associates found the presence of pancreatic antibodies in the sera of 27% of 212 patients with Crohn's disease.[26] These pancreatic antibodies were directed against the exocrine pancreas and were located in the acinar lumen or acinar cells. However, a direct pathogenetic role for autoantibodies in inflammatory bowel disease–associated pancreatitis cannot be concluded. These autoantibodies may reflect an immune deregulation triggered by bowel mucosal ulcerations, or they may be due to cross reactivity, as it has been shown for other autoantibodies.[27]

The diagnosis of AIP during the course of inflammatory bowel disease is difficult because many cases have been attributed to drug intake. We previously demonstrated that approximately half of these cases were associated with pancreatic insufficiency (assessed with fecal elastase test), leading to the conclusion that half of these attacks of acute pancreatitis are likely related to AIP.[7] The clinical presentation could be a pseudotumorous pattern, acute pancreatitis, liver cholestasis, or abdominal pain with weight loss and steatorrhea. The methods for diagnosing AIP in a patient suffering from inflamma-

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tory bowel disease are not always specific or sensitive. In the literature, abnormal serum levels of amylase were shown in 5.8–15.8% of patients with ulcerative colitis or Crohn's disease.[28-30] Pancreatic insufficiency could be the most frequent feature in the case of pancreatitis related to inflammatory bowel disease. By using the secretin-cerulein test, Angelini and colleagues found a decrease in bicarbonate and enzyme output in 11 of 27 patients and an isolated decrease of lipase output in 18 of 27 patients in a series of 27 patients with inflammatory bowel disease.[31] Heikius and coworkers, in a series of patients with ulcerative colitis or Crohn's disease, found abnormal para-aminobenzoic acid test results in 21.8% and 26% of cases, respectively.[28] An increased serum level of immunoglobulin (Ig)G4 has been recently considered as a new biologic sign of autoimmunity in AIP that decreased with steroid therapy.[32-35] The increase of the IgG4 serum level has occurred in 71–92% of patients with AIP in the Japanese and American literatures and less frequently in the French.[4,7,32,35] The increased serum level of IgG4 should decrease with steroid treatment. The useful threshold of IgG4 levels range from 135 mg/L to 280 mg/L in the literature.[32-35]

The rate of pancreatic ductal changes in patients with inflammatory bowel disease remains controversial.[7,28] The rate found in our series was 10.8% and was not different in patients with or without a past history of pancreatitis. In the series by Heikius and associates, an 8.4% frequency of pancreatic duct abnormalities was found in patients with inflammatory bowel disease without a clear relationship to impaired exocrine function.[28] These anomalies included irregularities or short stenosis of the main pancreatic duct (MPD), which is the most frequent feature in our series, with a rate of 87% of all MPD irregularities or slight dilatation (≤4 mm).[2,3,15,17,28,32] In previous series, no cysts or calcifications were found, unlike in this series.[2,3,15,17,28,32] Stenosis or obstruction of the MPD or upstream dilation observed in some inflammatory bowel disease patients could, according to Ectors and colleagues,[36] be due to severe periductal inflammation. These authors demonstrated the presence of periductal lymphocytic inflammatory infiltrates as well as perilobular fibrosis often being more extensive than intralobular fibrosis and acinar fibrosis, and they concluded that ductal changes were the primary event of the inflammatory process.[36]

Useful imaging procedures for the diagnosis of AIP are computed tomography scan, magnetic resonance imaging, and endoscopic ultrasound, sometimes associated with fine-needle aspiration.[32] These criteria are lacking in the case described in this issue. Patients suffering from acute pancreatitis during inflammatory bowel disease should undergo serum measurement of IgG4, magnetic resonance imaging of the pancreas and, if possible, computed tomography scan and endoscopic ultrasound examination of the pancreas and bile duct. Thereafter, patients must be classified according to the HISORT classification criteria developed by the Mayo Clinic.[32] This classification is based upon pathologic criteria, biologic criteria (IgG4), radiologic criteria, and response to the steroid therapy, distributing the patients into three groups: A, B, C. This classification could improve with a 69% rate, the sensitivity for diagnosing AIP in the setting of idiopathic pancreatitis.

Finally, inflammatory bowel disease could become the most frequent disease associated with AIP. Autoimmune diseases are associated with 16–56% of the patients presenting with AIP.[6,7] In the literature, inflammatory bowel disease is associated with 13–17% of the AIP cases reported, reaching 38% in a recent multicenter French study.[5] Therefore, in patients suffering from inflammatory bowel disease, any acute pancreatitis has to be investigated, keeping in mind the diagnosis of AIP, which might represent 30–50% of the etiology overall.

References

1. Halabi IM. Ulcerative colitis presenting as acute pancreatitis in a 6-year-old patient. *Gastroenterol Hepatol.* 2009;5:429-430.
2. Toomey DP, Swan N, Torreggiani W, Conlon KC. Autoimmune pancreatitis. *Br J Surg.* 2007;94:1067-1074.
3. Finkelberg DL, Sahani D, Deshpande V, Brugge WR. Autoimmune pancreatitis. *N Engl J Med.* 2006;355:2670-2676.
4. Nahon-Uzan K, Levy P, O'Tolle D, Belmatoug N, Vuillerme MP, et al. Is idiopathic pancreatitis an autoimmune disease? *Clin Gastroenterol Hepatol.* 2005; 3:903-909.
5. Barthet M, Rebours V, Buscail L, Palazzo L, Alric L, et al. Autoimmune pancreatitis: results of a multicenter study from the French pancreatic club. *Gut.* 2007;39(S1):A177.
6. Barthet M, Hastier P, Bernard JP, Bordes G, Frederick J, et al. Chronic pancreatitis and inflammatory bowel disease: evidence for the existence of sclerosing pancreatitis? *Am J Gastroenterol.* 1999;94:2141-2148.
7. Barthet M, Lesavre N, Desplats-Jego S, Panuel M, Grimaud JC, et al. Frequency and characteristics of pancreatitis in patients with inflammatory bowel disease. *Pancreatology.* 2006;6:464-471.
8. Lankish PG, Droge M, Gottesleben F. Drug induced acute pancreatitis: incidence and severity. *Gut.* 1995;37:565-567.
9. Deprez P, Descamps CH, Fiasse R. Pancreatitis induced by 5-aminosalicylic acid. *Lancet.* 1989;2:445-446.
10. Altman HS, Philips G, Bank S, Klotz H. Pancreatitis associated with duodenal Crohn's disease. *Am J Gastroenterol.* 1983;78:174-177.
11. Legge DA, Hofman HN, Carlson HC. Pancreatitis as a complication of regional enteritis of the duodenum. *Gastroenterology.* 1971;61:834-837.
12. Matsumoto T, Matsui T, Iida M, Nunoi K, Fujishima M. Acute pancreatitis as a complication of Crohn's disease. *Am J Gastroenterol.* 1989;84:804-807.
13. Moolsintong P, Loftus EV, Chari ST, Egan LJ, Tremaine WJ, Sandborn WJ. Acute pancreatitis in patients with Crohn's disease: clinical features and outcomes. *Inflamm Bowel Dis.* 2005;11:1080-1084.
14. Seyrig JA, Jian R, Modigliani R, Golfai D, Florent CH, et al. Idiopathic pancreatitis associated with inflammatory bowel disease. *Dig Dis Sci.* 1985; 30:1121-1126.
15. Sahel J, Barthet M, Gasmi M. Autoimmune pancreatitis: increasing evidence for a clinical entity with various patterns. *Eur J Hepatogastroenterol.* 2004;16: 1265-1268.
16. Heikius B, Niemela S, Lehtola J, Karttunen KJ. Elevated pancreatic enzymes in inflammatory bowel disease are associated with extensive disease. *Am J Gastroenterol.* 1999;94:1062-1069.

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17. Horiuchi A, Kawa S, Akamatsu T, Aoki Y, Mukawa K, et al. Characteristic pancreatic duct appearance in autoimmune chronic pancreatitis: a case report and review of the Japanese literature. *Am J Gastroenterol.* 1998;93:260-263.
18. Furakawa N, Muranaka T, Yasumori K, Matsubayashi R, Hayashida K, Arita Y. Autoimmune pancreatitis: radiologic findings in three histologically proven cases. *J Comput Assit Tomogr*. 1998;22:880-883.
19. Yoshida K, Toki F, Takeuchi T, Watanabe QI, Shiratori K, Hayashi N. Chronic panceatitis caused by an autoimmune pancreatitis. *Dig Dis Sci.* 1995;40: 1561-1568.
20. Ito T, Nakano I, Koyanagi S, Miyahara T, Migita Y, et al. Autoimmune pancreatitis as a new clinical entity. Three cases of autoimmune pancreatitis with effective steroid therapy. *Dig Dis Sci*. 1997;42:1458-1468.
21. Ohana M, Okazaki K, Kobashi Y. Multiple pancreatic masses associated with autoimmunity. *Am J Gastroenterol.* 1998;93:99-102.
22. Barthet M, Dubucquoy L, Garcia S, Gasmi M, Desreumaux P, et al. Pancreatic changes in TNBS-induced colitis in mice. *Gastroenterol Clin Biol.* 2003;27: 895-900.
23. Grandval PH, Barthet M, Gargia S, Boustiere C, Poilroux B, et al. Pseudotumorous chronic pancreatitis associated with inflammatory bowel disease. *Dig Dis Sci.* 2001;46:898-900.
24. Wakabayashi T, Kawaura Y, Satomura Y, Fujii T, Motoo Y, et al. Clinical study of chronic pancreatitis with focal irregular narrowing of the main pancreatic duct and mass formation: Comparison with chronic pancreatitis showing diffuse irregular narrowing of the main pancreatic duct. *Pancreas.* 2002;25:283-289.
25. Stocker W, Otte M, Ulrich S, Normann D, Finkbeiner H, et al. Autoimmunity to pancreatic juice in Crohn's disease. *Scand J Gastroenterol.* 1987;22:41-52.
26. Seibold F, Mork H, Muller A, Holzhuter C, Weber P, Scheurlen M. Pancreatic autoantibodies in Crohn's disease: a family study. *Gut.* 1997;40:481-484.
27. Targan SR, Landers CJ, Cobb L, Mac Dermott RP, Vidrich A. Perinuclear anti-neutrophil cytoplasmic antibodies are spontaneously produced by mucosal B cells of ulcerative colitis patients. *J Immunol.* 1995;155:3262-3267.
28. Heikius B, Niemela S, Lehtola J, Karttunen T, Lahde S. Pancreatic duct abnormalities and pancreatic function in patients with chronic inflammatory bowel disease. *Scand J Gastroenterol*. 1996;31:517-523.
29. Tromm A, Höltmann B, Hüppe D, Kuntz HD, Schwegler U, May B. Hyperamylasemia, hyperlipasemia and acute pancreatitis in chronic inflammatory bowel diseases [in German]. *Leber Magen Darm*. 1991;21:15-22.
30. Katz S, Bank S, Greenberg R, Lendvai S, Lesser M, Napolitano B. Hyperamylasemia in inflammatory bowel disease. *J Clin Gastroenterol.* 1988;6:627-630.
31. Angelini G, Cavallini G, Bovo P, Brocco G, Castagnini A, et al. Pancreatic function in chronic inflammatory bowel disease. *Int J Pancreatol*. 1988;3:185-193.
32. Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, et al. Diagnosis of autoimmune pancreatitis. The Mayo Clinic experience. *Clin Gastroenterol Hepatol.* 2006;4:1010-1016.
33. Hamano H, Hawa S, Horiuchi A, Unno H, Furuya N, et al. High serum IgG4 concentrations in patients with sclerosing cholangitis. *N Engl J Med.* 2001; 344:732-738.
34. Choi EK, Kim MH, Lee TY, Kwon S, Oh HC, et al. The sensitivity and specificity of serum immunoglobulin G and immunoglobulin G4 leveles in the diagnosis of autoimmune pancreatitis: Korean experience. *Pancreas.* 2007;35: 156-161.
35. Ghazale A, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, et al. Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. *Am J Gastroenterol.* 2007;102:1646-1653.
36. Ectors N, Maillet B, Aerts R, Geboes K, Donner A, et al. Non-alcoholic duct destructive chronic pancreatitis. *Gut.* 1997;41:263-268.