

# Ulcerative Colitis Presenting as Acute Pancreatitis in a 6-Year-Old Patient

Issam M. Halabi, MD, FAAP

Department of Pediatric Gastroenterology,  
University of Illinois at Peoria

The association of pancreatitis and ulcerative colitis has been well described in the literature.<sup>1-11</sup> Most reported patients have experienced acute pancreatitis due to drug toxicity.<sup>1,5-9,11</sup> The association of pancreatic duct abnormalities and ulcerative colitis has also been described in the literature.<sup>12,13</sup> Idiopathic pancreatitis is the term used to describe pancreatitis when no causes or associations are identified.<sup>3</sup> We report the case of a young patient with acute idiopathic pancreatitis as a presentation of ulcerative colitis.

## Case Report

A 6-year-old girl presented with severe abdominal pain and bilious vomiting. There was no history of abdominal trauma or drug intake nor any family history of pancreatitis. Physical examination was remarkable for epigastric tenderness. Serum amylase measured 1,654 IU/L (normal, 5–83 IU/L), and lipase measured 2,343 IU/L (normal, 27–254 IU/L). Urinalysis, serum electrolytes, cholesterol, serum triglycerides, calcium, aspartate aminotransferase, alanine transaminase, bilirubin, alkaline phosphatase, blood urea nitrogen, and creatinine were all normal. Abdominal ultrasound demonstrated increased echogenicity and edema of the pancreas, but there were no biliary duct abnormalities or stones.

The patient was admitted to the hospital with nothing to eat. A central line was placed, with total parenteral nutrition and analgesia administered to the patient. She continued to be symptomatic, with no significant improvement in abdominal pain or pancreatic enzymes over the next week. On the eighth day of admission, the patient developed bloody diarrhea with lower abdominal cramping and tenesmus. Stool specimens for culture and *Clostridium difficile* infection were negative. Colonoscopy

revealed diffuse confluent inflammation of the colonic mucosa with ulcers extending from the rectum to mid-transverse colon. The ascending colon and rectum were spared, and terminal ileum intubation did not show any abnormality. Biopsies of the abnormal mucosa showed cryptitis and crypt abscesses with a predominance of chronic inflammatory cells. Inflammatory bowel disease serology was ordered. The result was positive for anti-neutrophil cytoplasmic antibodies. A diagnosis of ulcerative colitis was thus made based on the combination of clinical symptoms and signs and endoscopic, histologic, and serologic data.

Meanwhile, the patient was started on methylprednisolone sodium succinate (Solu-Medrol, Pharmacia & Upjohn) 1 mg/kg. Forty-eight hours later, the patient's amylase and lipase levels started to drop, and her abdominal pain improved. The number of stools decreased from 8 to 3 per day, free from blood. Over the next 3 days, the patient resumed a low-residue diet with normalization of pancreatic enzymes and no gastrointestinal symptoms. Magnetic resonance cholangiopancreatography (MRCP) was performed 2 weeks later and did not show any abnormalities in the pancreatic or biliary ducts. The patient was followed for the next 3 years. She did not develop any more episodes of pancreatitis, and her ulcerative colitis remained in remission on mesalamine.

## Discussion

A thorough review of the literature was conducted to identify children with reports of pancreatitis in association with ulcerative colitis. Prior to our patient, the youngest child previously reported was 15 years old and was on mesalamine for 2 weeks prior to presentation.<sup>1</sup>

Identifiable causes of acute pancreatitis include trauma in 13–20% of cases, infection in 3–15%, biliary tract disease in 10–14%, drugs in 11–13%, hereditary predisposition in 7–10%, congenital anomalies in 5%, hypercalcemia in 1–3%, hypertriglyceridemia in up to 3%, and cystic fibrosis in even fewer cases.<sup>14,15</sup> In our

Address correspondence to:

Dr. Issam Halabi, Professor and Chief, Department of Pediatric Gastroenterology,  
420 N E Glen Oak Ave, Suite 401, Peoria, IL 61603; Tel: 309-573-5373;  
Fax: 309-624-3273; E-mail: ihalabi@uicomp.uic.edu

patient, however, no cause was identified. Drugs used in ulcerative colitis and implicated in the etiology include: 6-mercaptopurine,<sup>5</sup> mesalamine,<sup>1,6,7,9,11</sup> steroids,<sup>8,11</sup> and metronidazole.<sup>10,11</sup> Our patient was not on any of these medications and did not have any of the predisposing factors. In addition, MRCP ruled out any pancreatic or biliary duct abnormalities, unlike the cases previously reported.<sup>12,13</sup>

It remains a matter of debate whether idiopathic pancreatitis is coincidental or can be considered a rare extraintestinal manifestation of inflammatory bowel disease.<sup>16</sup> Autopsy studies in ulcerative colitis have revealed the presence of macroscopic or microscopic pancreatic lesions in 14–53% of 86 cases.<sup>17</sup> As in this case report, only 1 previously reported case had similar simultaneous presentation.<sup>4</sup> However, this patient was 57 years old. In all other reported cases, there was a significant length of time between the episode of pancreatitis and the onset of ulcerative colitis,<sup>2,3</sup> or the patient had been on medications as mentioned earlier. Furthermore, our patient did not experience a recurrence of her pancreatitis as long as her ulcerative colitis was in remission.

It has been speculated that papillary edema due to duodenal mucosal involvement in Crohn's disease may comprise the pathophysiology of associated idiopathic pancreatitis.<sup>18</sup> Such an etiology is not valid in ulcerative colitis because of the absence of duodenal involvement.

## Conclusion

Although rare, acute idiopathic pancreatitis can be a presentation of ulcerative colitis. Pediatric gastroenterologists are urged to consider expanding the work-up of acute idiopathic pancreatitis to include screening for ulcerative colitis when management of the condition does not result in clinical improvement. Prospective controlled trials are needed in this age group to attempt to determine the frequency. This will direct further recommendations in regard to guidelines for such screen-

ing. Studies that seek the possible pathophysiology of such associations are also needed.

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# Review

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

Marc Barthelet, MD

*Department of Gastroenterology and Hepatology,  
Hôpital Nord, Marseille, France*

Halabi reported a case of acute pancreatitis with concomitant ulcerative colitis in a 6-year-old girl.<sup>1</sup> 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).<sup>2–5</sup> 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.<sup>6,7</sup>

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.<sup>8,9</sup> Duodenal reflux or papillary obstruction was also potentially considered responsible for pancreatitis observed during inflammatory bowel disease.<sup>10–12</sup> A large recent series has evaluated the etiology and outcome of acute pancreatitis occurring during the course of Crohn's disease.<sup>13</sup> 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.<sup>13</sup> 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%.<sup>14</sup> 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.<sup>6,7</sup> 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.<sup>15</sup> 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.<sup>16–21</sup> 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.<sup>6,15,22–24</sup> 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.<sup>6,7</sup> Stocker and coworkers demonstrated the presence of pancreatic antibodies in the sera of 4–39% of patients with inflammatory bowel disease.<sup>25</sup> 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.<sup>26</sup> 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.<sup>27</sup>

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.<sup>7</sup> 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-

Address correspondence to: Dr. Marc Barthelet, Department of Gastroenterology and Hepatology, Hôpital Nord, Chemin des Bourrelly, 13915 Marseille cedex 20, France; Tel: 00 33 4 91 96 87 37; Fax: 00 33 4 91 96 13 11; E-mail: marc.barthelet@ap-hm.fr

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.<sup>28-30</sup> Pancreatic insufficiency could be the most frequent feature in the case of pancreatitis related to inflammatory bowel disease. By using the secretin-creolein 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.<sup>31</sup> 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.<sup>28</sup> 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.<sup>32-35</sup> 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.<sup>4,7,32,35</sup> 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.<sup>32-35</sup>

The rate of pancreatic ductal changes in patients with inflammatory bowel disease remains controversial.<sup>7,28</sup> 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.<sup>28</sup> 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 ( $\leq 4$  mm).<sup>2,3,15,17,28,32</sup> In previous series, no cysts or calcifications were found, unlike in this series.<sup>2,3,15,17,28,32</sup> Stenosis or obstruction of the MPD or upstream dilation observed in some inflammatory bowel disease patients could, according to Ectors and colleagues,<sup>36</sup> 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.<sup>36</sup>

Useful imaging procedures for the diagnosis of AIP are computed tomography scan, magnetic resonance imaging, and endoscopic ultrasound, sometimes associated with fine-needle aspiration.<sup>32</sup> 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.<sup>32</sup> 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.<sup>6,7</sup> In the literature, inflammatory bowel disease is associated with 13–17% of the AIP cases reported, reaching 38% in a recent multicenter French study.<sup>5</sup> 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.

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