CASE REPORT

Presymptomatic Crohn’s Disease in a Young Patient Diagnosed Just After the Onset of Idiopathic Acute Pancreatitis

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Abstract:
Acute pancreatitis is an extraintestinal manifestation of inflammatory bowel disease. There have been few reports describing acute pancreatitis preceding a diagnosis of inflammatory bowel disease. We herein report a rare case of a 16-year-old boy with presymptomatic Crohn’s disease that was newly diagnosed just after the onset of idiopathic acute pancreatitis. Crohn’s disease of any stage, much less in the presymptomatic stage, is rarely diagnosed just after the development of acute pancreatitis. The present case suggests that acute pancreatitis without an apparent cause in young or pediatric population can precede a diagnosis of presymptomatic Crohn’s disease.

Key words: inflammatory bowel disease, crohn’s disease, acute pancreatitis, extraintestinal manifestation, presymptomatic

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Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract with unknown etiology. IBD includes two major diseases of ulcerative colitis (UC) and Crohn’s disease (CD) and may be regarded as a systemic disease because patients occasionally develop extraintestinal manifestations (EIMs). Previous studies have indicated that between 6% and 47% of IBD patients experience EIMs, such as joint, skin, ocular, oral, hepatobiliary, and pancreatic disorders (1).

Acute pancreatitis (AP) is a rare EIM associated with IBD (2, 3). AP is known to develop more frequently in patients with CD than in those with UC, and its incidence rate in CD has been reported to range from 1.4% to 4.3% (4, 5). More than 70% of EIMs develop after a diagnosis of IBD (6). Likewise, AP as an EIM usually presents after the diagnosis of IBD. A previous study described a very low frequency of AP that preceded the diagnosis of IBD (7). Therefore, diagnosing CD in the preclinical stage after AP is extremely rare. Since CD is usually diagnosed in patients presenting with associated clinical symptoms, such as diarrhea, abdominal pain, or perianal pain, a first diagnosis at the presymptomatic or asymptomatic stage itself is unusual.

We herein report a rare case of presymptomatic CD that was newly diagnosed just after the onset of idiopathic AP. This case report was approved by the institutional ethics committee, and informed consent was provided by the patient.

Case Report

A 16-year-old boy was emergently admitted to our hospital complaining of severe epigastric pain and a fever lasting for 2 days. The patient had no previous illness or remark-
Serum IgG4 levels were within the normal range. Magnetic resonance imaging of the pancreas revealed an increased signal intensity on T2-weighted images, raising the suspicion of idiopathic AP. Screening for autoimmune pancreatitis (AIP) indicated that there were no specific causes for AP, we finally diagnosed the patient with idiopathic AP. However, we were unable to identify any common causes of AP, such as biliary stones, intake of alcohol, congenital pancreaticobiliary malformation, history of medication, or hypertriglyceridemia. Screening for autoimmune pancreatitis (AIP) indicated that serum IgG4 levels were within the normal range. Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) performed on the 11th hospital day revealed normal findings in the pancreatic parenchyma and duct (Fig. 2). There were no findings suggesting AIP, such as parenchymal enlargement, stricture, or narrowing of the pancreatic duct. Based on the lack of evidence for any specific causes for AP, we finally diagnosed the patient with idiopathic AP.

The patient’s anemia prompted us to perform an endoscopic screening of the gastrointestinal tract after the pain had improved. Ileocolonoscopy (ICS) revealed longitudinal erosions and ulcers in the terminal ileum, ulcers with a cobblestone appearance in the cecum, longitudinal ulcers in the ascending colon, and a deep ulcer in the rectum (Fig. 3). Esophagogastroduodenoscopy (EGD) revealed edematous changes in the cardiac lesion of the stomach, which was similar to the bamboo joint-like appearance characteristic of CD. Erosions were also present in the duodenum (Fig. 4). Small-bowel capsule endoscopy (SBCE) revealed multiple small discrete ulcers mainly in the ileum (Fig. 4). A histological examination of the ileum and colon showed the marked infiltration of lymphocytes and plasma cells in the lamina propria (Fig. 5). There were no additional findings suggestive of infectious diseases, including tuberculosis. Based on these findings, we diagnosed the patient with CD. We also concluded that the patient’s AP was an EIM of CD.

We initiated treatment for CD with oral 5-aminosalicylic acid (5-ASA) and oral budesonide. The patient had no recurrence of pancreatitis and was discharged on the 29th hospital day. The serum albumin and C-reactive protein (CRP) levels normalized after the administration of oral budesonide.

Table. Laboratory Data on Admission

| WBC | 14,500 μL | AST | 15 IU/L | TP | 6.6 g/dL |
|-----|----------|-----|----------|----|----------|
| Neut | 85.8 % | ALT | 9 IU/L | Alb | 2.8 g/dL |
| Eosi | 0.1 % | LDH | 196 IU/L | T-Chol | 150 mg/dL |
| Baso | 0.2 % | T-Bil | 1.1 mg/dL | TG | 132 mg/dL |
| Lymph | 5 % | D-Bil | 0.1 mg/dL | HDL-C | 24 mg/dL |
| Mono | 8.9 % | ALP | 245 U/L | FBS | 90 mg/dL |
| RBC | 412 x10^12/L | γ-GTP | 24 IU/L | HbA1c | 5.5 % |
| Hb | 10.5 g/dL | S-AMY | 220 U/L | |
| Ht | 33.2 % | Lipase | 353 U/L | CRP | 31.4 mg/dL |
| MCV | 80.6 fl | BUN | 11.4 mg/dL | IgG | 1,442 mg/dL |
| MCH | 25.5 pg | Cr | 0.6 mg/dL | IgA | 155 mg/dL |
| MCHC | 31.6 % | Na | 133 mEq/L | IgM | 67 mg/dL |
| plt | 41.3 x10^12/L | K | 4.2 mEq/L | IgG4 | 46 mg/dL |
| Cl | 96 mEq/L | Ca | 8.9 mg/dL | |

WBC: white blood cells, Neut: neutrophils, Eosi: eosinophils, Baso: basophils, Lymph: lymphocytes, Mono: monocytes, RBC: red blood cells, Hb: hemoglobin, Ht: Hematocrit, MCV: mean corpuscular volume, MC: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, Pt: platelets, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, T-Bil: total bilirubin, D-Bil: direct bilirubin, ALP: alkaline phosphatase, γ-GTP: gamma-glutamyl transpeptidase, S-AMY: serum amylase, BUN: blood urea nitrogen, Cr: creatinine, Na: sodium, K: potassium, Cl: chloride, Ca: calcium, TP: total protein, Alb: albumin, T-chol: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, FBS: fasting blood sugar, HbA1c: hemoglobin Al c, CRP: C-reactive protein, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, IgG4: immunoglobulin G4

At admission, he was 170.0 cm tall and weighed 54.4 kg, with a body mass index of 18.8. The body temperature was 38.0°C. A physical examination revealed strong tenderness in the epigastric region. The laboratory data revealed elevated white blood cell counts, anemia, elevated platelet counts, elevated serum amylase and lipase levels, hyperalbuminemia, decreased sodium and chloride levels, and elevated C-reactive protein levels (Table). Abdominal contrast-enhanced computed tomography (CT) revealed interstitial edematous pancreatitis with acute peripancreatic fluid collection (Fig. 1). Based on the patient’s clinical symptoms, laboratory data, and contrast-enhanced CT findings, we diagnosed him with AP.

We commenced conservative medical treatment, which included adequate fluid therapy, and the patient’s symptoms immediately resolved. The AP improved within a week without any sign of organ failure or local complication. He was able to recommence eating with no recurrence of abdominal pain. In parallel with the medical treatment, we also investigated the cause of the AP. However, we were unable to identify any common causes of AP, such as biliary stones, intake of alcohol, congenital pancreaticobiliary malformation, history of medication, or hypertriglyceridemia. Screening for autoimmune pancreatitis (AIP) indicated that serum IgG4 levels were within the normal range.
Discussion

We herein report a rare case of presymptomatic CD that was first diagnosed soon after the development of idiopathic AP. As the diagnosis of presymptomatic or asymptomatic CD is extremely rare, our case has important implications for the diagnosis of IBD preceded by its EIMs.

It is important to recognize that CD is a chronic progressive and destructive condition that can cause irreversible bowel damage or dysfunction. Recently, treatment strategies for CD have shifted from the mere control of symptoms toward blocking disease progression in order to prevent permanent bowel damage. Starting effective treatments at an early disease stage, during the so-called ‘window of opportunity’, can help prevent disease progression and reduce bowel damage (8). Thus, the diagnosis of CD in the early clinical stages allows for prompt intervention that can lead to a better long-term prognosis. In the present case, we were able to diagnose the patient with CD in the presymptomatic stage. Therefore, despite the absence of any clinical symptoms associated with CD, we were able to administer medication to prevent disease progression. We believe that this...
Figure 3. Endoscopic findings of the ileum, colon, and rectum. (A, B) The images show longitudinal erosions and ulcers in the ileum. (C) This image shows ulcers with a cobblestone appearance in the cecum. (D, E) These images show longitudinal ulcers in the ascending colon. (F) This image shows a deep ulcer in the rectum. Ileocolonoscopy revealed longitudinal erosions and ulcers in the terminal ileum, ulcers with a cobblestone appearance in the cecum, longitudinal ulcers in the ascending colon, and a deep ulcer in the rectum. These findings are consistent with Crohn’s disease.

Figure 4. Endoscopic findings of the upper gastrointestinal tract and small intestine. (A) This picture shows edematous changes in the cardiac lesion of the stomach, similar to the bamboo joint-like appearance characteristic of CD. (B, C) These images show erosion in the duodenum. (D) The papilla of Vater in the duodenum appeared to be normal. (E, F) These images show multiple discrete ulcers, mainly in the ileum. Esophagogastroduodenoscopy (EGD) revealed edematous changes in the cardiac lesion of the stomach, similar to the bamboo joint-like appearance characteristic of CD. Erosions were also present in the duodenum. Small-bowel capsule endoscopy (SBCE) revealed multiple small discrete ulcers mainly in the ileum.
CD patients tend to develop AP more frequently than UC patients (2). More than 70% of EIMs develop after the diagnosis of IBD (6), and only one quarter of EIMs appear prior to the IBD diagnosis (1). There are very few reports that describe AP presenting as an EIM prior to a diagnosis of IBD; however, we found one noteworthy study that investigated the frequency of AP preceding the diagnosis of IBD. The study retrospectively surveyed 3,960 IBD patients and found only 12 patients (0.3%) in whom AP preceded the diagnosis of IBD (7). In that study, the incidence rate of AP preceding the diagnosis of IBD was higher in pediatric patients (10 in 440 patients; 2.17%) than in adult patients (2 in 3,500 patients; 0.06%) (7). The median lag time between the episode of AP and the diagnosis of IBD was found to be 24 weeks (range: 1-156) (7). This evidence suggests that any diagnosis of CD after the development of AP is rare, much less CD in the presymptomatic stage. In the present case, the interval from the onset of AP to the diagnosis of CD was about three weeks. This suggests that asymptomatic CD had been present before the onset of AP; however, it was difficult to estimate the duration of CD before the AP onset.

CD is usually diagnosed in cases with associated clinical symptoms, such as diarrhea, abdominal pain, body weight loss, anal pain, and perianal discharge. The initial diagnosis of CD in the absence of any related symptoms occurs only very rarely. Therefore, after making the diagnosis of CD, we carefully asked the patient again if he had any chronic symptoms, including diarrhea, abdominal pain, perianal pain, or weight loss. Based on the precise re-interview, we confirmed that there had certainly been no symptoms associated with CD before the onset of AP. It is generally known that endoscopic lesions precede the symptomatic manifestations in the clinical practice of IBD; we therefore consider the presence of endoscopic findings to not necessarily be accompanied by any CD-related symptoms. Our case may be considered extremely rare since CD was unexpectedly diagnosed in the presymptomatic stage by endoscopic screening of the gastrointestinal tract after the development of idiopathic AP. In our patient, the presence of anemia prompted an examination of the gastrointestinal tract, resulting in the diagnosis of CD. From a retrospective review of the abdominal CT findings at admission, partial wall thickening and contrast enhancement in the ileocecal regions were found, which were regarded as the involved lesions of CD. The findings of this case report together with those of the previously mentioned study (7) suggest that the possibility of underlying IBD should be considered, especially in young or pediatric patients with idiopathic AP. Screening for IBD should be recommended for these patients, particularly if they exhibit suggestive symptoms, abnormal laboratory data, or abnormal cross-sectional images of the gastrointestinal tract indicative of IBD.

It is also important to examine the causes of AP in IBD. Common causes of AP in the general population include biliary stones, alcohol consumption, endoscopic retrograde cholangiopancreatography, pancreaticobiliary malformation, and hypertriglyceridemia. In our case, we failed to find any evidence of these common contributors to AP. In IBD patients, other special factors can contribute to the development of AP, such as medications for IBD, duodenal papillary involvement in CD, primary sclerosing cholangitis, and AIP. In recent years, increasing attention has been paid to AIP as a cause of pancreatitis in IBD. AIP is defined as a distinct form of pancreatitis characterized by frequent presentation with obstructive jaundice with or without a pancreatic mass, histologically by a lymphoplasmacytic infiltrate and fibrosis, and therapeutically by a dramatic response to steroids (11). AIP can be classified into two subtypes (Type 1 and Type 2) and can be diagnosed using international consensus diagnostic criteria (ICDC) for AIP (11). Type 1 AIP has been regarded as a pancreatic manifestation of systemic IgG4-related disease. Type 2 AIP is not correlated with IgG4 and is characterized by the presence of an abnormality in the pancreas and its ducts on imaging, histological duct-centric
pancreatitis with granulocyte infiltration, and response to steroids. IBD patients can develop both types of AIP but more frequently develop Type 2 AIP, especially patients with UC (12). Type 2 AIP in CD is reported to be extremely rare, especially in the Asian population (13, 14). Follow-up observations in our patient did not reveal any typical findings of either Type 1 or Type 2 AIP, such as pancreatic parenchymal enlargement and main pancreatic duct stricture. After ruling out the various possible causes of AP in our patient, we diagnosed him with idiopathic AP. Because the patient was shown to have early-stage CD as a background, we regarded the AP as an EIM of CD. Our patient has not developed recurrence of pancreatitis for more than one year since the initial attack. The patient’s CD remained in a state of clinical and endoscopic remission at one year after the diagnosis. Since the patient’s AP was regarded as idiopathic and there have been few reports concerning the recurrence rate of idiopathic AP in IBD, careful follow-up, including the surveillance of pancreatic enzymes and pancreatic imaging tests, will be required for our patient.

In conclusion, we herein report a rare case of a young patient with presymptomatic CD newly diagnosed soon after the development of idiopathic AP. Any diagnosis of CD just after the development of AP is rare, much less CD in the presymptomatic stage. Making a new diagnosis and starting medications for CD in the early stages can prevent disease progression and improve the long-term prognosis. The present case suggests that AP without an apparent cause in a young or pediatric case can suggest a diagnosis of presymptomatic CD. The possibility of underlying IBD should be considered, especially for young or pediatric patients with idiopathic AP. Screening for IBD is recommended if these patients have suggestive symptoms, abnormal laboratory data, or abnormal cross-sectional images of the gastrointestinal tract indicative of IBD.

The authors state that they have no Conflict of Interest (COI).

References

1. Vavricka SR, Schoepfer A, Scharl M, Lakatos PL, Navarini A, Rogler G. Extraintestinal manifestations of inflammatory bowel disease. Inflamm Bowel Dis 21: 1982-1992, 2015.
2. Foussakis FS, Theopistos VI, Katsanos KH, Christodoulou DK. Pancreatic involvement in inflammatory bowel disease: a review. J Clin Med Res 10: 743-751, 2018.
3. Iida T, Wagatsuma K, Hirayama D, Yokoyama Y, Nakase H. The etiology of pancreatic manifestations in patients with inflammatory bowel disease. J Clin Med 8: 916, 2019.
4. Bermejo F, Lopez-Sanroman A, Taxonera C, et al. Acute pancreatitis in inflammatory bowel disease, with special reference to azathioprine-induced pancreatitis. Aliment Pharmacol Ther 28: 623-628, 2008.
5. Rasmussen HH, Fonager K, Sorensen HT, Pedersen L, Dahlerup JF, Steffensen FH. Risk of acute pancreatitis in patients with chronic inflammatory bowel disease. A Danish 16-year nationwide follow-up study. Scand J Gastroen 34: 199-201, 1999.
6. Vavricka SR, Rogler G, Gantenbein C, et al. Chronological order of appearance of extraintestinal manifestations relative to the time of IBD diagnosis in the Swiss inflammatory bowel disease cohort. Inflamm Bowel Dis 21: 1794-1800, 2015.
7. Broide E, Dotan I, Weiss B, et al. Idiopathic pancreatitis preceding the diagnosis of inflammatory bowel disease is more frequent in pediatric patients. J Pediatr Gastroent Nutr 52: 714-717, 2011.
8. Colombel JF, Narula N, Peyrin-Biroulet L. Management strategies to improve outcomes of patients with inflammatory bowel diseases. Gastroenterology 152: 351-361.e355, 2017.
9. Heikius B, Niemela S, Lehtola J, Karttunen TJ. Elevated pancreatic enzymes in inflammatory bowel disease are associated with extensive disease. Am J Gastroent 94: 1062-1069, 1999.
10. Chen YT, Su JS, Tseng CW, Chen CC, Lin CL, Kao CH. Inflammatory bowel disease on the risk of acute pancreatitis: a population-based cohort study. J Gastroen Hepatol 31: 782-787, 2016.
11. Shimosegawa T, Char ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas 40: 352-358, 2011.
12. Tsen A, Alishahi Y, Rosenkranz L. Autoimmune pancreatitis and inflammatory bowel disease: an updated review. J Clin Gastroenterol 51: 208-214, 2017.
13. Ueki T, Kawamoto K, Otsuka Y, et al. Prevalence and clinicopathological features of autoimmune pancreatitis in Japanese patients with inflammatory bowel disease. Pancreas 44: 434-440, 2015.
14. Suk Lee Y, Kim NH, Hyuk Son J, et al. Type 2 autoimmune pancreatitis with Crohn’s disease. Intern Med 57: 2957-2962, 2018.

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