【 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-

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 ×10^4/µL	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 ×10^4/µL	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: eonsinophils, Baso: basophils, Lymph: lympho-cytes, Mono: monocytes, RBC: red blood cells, Hb: hemoglobin, Ht: Hematocrit, MCV: mean cor-puscular volume, MC: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin con-centration, Plt: 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 creati-nine, 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, HbAl c: hemoglobin Al c, CRP: C-reactive protein, IgG: immunoglobulin G, IgA: immuno-globulin A, IgM: immunoglobulin M, IgG4: immunoglobin G4

able family history, including pancreatic disease or IBD. Prior to the onset of the epigastric pain and fever, there had been no symptoms suggestive of CD, such as diarrhea, ab-dominal pain, or perianal pain.

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℃. A physical examination revealed strong tenderness in the epigastric region. The laboratory data revealed ele-vated white blood cell counts, anemia, elevated platelet counts, elevated serum amylase and lipase levels, hypoalbu-minemia, 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 collec-tion (Fig. 1). Based on the patient's clinical symptoms, labo-ratory data, and contrast-enhanced CT findings, we diag-nosed him with AP.

We commenced conservative medical treatment, which in-cluded 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 ab-dominal pain. In parallel with the medical treatment, we also investigated the cause of the AP. However, we were un-able to identify any common causes of AP, such as biliary stones, intake of alcohol, congenital pancreaticobiliary mal-formation, 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 cholan-

giopancreatography (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 endo-scopic screening of the gastrointestinal tract after the pan-creatitis had improved. Ileocolonoscopy (ICS) revealed lon-gitudinal erosions and ulcers in the terminal ileum, ulcers with a cobblestone appearance in the cecum, longitudinal ul-cers in the ascending colon, and a deep ulcer in the rectum (Fig. 3). Esophagogastroduodenoscopy (EGD) revealed ede-matous changes in the cardiac lesion of the stomach, which was similar to the bamboo joint-like appearance characteris-tic 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 find-ings 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 re-currence of pancreatitis and was discharged on the 29th hos-pital day. The serum albumin and C-reactive protein (CRP) levels normalized after the administration of oral budesonide
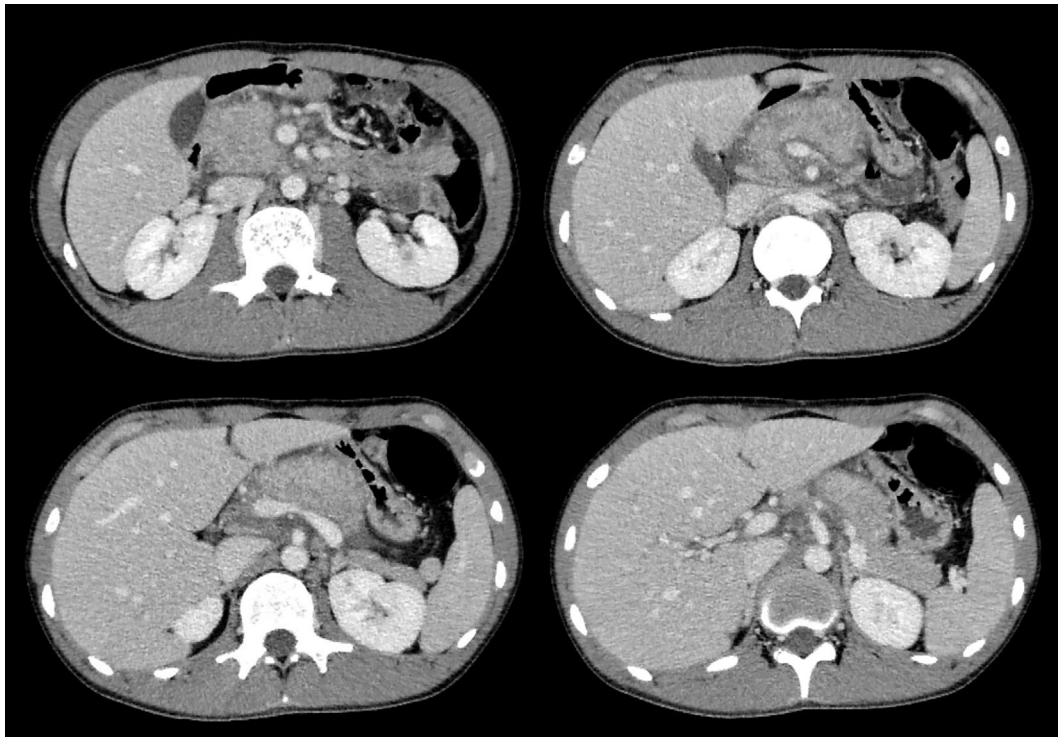
Figure 1. Abdominal contrast-enhanced computed tomography scan at admission. Abdominal contrast-enhanced computed tomography (CT) revealed interstitial edematous pancreatitis with acute peripancreatic fluid collection, supporting the diagnosis of acute pancreatitis.
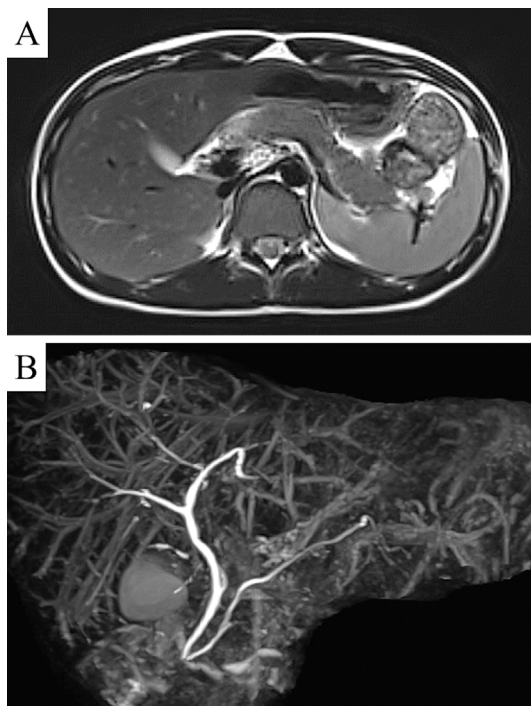

Figure 2. Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) images taken on hospital day 11. (A) Axial T2-weighted imaging showed normal pancreatic parenchyma. (B) MRCP showing normal pancreatic and bile ducts. MRI and MRCP on hospital day 11 showed a normal pancreatic parenchyma and normal pancreatic and bile duct findings with no biliary stones present in the common bile duct.

for eight weeks, and maintenance therapy with oral 5-ASA was continued. At one year after the diagnosis of CD, endoscopic remission with mucosal healing was confirmed by EGD, SBCE, and ICS. No recurrence of pancreatitis has been observed for more than one year since the initial attack of AP.

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 disfunction. 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
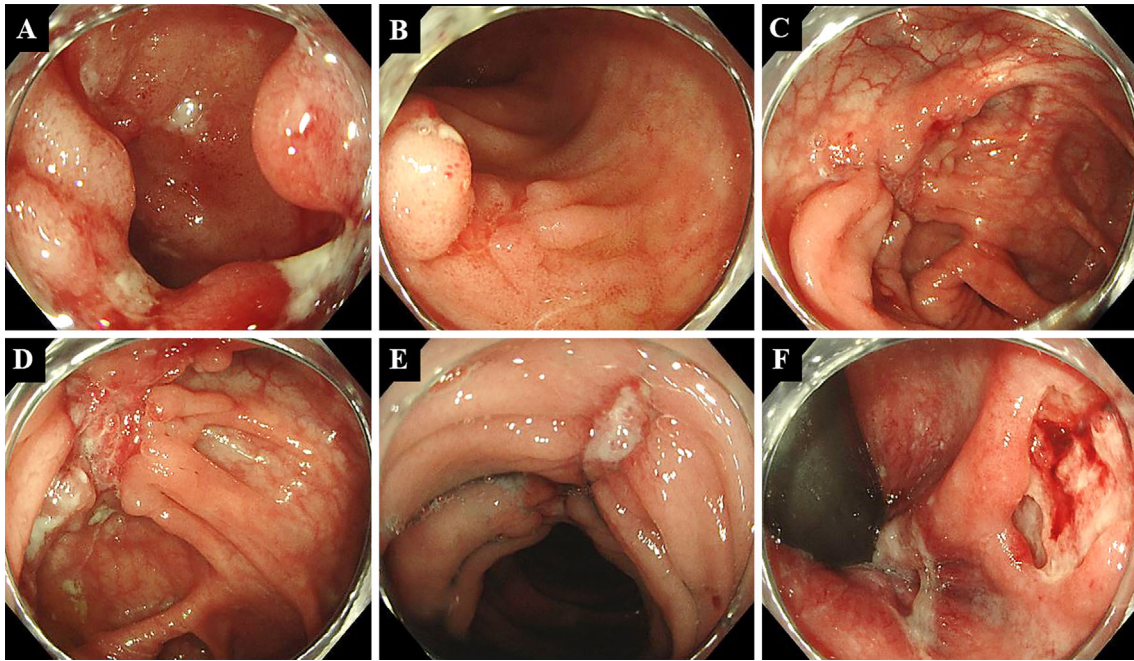
Figure 3. Endoscopic findings of the ileum, colon, and rectum. (A, B) The images show longitudinal erosions and ulcers in the ileum. (C) This image shows ulcers with a cobblestone appearance in the cecum. (D, E) These images show longitudinal ulcers in the ascending colon. (F) This image shows a deep 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.
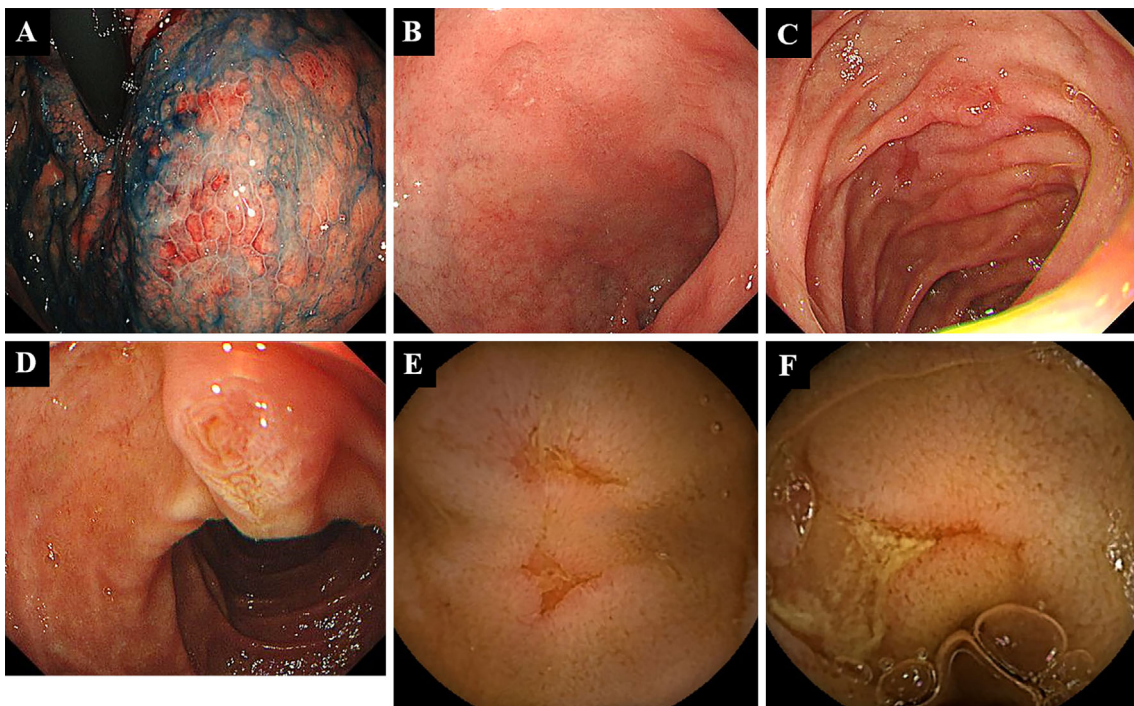

Figure 4. Endoscopic findings of the upper gastrointestinal tract and small intestine. (A) This picture shows edematous changes in the cardiac lesion of the stomach, similar to the bamboo joint-like appearance characteristic of CD. (B, C) These images show erosion in the duodenum. (D) The papilla of 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.
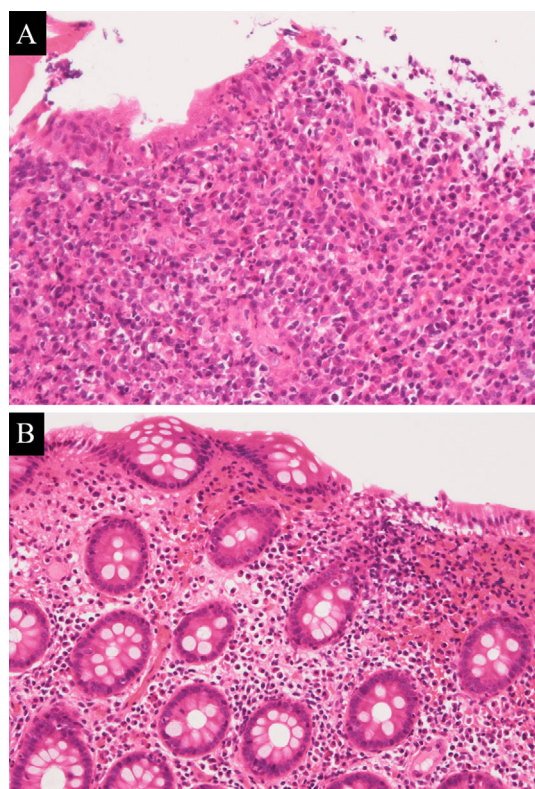
Figure 5. Pathological findings of the biopsy specimens. (A) This picture shows ileum tissue with Hematoxylin and Eosin (H&E) staining. (B) This image shows tissue from the ascending colon with H&E staining. A histological examination of the ileum and ascending colon showed the marked infiltration of lymphocytes and plasma cells in the lamina propria. No noncaseating epithelioid cell granulomas were identified in the specimens.

timely management strategy can improve the long-term outcome of his disease.

AP is a rare EIM in IBD patients, but it is known to have a higher incidence rate in IBD patients than in the general population (5, 9, 10). 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 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.

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