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Acute Pancreatitis due to pH-Dependent Mesalazine That Occurred in the Course of Ulcerative Colitis

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Key Words
Ulcerative colitis · Pancreatitis · Mesalazine

Abstract
We report the case of a 26-year-old male who presented with acute pancreatitis during the course of treatment for pancolitic ulcerative colitis (UC) with a time-dependent mesalazine formulation, prednisolone and azathioprine (AZA). Despite a review of his clinical history and various tests, the cause of pancreatitis could not be determined. Since drug-induced pancreatitis was considered possible, administration of the time-dependent mesalazine preparation and AZA was discontinued, and conservative treatment for acute pancreatitis was performed. The pancreatitis promptly improved with these treatments, but drug lymphocyte stimulation test (DLST) for both the time-dependent mesalazine formulation and AZA was negative. A pH-dependent mesalazine formulation was given for maintenance therapy of UC. Subsequently, as the pancreatitis relapsed, drug-induced pancreatitis was strongly suspected. Administration of mesalazine was discontinued, and pancreatitis was smoothly in remission by conservative treatment. According to the positive DLST result for the pH-dependent mesalazine formulation and the clinical course, a diagnosis of pH-dependent mesalazine-induced pancreatitis due to this formulation was made. During the clinical course of UC, occurrence of drug-induced pancreatitis must always be considered.

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Introduction

Pancreatitis is known to occur more frequently in patients with ulcerative colitis (UC) than in healthy individuals. The incidence of acute pancreatitis is 1.5–3.5% in patients with inflammatory bowel disease [1, 2]. Pancreatitis is an extraintestinal complication of UC. In addition, drug-induced pancreatitis is caused by adverse effects of various drugs used to treat UC, so it might be difficult to distinguish these two causes of pancreatitis in patients with UC. Azathioprine (AZA), prednisolone (PSL) and mesalazine, which are usually taken for inflammatory bowel disease, have been reported to be drugs that can possibly cause pancreatitis. Mesalazine is the most widely used first-choice drug for treatment of inflammatory bowel disease. It is a bowel-specific aminosalicylate drug and is metabolized in the gut, and thereby has fewer systemic side effects. However there are some reports of acute pancreatitis caused by this drug [3]. In Japan, two types of mesalazine with different outer chemical coating are used: time-dependent (Pentasa®) and pH-dependent mesalazine (Asacol®).

Presented in this report is a case of acute pancreatitis occurring during the course of treatment for UC with both time- and pH-dependent mesalazine. A final diagnosis of mesalazine-induced acute pancreatitis was made due to the clinical course and laboratory data which included the drug lymphocyte stimulation test (DLST).

Case Report

The patient was a 26-year-old male. He had been healthy, but consulted our hospital with a chief complaint of bloody stools for 6 months, and was hospitalized due to severe anemia (hemoglobin 5.4 g/dl). Endoscopic investigation revealed moderate active pancolitis-type UC (**fig. 1**a). Treatment with both an intensive intravenous regimen of 60 mg (1 mg/kg body weight) PSL per day and leukocytapheresis was carried out. His symptoms began to be alleviated, his laboratory data improved, and the dosage of PSL was gradually reduced. As maintenance therapy, oral administration of a time-dependent mesalazine preparation at 4,000 mg/day was started. Just after decreasing the dosage of PSL to 15 mg, his symptoms, including bloody stools and frequent diarrhea, appeared again. As recurrence of UC was suspected, the dosage of PSL was increased and AZA was added at 50 mg/day. His symptoms of bloody stools and frequent diarrhea both improved with these additional therapies. However, he asked for emergency consultation with sudden abdominal pain and a high fever 1 month after receiving these additional therapies. He was admitted with a diagnosis of mild acute pancreatitis because of his high serum amylase (792 IU/l) and the finding of a swollen pancreas on abdominal contrast-enhanced CT (**fig. 2**a, b). Since drug-induced pancreatitis is possible with time-dependent mesalazine formulation and AZA, both drugs were discontinued despite the negative results of the DLST. He was discharged from our hospital as his symptoms had completely disappeared and there were no abnormal findings on both abdominal ultrasonographic examination and magnetic resonance cholangiopancreatography. After discharge, administration of low-dose salazosulfapyridine was started for maintenance therapy of UC. That formulation was switched to a pH-dependent mesalazine formulation at 2,400 mg/day because liver damage due to salazosulfapyridine was suspected after several weeks. After this change in drug regimen, abdominal pain gradually appeared. After 2 weeks of treatment with pH-dependent mesalazine, serum amylase increased again to 1,555 IU/l. A second episode of acute pancreatitis was then diagnosed, and the patient was readmitted. Abdominal contrast-enhanced CT images revealed enlargement of the entire pancreas, but no turbidity in the adipose tissue around the pancreas (fig. 2c). His clinical course (**fig. 3**) suggested drug-induced pancreatitis due to the pH-dependent mesalazine formulation because his acute pancreatitis became worse just after the change of drug regimen. Conservative treatment resulted in rapid improvement in his symptoms and laboratory data, with normalization of amylase 4 days after drug discontinuation. The DLST of the pH-dependent mesalazine preparation was strongly positive with a stimulation index of 426% compared to normal controls. According to the DLST results and his clinical course, drug-induced pancreatitis due to this formulation was suspected. After discharge, the patient was

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followed up with low-dose PSL, with no recurrence of pancreatitis noted since then (table 1). Colonoscopy was performed at each of the two episodes of pancreatitis, but no exacerbation of UC was noted at either time point (fig. 1b, c).

Discussion

The complication of pancreatitis in UC could possibly be due to an extraintestinal complication of UC and/or drug-induced pancreatitis due to certain drugs that are used for treatment of UC. Though the mechanisms of pancreatitis as an extraintestinal complication of UC remain unclear, there are some reports that have suggested possible mechanisms: malnutrition in UC, activation of trypsinogen due to intestinal bacteria, existence of a local circulatory disorder due to stimulation of the sympathetic nervous system, stimulation in cavities around the pancreatic acinus by proteases and cytokines derived from the colon mucosa via the portal lymphatic system, and exocrine disorders associated with an increase in the viscosity of pancreatic juice due to intestinal paralysis or dehydration [4–6]. On the other hand, UC may be associated with autoimmune pancreatitis from the consideration of autoimmune disease [7] and involvement of anti-carbonic anhydrase II antibody [8]. The occurrence of autoimmune pancreatitis is known to be strongly related to the disease activity of UC.

Among the drugs used for treatment of UC, mesalazine, PSL, and immunomodulators such as AZA are well known to cause drug-induced pancreatitis. The pathogenic mechanism of drug-induced pancreatitis remains unclear; however, some reasons, such as direct toxicity and allergic mechanism, have been proposed [9, 10]. Although the mechanism of pancreatitis due to mesalazine is also unclear, an allergic mechanism is considered to be involved in its formation, as it often occurs a few days after the beginning of administration of these drugs [11] and occurs within 1 month in 71.4% of patients [12]. Mallory and Kern [9] reported that the diagnosis of drug-induced pancreatitis requires (1) occurrence of the condition during treatment with the drug, (2) resolution by discontinuation of administration, and (3) recurrence on readministration (readministration of the suspicious drug being difficult). The DLST is an in vitro test of type IV allergic reactions to drugs, so the test is both safe and useful as an accessory diagnostic tool for drug-induced pancreatitis. However, DLST results should be evaluated carefully and considering the patient's clinical course, as false-negatives or false-positives may be influenced by many factors such as antigen exposure duration to DLST and some concomitant medications [13].

In this case, the second episode of pancreatitis was diagnosed as drug-induced pancreatitis due to a pH-dependent mesalazine formulation, because the disease was diagnosed 14 days after the beginning of its administration, it resolved immediately 4 days after its discontinuation, and the DLST was positive. From this result and the clinical course, the first episode of pancreatitis was suspected to be caused by a time-dependent mesalazine formulation since the DLST of this drug was negative. AZA could also have been a potential drug that caused pancreatitis despite the negative DLST in the present case. AZA-induced pancreatitis is considered to be an allergic disorder and its incidence is 2.3%, higher than mesalazine-induced pancreatitis [10]. PSL can also cause pancreatitis [9], however it was administered continuously throughout the present course, and was therefore considered unlikely to have been related to pancreatitis.

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The pathogenic mechanism of mesalazine-induced pancreatitis remains unknown. The proposed pathogenic mechanism is increased permeability of the pancreatic duct due to the direct effect of salicylic acid [14]. Although there is a chemical similarity between 5-aminosalicylic acid (5-ASA) and salicylic acid, the former should not directly stimulate the pancreatic ducts, since it is delivered as an active drug only in the terminal ileum and colon. It is therefore postulated that systemic absorption might occasionally occur for 5-ASA in high doses, and therefore could possibly cause toxicity in the pancreas [15]. On the other hand, even low blood levels of salicylate may be involved in acute pancreatitis in individual subjects in the setting of a hypersensitivity reaction, similar to Reye's syndrome [14]. In the present case, no information on the drug serum concentration was available. However, it was confirmed by the lymphocyte proliferation test that the present patient had an allergic reaction to 5-ASA, considering his clinical course. Time- and pH-dependent mesalazine formulations differ only in their coating material and have the same active component. Since the courses of pancreatitis caused by the two formulations were similar according to the reports to date [3, 12], mesalazine itself might be considered to cause pancreatitis.

Conclusions

During the clinical course of UC, occurrence of acute pancreatitis should be monitored carefully. Once acute pancreatitis has occurred, drug-induced pancreatitis must always be considered a differential diagnosis in addition to exacerbation of the primary inflammatory bowel disease. When the possibility of drug-induced pancreatitis is considered, discontinuation of its administration must be weighed. Further discussion of the safety of mesalazine preparations and the pathogenic mechanism of drug-induced pancreatitis is needed.

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Table 1. Laboratory data

Biochemistry		Peripheral blood	
AST, IU/l	17	WBC, /μl	11,600
ALT, IU/l	32	Neutrophils, %	71.0
LDH, IU/l	136	Lymphocytes, %	14.4
ChE, U/l	267	Mono, %	7.4
T-bil, mg/dl	0.7	Eosino, %	6.9
γGTP, IU/l	64	Baso, %	0.3
AMY, IU/l	1,555	RBC ($\times 10^6$/μl)	464
Lipase, IU/l	5,651	Hb, g/dl	14.4
TP, g/dl	7.5	Ht, %	43.4
Alb, g/dl	4.0	MCV, fl	93.5
BUN, mg/dl	7	MCH, pg	31.0
Cr, mg/dl	0.79	MCHC, %	33.2
Na, mmol/l	139	Plt, $\times 10^4$/μl	25.8
K, mmol/l	3.8	Coagulation	
Cl, mmol/l	102	PT, %	93
CRP, mg/dl	3.49	APTT, s	30.5
ESR1Hr, mm	33	Fbg, mg/dl	432
IgG, mg/dl	1,197		
IgA, mg/dl	182		
IgM, mg/dl	81		
Elastase1, ng/dl	>5,000		
PSTI, ng/ml	109.0		
PLA_2, ng/dl	3,990		
IgG_4, mg/dl	33.8		

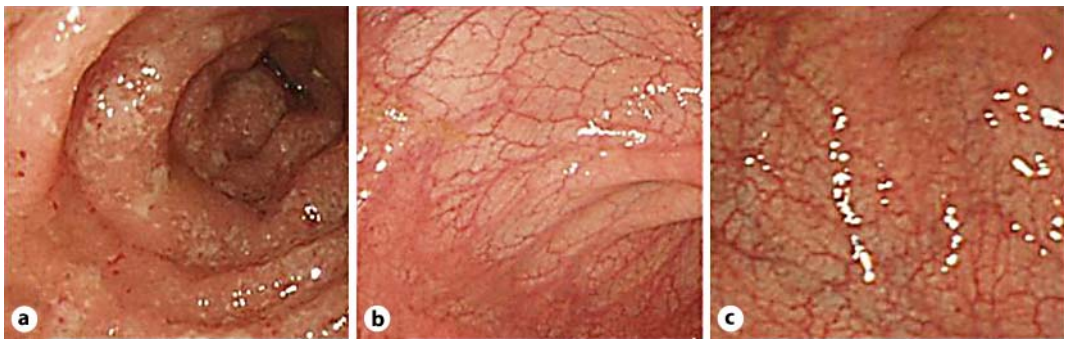

Fig. 1. Lower gastrointestinal endoscopy. **a** At the onset of UC. Sigmoid colon. Coarseness of the mucosa, disappearance of blood vessels seen through the mucosa, reddening, and erosion are observed continuously from the rectum to the ascending colon. **b** At the onset of the initial episode of pancreatitis. Sigmoid colon. Blood vessels are observed clearly through the mucosa, and no sign of inflammation is noted. **c** At the recurrence of pancreatitis. Sigmoid colon. No sign of inflammation is noted, as in **b**.

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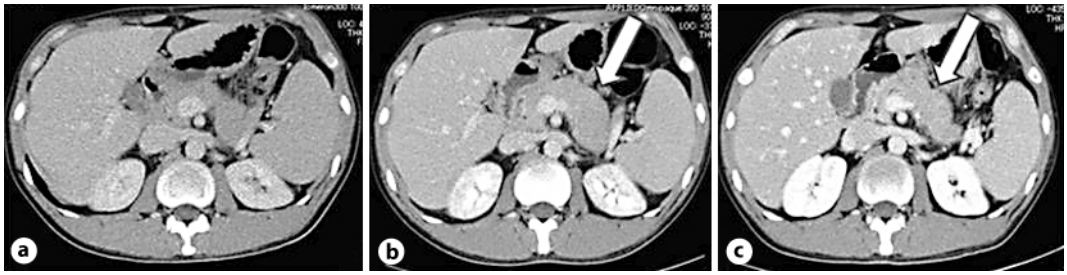

Fig. 2. Abdominal contrast-enhanced CT. **a** At the onset of UC. No abnormalities are noted in the pancreas. **b** At the onset of the initial episode of pancreatitis. The pancreas is mildly enlarged (arrow). **c** At the recurrence of pancreatitis. The pancreas is mildly enlarged, as in **b** (arrow).

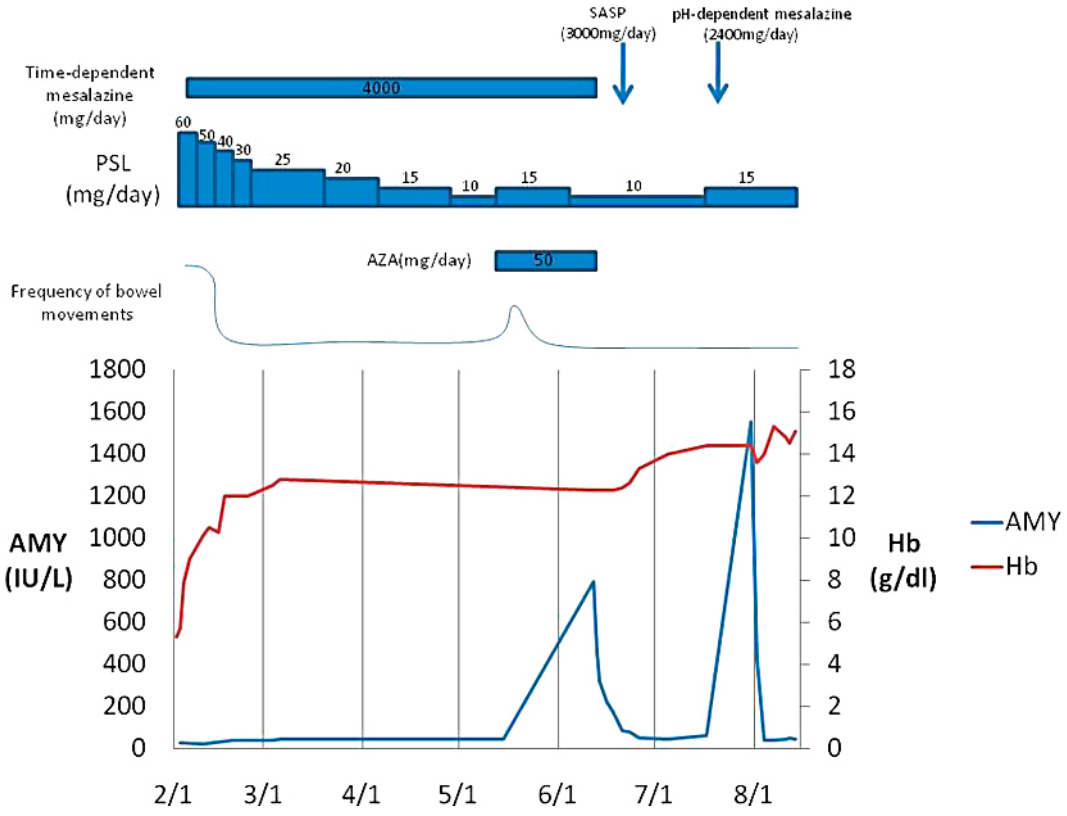

Fig. 3. Clinical course.

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