pISSN: 2234-8646 eISSN: 2234-8840
http://dx.doi.org/10.5223/pghn.2012.15.4.272
Pediatric Gastroenterology, Hepatology & Nutrition 2012 December 15(4):272-275

Case Report

PGHN

Acute Pancreatitis Induced by Azathioprine and 6-mercaptopurine Proven by Single and Low Dose Challenge Testing in a Child with Crohn Disease

Geum-Chae-Won Yi, Ka-Hyun Yoon and Jin-Bok Hwang

Department of Pediatrics, Keimyung University School of Medicine, Daegu, Korea

We report here a case of drug-induced acute pancreatitis proved by elimination and single, low dose challenge test in a child with Crohn disease. A 14-year-old boy with moderate/severe Crohn disease was admitted due to high fever and severe epigastric pain during administration of mesalazine and azathioprine. Blood test and abdominal ultrasonography revealed acute pancreatitis. After discontinuance of the medication and supportive care, the symptoms and laboratory findings improved. A single, low dose challenge test was done to confirm the relationship of the adverse drug reaction and acute pancreatitis, and to discriminate the responsible drug. Azathioprine and 6-mercaptopurine showed positive responses, and mesalazine showed a negative response. We introduce the method of single, low dose challenge test and its interpretation for drug-induced pancreatitis. **(Pediatr Gastroenterol Hepatol Nutr 2012; 15: 272～275)**

Key Words: Crohn disease, Inflammatory bowel diseases, Acute pancreatitis, Azathioprine, 6-mercaptopurine, Mesalamine, Child

INTRODUCTION

In a patient with inflammatory bowel disease (IBD), the incidence of acute pancreatitis is higher than healthy people. General causes of acute pancreatitis and extraintestinal manifestations of IBD and adverse reactions of the drugs should be considered as the cause of pancreatitis. Drugs like azathioprine, 6-mercaptopurine, sulfasalazine, mesalazine and steroids used in IBD treatment can induce an acute pancreatitis. Acute pancreatitis during medication has been reported [1-4].

But no case of single and low dose challenge test to confirm the relationship of adverse drug reactions and acute pancreatitis has been reported, and no report concerning discrimination of the responsible drug has been published. We report here a case of drug-induced pancreatitis proved by single and low dose challenge test in a child with Crohn disease.

Received : September 15, 2012, Revised : October 4, 2012, Accepted : October 11, 2012

Corresponding author: Jin-Bok Hwang, Department of Pediatrics, Keimyung University Dongsan Medical Center, 56, Dalseong-ro, Jung-gu, Daegu 700-712, Korea. Tel: +82-53-250-7331, Fax: +82-53-250-7783, E-mail: pedgi@kmu.ac.kr

CASE REPORT

A 14-year-old boy who had been diagnosed with Crohn disease was admitted suffering from high fever and epigastric pain for 5 days. High fever and epigastric pain developed after 34 days of mesalazine and 15 days of azathioprine, after completion of initial treatment with antibiotics and steroid tapering.

Prior to 40 days before admission, the patient had been admitted suffering from intermittent hematochezia, diarrhea and weight loss for 3 months. Colonoscopy and biopsy had diagnosed Crohn disease. Pediatric Crohn Disease Activity Index score was 57 as moderate/severe degree. The patient had initially been administered antibiotics and steroid, followed by mesalazine (1,500 mg/ day) first and later switching this to azathioprine (75 mg/day) only, allowing overlapping period of the two medications before reaching azathioprine-only regimen. No family history of IBD or pancreatitis was identified. Parity was unremarkable. The patient had been born full term with a birth weight of 3,400 g by normal vaginal delivery.

The patient's vital sign was 110/60 mmHg of blood pressure, 98/min of heart rate, 20/min of respiratory rate, and body temperature of 39.1^{o}C. The patient showed mild dehydration, soft and non-distended abdomen, and there was no hepatosplenomegaly. Epigastric and periumbilical area tenderness were evident, but no rebound tenderness. Hemoglobin was 11.1 g/dL, hematocrit was 31.5%, white blood cell count was 11,660/mm^{3} (neutrophil 86%, lymphocyte 8%), platelet was 312,000/mm^{3}. Serum sodium was 138 mEq/L, potassium 3.6 mEq/L, aspartate aminotransferase/alanine aminotransferase 15/7 U/L, total/direct bilirubin 0.9/0.3 mg/dL, calcium 8.6 mg/dL, and phosphorus 3.3 mg/dL. Erythrocyte sedimentation rate was elevated to 54/26 mm/hr, C-reactive protein to 13.32 mg/dL, and amylase and lipase to 227 U/L (normal range, 0-220) and 363 U/L (normal range, 3-110). Anti-nuclear antibody, lupus anticoagulant antibody, rheumatoid factor, anti-smooth antibody, anti-microsomal antibody, antineutrophil cytoplasmic autoantibodies profile were all negative, and serum IgG was 813.96 mg/dL (normal range, 800-1,700). Abdominal ultrasonography showed mild swelling of the pancreas with no demonstrable pancreatic fluid collection.

The patient was diagnosed with acute pancreatitis and received supportive care, but the fever and abdominal pain continued. Two days later after admission, amylase and lipase was more elevated as 1,080 U/L and 1,912 U/L, abdominal ultrasonography showed aggravated pancreatitis with marked swelling. Drug-induced pancreatitis was presumed, and mesalazine and azathioprine were discontinued. The patient was fasted and was given total parenteral nutrition. Two days later after drug discontinuance, the fever and epigastric pain subsided, and 4 days after drug discontinuance, amylase and lipase had decreased (93 U/L and 150 U/L, respectively).

At that time, the biological medication for Crohn disease in children was not included in the approved lists of Korean Medical Insurance. Therefore, we had to confirm exactly the relationship between prescribed medications and pancreatitis. When we had a plan ahead of a medication challenge test, we were also afraid of serious adverse reaction of pancreatitis in an ethical aspect for the patient. However, the benefits from the challenge test thought to be overweight the possible risks in the aspect of deciding the patient's present and future treatment regimen.

Therefore, single and low dose challenge tests were performed to confirm the relationship of drug adverse drug reactions and acute pancreatitis (Fig. 1). Before the challenge tests, amylase and lipase values were 132 U/L and 110 U/L, respectively. Two hours after a single administration of azathioprine (50 mg), the patient developed epigastric pain without vomiting. Seven hours after the single administration, the symptom had subsided. Six hours after the challenge test, amylase and lipase values were markedly increased (303 U/L and 443 U/L, respectively) and were further elevated (458 U/L and 909 U/L, respectively) 18 hours later. Three days following the challenge test, the amylase and lipase values had normalized. One day later, the challenge test was repeated with a single administration of 6-mer-

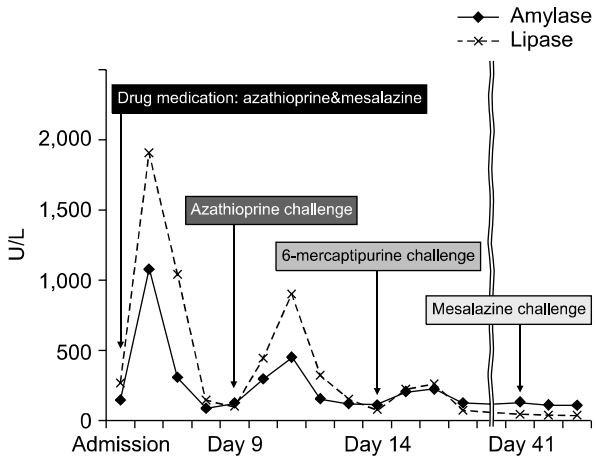

Fig. 1. Change in amylase and lipase levels with drug administration, azathioprine, 6-mercaptopurine and mesalazine.

captopurine (25 mg) to select an alternative drug. Before the challenge test, amylase and lipase values were 114 U/L and 83 U/L, respectively. Six hours later, the patient developed epigastric pain without vomiting. The symptom had subsided 12 hours later. Six hours later from the challenge test, the amylase and lipase values were increased (155 U/L and 156 U/L, respectively). Eighteen hours later, the amylase and lipase values were further increased (161 U/L and 193 U/L, respectively). Two days from the challenge test, the amylase and lipase values had normalized.

After 1-month steroid maintenance therapy, the mesalazine challenge test was done. The challenge test with a single administration of mesalazine (500 mg) did not elicit vomiting or epigastric pain. Before the test, amylase and lipase values were 139 U/L and 48 U/L, respectively. Twelve hours later, the amylase and lipase values were 114 U/L and 41 U/L, respectively, and were 110 U/L and 39 U/L, respectively, 18 hours later. This was interpreted as a negative response.

The patient was administered solely with mesalazine. Despite regular medication for 1 year, Crohn disease relapsed as intermittent perianal abscess and diarrhea with hematochezia. Symptoms subsided after administration of infliximab. Presently, the patient is symptom-free and is being followed-up on an outpatient basis.

DISCUSSION

In patients with IBD, the incidence of acute pancreatitis is 4.3-times more frequent in those with Crohn disease, and 2.1-times more frequent in those with ulcerative colitis, as compared to healthy people [5]. Possible causes of acute pancreatitis in Crohn disease are gallbladder stone, drugs, alcohol, duodenal involvement of Crohn disease, complication of endoscopic retrograde cholangiopancreatography (ERCP), and complication of surgery [6]. Hypercalcemia, hypertriglyceridemia, infection, trauma, and autoimmune disease also induce acute pancreatitis [4,7], and extraintestinal manifestation of IBD should be considered [8].

In the case of acute pancreatitis in a patient with IBD, drug-induced acute pancreatitis varies in incidence from 15-63% [6,9]. The pathophysiology of drug-induced pancreatitis is unclear, but azathioprine, sulfasalazine, and 5-aminosalicylic acid have been linked to the development of pancreatitis with a dose-independent, hypersensitivity reaction [9,10]. Clinical course of drug-induced pancreatitis is usually mild, and improves in a short time with discontinuance of the drug [11].

Trivedi and Pitchumoni [4] published a review about the reported cases of drug-induced pancreatitis between 1966 and 2004 including a few case of challenge test, and reported no cases of low dose challenge test with a drug, serial check about serum amylase, lipase, and clinical course. In the present case, an acute pancreatitis developed in a child with Crohn disease who was administered maintenance therapy with mesalazine and switching this to azathioprine after antibiotics and steroid therapy. The patient did not have a history of alcohol ingestion, ERCP, surgery, or trauma, and had no familial history of pancreatitis or similar symptoms. No evidence of hypercalcemia, hypertriglyceridemia, and autoimmune disease was evident in the blood test, and no evidence of gallbladder stone was evident upon abdominal ultrasonography. Symptoms of pancreatitis were improved with discontinuance of drugs and with supportive care. We considered drug induced pan-

creatitis, which prompted the drug challenge testing.

Because drug-induced pancreatitis usually develops after 2-3 weeks from the commencement of medication [10,12], azathioprine was considered the possible cause of the pancreatitis in the present case. After the single administration of azathioprine, the patient developed symptom of pancreatitis in 2 hours, and amylase and lipase levels became elevated within 6 hours. The symptom abated by 7 hours and blood test results had normalized by 3 days. As azathioprine and 6-mercaptopurine are purine analogues, generally administration of 6-mercaptopurine in a patient with a history of azathioprine-induced pancreatitis is a contraindication. However, Alexander and Dowling [13] reported a case of successful subsequent treatment with 6-mercaptopurine in a patient with history of IBD and azathioprine-induced pancreatitis. The challenge test with 6-mercaptopurine was presently done to find an alternative drug for azathioprine. As detailed above, administration of 6-mercaptopurine caused a transient appearance of pancreatitis symptom and elevation of his amylase and lipase levels. Challenge with mesalazine did not produce symptoms or alterations in the activities of amylase or lipase.

When acute pancreatitis develops in a patient with IBD, all medications should be discontinued, and supportive care with fasting and total parenteral nutrition should be initiated, while the cause of the pancreatitis is explored. After patient's symptoms are relieved and other causes excluded, the challenge test may be carried out with the drug that is used in treatment of Crohn disease [14]. We suggest that, after single administration of low dose drug, the recurrence of symptoms should be closely monitored for, including checking the level of amylase and lipase 6 hours following challenge or when symptoms develop.

For occurrence of pancreatitis in a patient with IBD, the elimination and low dose challenge test may be helpful in minimizing the symptom of pancreatitis and discrimination the responsible drug for pancreatitis.

REFERENCES

1. Son CN, Lee HL, Joo YW, Lee OY, Han DS, Yoon BC, et al. A case of acute pancreatitis induced by multiple drugs in a patient with ulcerative colitis. Korean J Gastroenterol 2008;52:192-5.
2. Lhee HY, Kim BI, Yoo TW, Lee HC, Jung CH, Shin HS, et al. Acute pancreatitis induced by 5-aminosalicylic acid in a patient with ulcerative colitis. Korean J Gastroenterol 2002;40:282-5.
3. Kim KH, Kim TN, Jang BI. A case of acute pancreatitis caused by 5-aminosalicylic acid suppositories in a patient with ulcerative colitis. Korean J Gastroenterol 2007;50:379-83.
4. Trivedi CD, Pitchumoni CS. Drug-induced pancreatitis: an update. J Clin Gastroenterol 2005;39:709-16.
5. Rasmussen HH, Fonager K, Sørensen 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 Gastroenterol 1999;34:199-201.
6. Moolsintong P, Loftus EV Jr, Chari ST, Egan LJ, Tremaine WJ, Sandborn WJ. Acute pancreatitis in patients with Crohn's disease: clinical features and outcomes. Inflamm Bowel Dis 2005;11:1080-4.
7. Choi IY, Jin SH, Choi KD, Kim KM. A case of autoimmune chronic pancreatitis in a child. Korean J Pediatr Gastroenterol Nutr 2007;10:215-20.
8. Park CB, Moon W, Choi PR, Im DH, Shin EK, Kim KJ, et al. A case of idiopathic pancreatitis in a patient with Crohn's disease. Korean J Gastroenterol 2009;53:251-6.
9. Bermejo F, Lopez-Sanroman A, Taxonera C, Gisbert JP, Pérez-Calle JL, Vera I, et al. Acute pancreatitis in inflammatory bowel disease, with special reference to azathioprine-induced pancreatitis. Aliment Pharmacol Ther 2008;28:623-8.
10. Sturdevant RA, Singleton JW, Deren JL, Law DH, McCleery JL. Azathioprine-related pancreatitis in patients with Crohn's disease. Gastroenterology 1979;77:883-6.
11. Herrlinger KR, Stange EF. The pancreas and inflammatory bowel diseases. Int J Pancreatol 2000;27:171-9.
12. Inoue H, Shiraki K, Okano H, Deguchi M, Yamanaka T, Sakai T, et al. Acute pancreatitis in patients with ulcerative colitis. Dig Dis Sci 2005;50:1064-7.
13. Alexander S, Dowling D. Azathioprine pancreatitis in inflammatory bowel disease and successful subsequent treatment with mercaptopurine. Intern Med J 2005;35:570-1.
14. Nitsche CJ, Jamieson N, Lerch MM, Mayerle JV. Drug induced pancreatitis. Best Pract Res Clin Gastroenterol 2010;24:143-55.