A Case of Nonalcoholic Steatohepatitis and Small Intestinal Bacterial Overgrowth with Peripheral Edema Caused by Intestinal Bypass Surgery and Relieved by Repair

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Intestinal bypass surgery, particularly jejuno-ileal bypass surgery, performed for the purpose of weight reduction may cause an unexpected exacerbation of nonalcoholic steatohepatitis (NASH). Here, we report a case of NASH caused by small intestinal bacterial overgrowth, which developed after jejuno-colic bypass surgery and resolved dramatically after surgical correction. (Gut Liver 2012;6:520-523)

Key Words: Nonalcoholic steatohepatitis; Bypass surgery; Small intestinal bacterial overgrowth

INTRODUCTION

Intestinal bypass surgery, particularly jejuno-ileal bypass, performed for the purpose of weight reduction may cause unexpected exacerbation of nonalcoholic steatohepatitis (NASH). Small intestinal bacterial overgrowth (SIBO) and subsequent stimulation of tumor necrosis factor (TNF) by bacterial endotoxin has been postulated as one of the etiologic factors, but the exact mechanism remains to be determined. Since morbid obesity is relatively rare in Korea and this type of operation has rarely been performed in the past. Here, we report a case of NASH and SIBO developed after intestinal bypass surgery, which was performed to improve symptoms related to intestinal adhesion, successfully treated by bypass repair.

CASE REPORT

A 45-year-old man was first seen in the outpatient gastrointestinal division of this hospital with complaining of diarrhea in 1996. He had diarrhea, bloating, postprandial fullness of 1 year's duration. The body weight was not changed during 1 year. The other multisystem review was unremarkable.

The past medical history revealed intra-abdominal operations in three times. In 1982, the patient has undergone appendectomy. In 1983, small bowel segmental resection and anastomosis was performed to relieve postoperative small bowel adhesion. In 1995, the recurrent abdominal pain related to small bowel adhesion was relieved by side to side jejuno-colostomy, from mid jejunum to transverse colon (between jejunum below 100 cm from the Treitz ligament and mid-transverse colon) because the greater omentum was densely adherent to about 1/2 to 2/3 of the distal ileum in a very tightly kinked and matted fashion. The amount of his alcohol consumption was less than 40 gm of alcohol each time, once or twice a week. He denied history of diabetes mellitus or any other disease. The family history was unremarkable.

Physical examination revealed no significant abnormal finding except paramedian abdominal incision scar. His vital signs were normal and his weight and height were 65 kg and 170 cm, respectively. Initial laboratory studies revealed a normal complete blood count and chemistry. Quantitative fecal fat test was negative. On the double contrast barium enema study, it was side to enterocolostomy without any passage disturbance or luminal narrowing.

Symptomatic treatment was initiated with loperamide, fenoverine under a suspicion of bile acid malabsorption or irritable bowel syndrome. In 1998, 2 years after since the first visit and 3 years after bypass surgery, lower extremities pitting edema and weight loss of 4 kg developed.

The laboratory tests were as follow: white cell count 5,900/mm³, hemoglobin 10.5 g/dL, platelet 402,000/mm³, total protein...
4.3 g/dL, albumin 1.9 g/dL, globulin 2.4 g/dL, AST 71 U/L, ALT 86 U/L, total bilirubin 0.2 mg/dL, alkaline phosphatase 167 U/L, cholesterol 100 mg/dL, fasting glucose 97 mg/dL, triglyceride 62 mg/dL, and serum ferritin 5 ng/mL. Prothrombin time was 11.8 seconds with an INR of 0.97 and partial thromboplastin time was 35.5 seconds. Serum immunoglobulin G (IgG), IgA, and IgM levels were in normal range. There was no evidence of cardiac disease or renal disease. Quantitative fecal fat test was positive. Serological markers for hepatitis B and hepatitis C were negative. Antibody to antinuclear antibodies, anti-smooth muscle antibody, and anti-mitochondrial antibody were all negative and ceruloplasmin level was within normal limit.

Upper gastrointestinal endoscopy was not remarkable. Colonoscopy revealed multifocal jejunitis. There was no significant passage disturbance or luminal narrowing on small bowel enteroclysis. Instead of direct culture of jejunal aspirate, hydrogen breath test was performed to identify the presence of SIBO. After intake of 10 g of lactulose in 200 mL water, breath samples were analyzed every 15 minutes for 4 hours. The air was analyzed for hydrogen concentrations with a QuinTron SC Microlyzer (Quintron Instrument Company, Milwaukee, WI, USA) with which minimal detectable concentration for hydrogen analysis was 1 part per million (ppm). Double peaks were observed in this test. The Technetium labeled $^{99m}$Tc human serum albumin scintigraphy was performed to detect gastrointestinal protein loss from small or large bowel, but the result was negative. The abdominal computed tomography scan revealed diffuse fatty infiltration of entire liver (Fig. 1) and multifocal mural thickening involving ileal loop and jejuno-colostomy site. Percutaneous liver biopsy demonstrated steatohepatitis with mild perisinusoidal and mild pericellular fibrosis (Fig. 2A and B).

He was diagnosed as NASH and SIBO caused by a complication of intestinal bypass surgery. The 10 days antibiotic treatments using amoxicillin 750 mg/day and clavulanic acid 375 mg/day enterally divided by three time was transiently improved gastrointestinal symptoms, hypoalbuminemia, and pitting edema related with hypoalbuminemia. The albumin level was improved from 2.2 to 3.4 g/dL. But it was not improved the elevated levels of liver enzymes and fatty infiltration on imaging. Furthermore, exercise and complete abstinence from alcohol did not improve the biochemical and radiological features of NASH and the aminotransferase levels was fluctuated from 90 to 210 IU/mL.

We continued the medical treatment using intermittent short term antibiotic treatments during about 10 years. Even though the jejuno-colostomy repair is the only curative choice, we considered it would be a very hard with high surgical complication rate as a result of recurrent bowel adhesion. Diarrhea, hypoalbuminemia, and pitting edema related with hypoalbuminemia was still wax and wane with antibiotic treatments. The aminotransferase levels were fluctuated from 50 to 400 IU/mL. He lost weight from 65 to 57 kg during 7 months in late 2006. Considering the risk and benefit of surgery, the jejuno-colostomy repair was performed in July 2007. Intestinal continuity was restored and adhesiolysis was performed. His gastrointestinal symptoms and pitting edema was improved completely and serum albumin level was normalized 2 months after intestinal reconstitution. The aminotransferase levels returned to completely normal level with marked improvement in the fatty infiltration.

**Fig. 1.** On the computed tomography imaging, the liver was darker than the spleen, suggesting fatty liver.

**Fig. 2.** On liver biopsy, the liver parenchyma had moderate fatty change, mild neutrophil infiltration suggesting steatohepatitis (A, H&E stain, ×100), and mild perisinusoidal and pericellular fibrosis (B, Masson trichrome stain, ×100).
NASH is a disease similar to alcoholic hepatitis in histology which has no relationship with alcohol abuse. Primary NASH is related to insulin resistance and its phenotypic manifestations like mainly overweight/obesity, visceral adiposity, type 2 diabetes, hypertriglyceridemia, and hypertension. Secondary NASH is rare, is not associated with insulin resistance or the metabolic syndrome, and is related to variable medical or surgical conditions or drug intake. NASH associated with intestinal bypass surgery was reported mainly in bariatric surgery performed before early 1980s. From the 1950s to early 1980s, the jejunoileal bypass was the most common malabsorptive operation in which the proximal jejunum was anastomosed to the distal ileum. A common variant form of jejunoileal bypass is jejunocolic bypass. Since these types of surgery have rarely been performed in Korea, we were not able to find a case of NASH caused by intestinal bypass surgery in Korean literatures. In our case, unlike the cases in Western countries, jejunoileal bypass was not performed to reduce weight, but to relieve symptoms related to intestinal adhesion.

The pathogenesis of NASH after bypass surgery is thought to be different from that of primary NASH associated with the metabolic syndrome, but the exact mechanism is not clear. Rapid weight loss after surgery, protein-calorie malnutrition, decreased carnitine concentrations, essential fatty acid deficiency and stimulation of TNF by bacterial overgrowth have been reported as possible etiologic factors. The relation between NASH and SIBO is unclear. However, there are some reports which described relationship between NASH and SIBO. SIBO was combined up to 50% of patients with NASH caused by intestinal bypass surgery. SIBO might play a role in the pathogenesis of NASH by affecting intestinal permeability and serum endotoxin. A slower small intestinal transit time and higher bacterial concentration of proximal small intestine was reported in an experimental model of NASH in rats and treatment with antibiotics accelerated the transit time, decreased TNF-α and lowered the severity of NASH.

The control of bacterial growth in small intestine is maintained by action of the immune system, gastric acid, pancreatic enzymes, small intestinal motility, and the ileocecal valve. The jejunoilec bypass can result in disruption of these mechanisms and it can be cause of SIBO. The symptoms related to SIBO include bloating, diarrhea, weight loss, weakness, and neuropathy. SIBO generally cause a malabsorption syndrome including cobalamin (vitamin B12), fat-soluble vitamin (vitamin A, D, E, and K), fat, carbohydrate, and iron. Edema of lower extremities is caused by more complicated causes such as anemia, malnutrition, hypoproteinemia, and vitamin B12 deficiency. Hypoproteinemia and hypoalbuminemia are related to amino acid uptake impairment by SIBO itself or protein losing enteropathy associated with SIBO.

The gold standards for the diagnosis of SIBO are considered direct culture of jejunal aspirates. There is no consensus in literature on the positive culture cut value for bacterial overgrowth, these cut values range from >10⁴ to >10⁶ colony-forming unit/mL. However, this test is rarely performed in clinical practice, because of invasiveness, possible contamination, and low reproducibility. Breath tests have been performed as non-invasive tests for diagnosis of SIBO. The most commonly used test for SIBO are hydrogen breath tests using glucose or lactulose. The positive lactulose hydrogen breath test is defined as early hydrogen peak (>10 ppm) occurring at least 15 minutes before the later prolonged peak or double peak (first peak before 90 minutes and second peak after at least 15 minutes from first peak). Therapeutic trials of antibiotics can be an alternative diagnostic strategy of SIBO.

The treatment of SIBO includes treating the underlying disease, eradicating overgrowth, nutritional support. When surgical correction of the clinical condition associated with SIBO is not possible, management is based on antibiotic therapy. The patient presented in the case, who had no risk factors for primary NASH, has undergone jejunoileal bypass surgery for the purpose of controlling symptoms related to small bowel adhesion. Rapid weight loss and malnutrition was not evident which excludes them as the cause of NASH in this case. Although the majority of intestinal bypass surgery associated with NASH is jejuno-ileal bypass, there is one reported case that is related to jejunoileal bypass in the literature. The pitting edema related to hypoalbuminemia was relieved by antibiotic treatment in our case. The hypoalbuminemia can be either related to SIBO itself or protein losing enteropathy caused by SIBO.
Although a negative result in the technetium labeled \(^{99m}\)Tc human serum albumin scintigraphy cannot exclude protein losing enteropathy due to its variable sensitivity (66% to 96%),\(^{26}\) the cause of hypoproteinemia and hypoalbuminemia in our case favored SIBO itself.

It is reported that SIBO and NASH can be improved when underlying cause is corrected, but there are some cases of NASH which does not resolve after surgical bypass correction.\(^{1}\) In our case, both NASH and SIBO improved dramatically after repair operation.

In conclusion, we report a case of NASH caused by SIBO after jejunocolic bypass surgery, resolved dramatically after surgical correction, with a review of literature.

**CONFLICTS OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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