A Case of Small Intestinal Ulcers with Severe Hypoproteinemia Induced by Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

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ABSTRACT. A 58-year-old woman with hypoproteinemia underwent surgery for adhesional ileus. Afterwards, she experienced pyothorax, and was treated with diclofenac sodium. Both her hypoproteinemia and anemia still remained following recovery from the pyothorax. A barium study of the small intestine disclosed multiple, longitudinal ulcers with eccentric deformities in the ileum. The patient had a long history of taking an analgesic-antipyretic agent, a type of non-steroidal anti-inflammatory drug (NSAID) for headache. After cessation of this NSAID, both the hypoproteinemia and anemia remarkably improved, and the small intestinal lesions were resolved. A diagnosis of NSAID-induced enteropathy was made. It is important to recognize NSAID-induced enteropathy as one cause of protein-losing gastroenteropathy.

Key words : drug-induced enteropathy — protein-losing — ileum

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed in clinical practice as antipyretics, analgesics, and for their anti-inflammatory properties. It is well known that they may adversely affect the gastrointestinal (GI) tract, particulary the gastroduodenum. Recently, with more frequent use of colonoscopic examinations, the entity of NSAID-induced colitis has been increasingly recognized.[1-3] However, it is less well known that NSAIDs may also cause damage to the small intestine. NSAID-induced small intestinal lesions may lead to protein loss and chronic bleeding, resulting in hypoproteinemia and anemia.[4] Therefore, NSAID-induced enteropathy should be considered as one of the various diseases manifesting hypoproteinemia. We report a case of NSAID-induced small intestinal ulcers accompanied by severe hypoproteinemia.

CASE REPORT

A 58-year-old woman was transferred to our hospital as an emergency case because of adhesional ileus on June 14, 1999. She had a history of partial gastrectomy for a submucosal gastric tumor and an oophorectomy for

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an ovarian tumor. On admission, physical examination revealed slight tenderness of the left lower abdomen. No chest abnormalities were noted. Laboratory data showed a serum C-reactive protein (CRP) level of 41.1 mg/dl, which suggested severe inflammation, hypoproteinemia (total protein 4.9 g/dl), and slight increases in creatinine (2.2 mg/dl) and blood urea nitrogen (67 mg/dl). There was no liver damage or proteinuria. No available data had suggested hypoproteinemia nor enteropathy before the onset of ileus. On the day of admission, the patient underwent only an adhesiotomy of the terminal ileum since there were no necrotic lesions of the intestine.

Her clinical course after surgery was uneventful, but the hypoproteinemia did not improve, being as low as 5.0 g/dl of total protein. From day 14 after surgery, the patient developed pyothorax and a continuing high fever. She was treated with antibiotics and diclofenac sodium (Voltaren® suppositorium) 25 mg once or twice a day for its antipyretic properties. The pyothorax was treated successfully and administration of diclofenac sodium was discontinued on August 18. However, laboratory data showed anemia (Hb 8.8 g/dl) with positive occult blood in stools and hypoproteinemia (total protein 5.6 g/dl) on August 23. Upper and lower endoscopic examinations

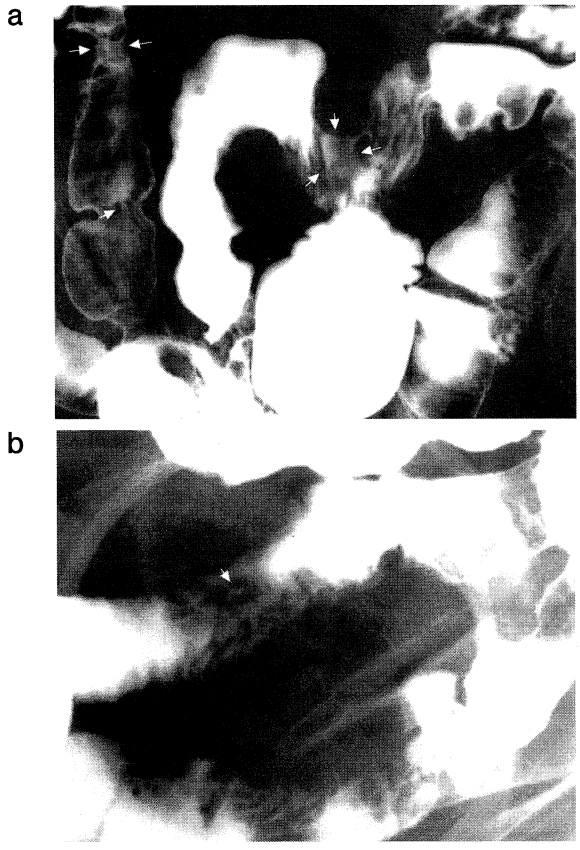

Fig 1. A barium follow-through study of the small intestine.
a. Multiple small ulcers were seen in the ileum (arrows).
b. A compression view showed a small ulcer (arrow).

disclosed no findings of hemorrahagic lesions, and there were no specific findings such as granuloma nor vasculitis in biopsy specimens taken from the stomach and ileum. Stool cultures revealed no significant bacteria. A barium follow-through study of the small intestine revealed edema, multiple small ulcers and eccentric or concentric narrowing with rough mucosa in the ileum (Fig 1a, b). Subsequently, a double-contrast study of the small intestine disclosed longitudinal ulcers and eccentric deformities of the ileum (Fig 2a, b) mimicking those of Crohn's disease. On September 27, one month after discontinuance of diclofenac sodium, the levels of serum total protein and hemoglobin were 5.2 g/dl and 9.8 g/dl, respectively. A carefully taken drug history revealed that she had been taking an analgesic-antipyretic agent (SedesG®) regularly, at a maximum dose of 3 g per day, for more than three years because of headache. From the time she resumed food intake after surgery, the patient had secretly taken the drug once or more a day. As a diagnosis of NSAID-induced small intestinal ulcers was strongly suspected, the drug was discontinued on October 1. Subsequently, both her

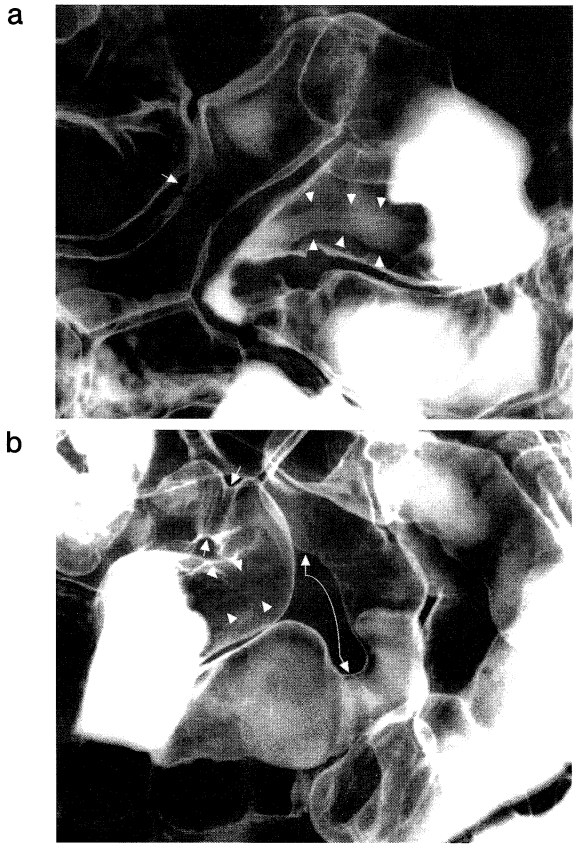

Fig 2. A double-contrast study of the small intestine.
a. A longitudinal ulcer (arrow heads) and a small ulcer were seen in the ileum (arrow).
b. A concentric deformity (arrows), an eccentric deformity (↓ ↓) and a longitudinal ulcer (arrow heads) were seen.

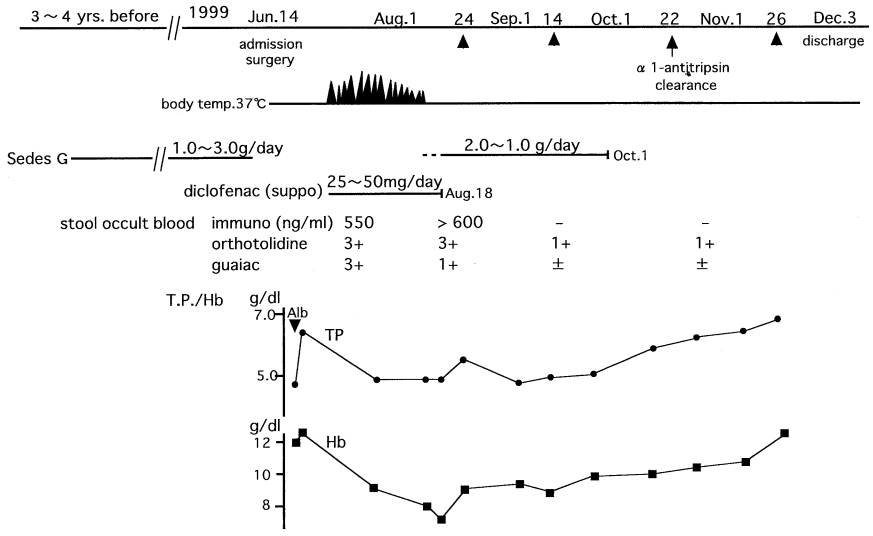

Fig 3. The clinical course showing a gradual increase in serum total protein (TP) and hemoglobin (Hb) after cessation NSAID. arrow head : a barium study of the small intestine. Alb : albumin

serum level of total protein and anemia dramatically improved. On October 29, the levels of serum total protein and hemoglobin had increased to 6.2 g/dl and 10.6 g/dl, respectively (Fig 3). Alpha-1 antitrypsin clearance after cessation of the NSAID was 9.6 ml/day (<24 ml/day). A follow-up barium study of the small intestine demonstrated marked improvement of the small intestinal lesions. Finally, a diagnosis of NSAID-induced small intestinal ulcers with severe hypoproteinemia was made.

DISCUSSION

Hypoproteinemia is a manifestation of various diseases. Usually it results in an imbalance in hepatic protein synthesis and excessive loss of protein from the affected lesions. In our case, there was no underlying disease such as rheumatoid arthritis, liver damage, or nephrotic syndrome. Therefore, together with positive occult blood in the patient's stool and protein loss from the GI tract, protein-losing gastroenteropathy was strongly suspected. Protein-losing gastroenteropathy is divided into three major subgroups[5] : 1) intestinal lymphatic obstruction, with direct leakage of intestinal lymph, 2) mucosal ulceration with inflammatory exudation, and 3) mucosal disease without ulceration, resulting in protein loss by an unclear mechanism.

Our case had multiple ulcers in the small intestine, which needed to be distinguished from other GI disorders that imply Crohn's disease, ischemic enteritis or non-specific ulcers of the small intestine. In our case, from the standpoints of age, onset, past history and clinical course, it was unlikely that these disorders were involved. From a carefully taken drug history, it became evident that the patient had been taking SedesG®, an analgesic-antipyretic agent and a type of NSAID, for a long period. In addition, the

patient was given diclofenac sodium for a short period.

NSAIDs cause asymptomatic small intestinal inflammations which may subsequently lead to protein loss and anemia in 70% of patients taking the drugs for a long-term period.[6,7] The pathogenesis of NSAID-induced small intestinal injury remains speculative. Recently, NSAIDs have been reported to increase the permeability of the small intestine.[8] The mechanism of such increased intestinal permeability induced by NSAIDs may be related to depletion of endogenous intestinal mucosal prostaglandins and/or damage to the mitochondrial energy metabolism.[9,10] Such an increase in intestinal permeability may expose the mucosa to endogenous and exogenous luminal toxins, finally allowing bacterial invasion to the intestinal mucosa, leading to macroscopic damage.[8]

Since SedesG® containing phenacetin has analgesic, antipyretic and weak anti-inflammatory activities due to its effect on the central nervous system, it could be considered as a NSAID in the broad sense. Although it is uncommon for an analgesic-antipyretic agent to provoke enteropathy, we previously reported a case of cecal ulcer caused by an analgesic-antipyretic agents.[11] The analgesic-antipyretic agent, therefore, may have adverse effects on the GI tract. On the other hand, it has been well reported that diclofenac sodium can cause small intestinal injuries.[12,13] In this case, neither hypoproteinemia nor anemia improved following cessation of the diclofenac sodium, but recovered after cessation of the analgesic-antipyretic agent. Therefore, it was suspected that the patient's long-term use of an analgesic-antipyretic agent had induced subclinical mucosal injuries of the small intestine, resulting in protein loss. The short-term use of diclofenac sodium may have further exacerbated the existing mucosal injuries and may have contributed to her anemia or hypoproteinemia.

There are no definite criteria for NSAID-induced enteropathy. Diagnosis of NSAID-induced gastroenteroapthy is based on a history of NSAID use, the absence of other GI disorders, and recovery after cessation of the causative drugs. Therefore, this case was diagnosed as NSAID-induced enteropathy. After the cessation of the NSAID, the remarkable healing of the intestinal lesions and improvement of hypoproteinemia strongly supported the diagnosis of NSAID-induced enteropathy. Alpha-1 antitrypsin clearance is useful to confirm the correctness of a diagnosis of protein-losing gastroenteropathy.[14] Although alpha-1 antitrypsin clearance did not increase in our case, it was difficult to evaluate it because measurements were made at three weeks after the complete cessation of the NSAID.

Serum protein loss from the GI tract is nonselective, in contrast to the selective loss of proteins in nephrotic syndrome. In protein-losing gastroenteropathy, therefore, the serum levels of proteins which have long half-lives, such as albumin, IgG, IgM, IgA, are markedly reduced. Although, in this case, the serum levels of immunoglobulins were not measured on admission, the complication of pyothorax could have been associated with a secondary hypoimmunological state provoked by the protein-losing enteropathy.

In conclusion, the incidence of NSAID-induced small intestinal lesions may be underestimated because their detection is more difficult than that of lesions in other parts of the GI tract. It is therefore necessary to pay

careful attention to small intestinal lesions even when the results of exact examinations of the upper and lower GI tract are normal. Likewise, it is important to recognize that chronic NSAID usage could be one cause of protein-losing enteropathy, and that a careful drug history, especially of NSAIDs, should be taken in evaluating any ulcerative condition of the bowel.

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