Protein-losing Enteropathy Associated with Collagenous Colitis Cured by Withdrawal of a Proton Pump Inhibitor

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Abstract

A 63-year-old woman was admitted with symptoms of watery diarrhea and generalized edema lasting for five months. She had been administered 15 mg/day of lansoprazole. Laboratory findings revealed severe hypoproteinemia with normal liver, renal, thyroid and adrenal functions and no proteinuria. Colonoscopy revealed edematous mucosa, minor diminished vascular transparency and apparent longitudinal linear lacera-tions. The histopathological findings were compatible with a diagnosis of collagenous colitis (CC). Protein leakage from the colon was identified on \(^{99m}\)Tc-human serum albumin scintigraphy. The results indicated CC associated with protein-losing enteropathy. Discontinuing lansoprazole ameliorated the watery diarrhea and generalized edema, increased the serum albumin level and improved the hypoproteinemia.

Key words: chronic diarrhea, collagenous colitis, protein-losing enteropathy, proton pump inhibitor, \(^{99m}\)Tc-human serum albumin scintigraphy

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Introduction

Collagenous colitis (CC) is a relatively rare disease that causes chronic nonbloody diarrhea and is characterized as a chronic inflammatory bowel disease. Since the first report of CC in 1976 (1), findings have shown that the disease is associated with a variety of conditions, including treatment with nonsteroidal anti-inflammatory drugs (2) and proton pump inhibitors (3). Collagenous colitis involves a macroscopically normal or nearly normal colonic mucosa with distinctive histopathological features of chronic inflammation in the lamina propria, thickening of the subepithelial collagen layer and epithelial cell damage with or without an increase in the number of intraepithelial lymphocytes. The incidence of CC is highest among women approximately 65 years of age (4), and the condition is usually histopathologically diagnosed as an increase of >10 μm in the thickness of the subepithelial collagen layer. Protein-losing enteropathy (PLE) is a rare and occasionally life-threatening syndrome characterized by the massive enteric loss of plasma proteins, resulting in hypoproteinemia, which can cause general edema, ascites, pleural and pericardial effusions and malnutri-tion. The primary causes of PLE are ulcerative and non-ulcerative enteropathies, while the secondary cause is lymphatic obstruction or increased lymphatic hydrostatic pressure (5). However, severe hypoproteinemia due to enteric protein loss is rare unless accompanied by a small bowel malabsorption syndrome, such as celiac sprue. To the best of our knowledge, CC associated with PLE in the absence of small bowel disease has been reported only twice (6, 7). We herein describe a case of PLE associated with CC in the absence of small bowel disease in which the PLE and CC were respectively diagnosed using \(^{99m}\)Tc-human serum albumin (HSA) scintigraphy, including single-photon emission computed tomography (SPECT) and colonoscopy (CS).

Case Report

A 63-year-old woman with a five-month history of continuous diarrhea and generalized edema was admitted to our hospital in March, 2012. The patient had been medicated with 15 mg/day of lansoprazole for the past year to treat a stomachache that was endoscopically diagnosed as erosive...
Superficial lymph nodes were palpable. The laboratory findings revealed the following: white blood cells, 4,800/mm³; hemoglobin, 14.3 g/dL; C-reactive protein, 0.10 mg/dL; total protein, 4.6 g/dL; serum albumin, 2.8 g/dL; normal liver, renal, thyroid and adrenal functions; negative serology for rheumatoid factor; normal urinalysis findings and no proteinuria. She had neither melena nor hematochezia and the absence of steatorrhea indicated the likely absence of malabsorption syndrome. Colonoscopy revealed a slightly edematous mucosa and diminished vascular transparency throughout the entire colon and rectum (Fig. 1A), with worse findings in the left compared to the right colon. A crowded tortuous vasculature (Fig. 1B), multiple apparent longitudinal linear lacerations of the mucosa (Fig. 1C, D) and an uneven fine granular surface texture (Fig. 1D) characterized the descending colon. Biopsy specimens revealed a sloughing surface epithelium and prominent subepithelial eosinophilic band-like deposits with increased lymphocytes and plasma cells (Fig. 2A, B). These findings were worse in the descending colon than in different portions of the colon and rectum. Azan (Fig. 2C) and Masson’s trichrome (Fig. 2D) staining revealed a subepithelial eosinophilic band recognized as a collagen layer that had thickened by over 10 μm to approximately 70 and 40 μm in the left and right colon and rectum, respectively. Cryptitis, crypt abscesses and superimposed infective inflammatory bowel disease were absent. Endoscopy and biopsies of other portions of the gastrointestinal tract revealed no obvious abnormalities of the stomach, duodenum or end portion of the ileum, and evidence of celiac sprue was undetectable. A barium examination and video capsule endoscopy (VCE) of the small intestine showed no abnormalities. Both 99mTc HSA scintigraphy (Fig. 3A) and SPECT (Fig. 3B) detected protein leakage in the descending portion of the colon that was considered to coincide with the longitudinal linear lacerations of the mucosa observed on CS. No leakage was apparent from the stomach or small intestine. Chest and abdominal computed tomography (CT) did not uncover any evidence of malignancy, and CT indicated no abnormalities in the small and large intestines. These findings indicated a diagnosis of CC associated with PLE. Immediately thereafter, lansoprazole was discontinued, which soon relieved the patient’s diarrhea and improved her general condition. The total serum protein and albumin levels increased to 5.7 and 3.4 g/dL, respectively, three weeks after stopping lansoprazole. Endoscopy performed two months after stopping lansoprazole indicated
apparently normal colonic mucosa (Fig. 4A, B). However, an ulcer scar slightly remained in the descending colon and a small amount of loss of vascularity was also found in the descending colon only (Fig. 4C). The biopsy specimens obtained two months after stopping lansoprazole showed decreased epithelial detachment, fewer inflammatory cells and a remarkably reduced collagen layer beneath the mucosa (Fig. 4D). Additional \(^{99m}\text{Tc}\) HSA scintigraphy and SPECT performed two months after stopping lansoprazole confirmed the absence of tracer accumulation in the large bowel, thus indicating that the PLE had gone into remission.

**Discussion**

Collagenous colitis is a chronic inflammatory bowel disease characterized by chronic watery, nonbloody diarrhea in the context of a macroscopically normal colonic mucosa demonstrated on endoscopy. Although initially underestimated, CC may be responsible for up to 5% of cases of chronic, watery diarrhea (8). The disease affects middle-aged and elderly women with a peak incidence around 65 years of age and a female: male ratio of approximately 7:1 (4). Generally, the colonic mucosa observed in patients with CC is macroscopically normal, although minor, non-
obstruction or other inflammatory diseases. Therefore, we did not have proteinuria, liver disease or cardiac diseases, as well as non-ulcerative enteropathies, such as viral enteritis, bacterial overgrowth, parasitic diseases, eosinophilic gastroenteritis, gluten-sensitive enteropathy, tropical sprue, polyposis syndromes and systemic lupus erythematosus. Secondary PLE is caused by lymphatic obstruction or increased lymphatic hydrostatic pressure (5). Our patient presented with generalized edema, particularly in the lower limbs, chronic diarrhea and severe hypoproteinemia. Colonoscopy and histopathology revealed CC in our patient, who did not have proteinuria, liver disease or cardiac diseases, such as increased lymphatic hydrostatic pressure, lymphatic obstruction or other inflammatory diseases. Therefore, we considered that the hypoproteinemia was enteric in origin. Severe enteric protein loss causing hypoproteinemia is considered extremely rare in patients with CC unless accompanied by small intestinal malabsorption syndrome. Coexistent malabsorption syndrome was unlikely in our patient given the absence of steatorrhea, which is a characteristic feature of malabsorption syndrome. Furthermore, a histopathological examination of the duodenum and ileum revealed no evidence of celiac sprue. Therefore, excessive enteric protein loss without malabsorption syndrome was considered to be the cause of hypoproteinemia. An examination of the small intestine using barium radiography and VCE uncovered no unusual findings, such as Crohn’s disease, malignant lymphoma or other diseases that could cause PLE. Furthermore, 99mTc HSA scintigraphy revealed the absence of tracer accumulation in the small intestine, but identified focal and limited tracer accumulation in the descending colon. Considering that obvious small intestinal diseases were absent, CC was diagnosed as the cause of PLE. Therefore, 99mTc HSA scintigraphy is useful under such circumstances (10, 11).

Although the mechanisms of enteric protein loss in patients with CC are not understood in detail, irregularities of the surface epithelium (12), superficial capillaries (13) and pericytial fibroblasts (14) have been supposed. The endoscopic findings of CC mostly indicate a normal mucosa or nonspecific findings (15). However, an endoscopic examina-
tion of our patient revealed slightly edematous mucosa, somewhat diminished vascular transparency, an uneven fine granular surface texture, a crowded tortuous vasculature and apparently specific longitudinal linear lacerations of the mucosa. A histological examination revealed sloughing of the surface epithelium, a thickened subepithelial collagen layer, epithelial damage and chronic inflammation of the lamina propria, indicating severe CC. The endoscopic and histological findings were more severe in the descending colon than in any other part of the colon and rectum. These findings may explain why our patient developed PLE. Long-term lansoprazole medication may have been associated with the pathogenesis of CC in our patient. A histological examination revealed obvious reductions in epithelial detachment together with clinical improvement after stopping lansoprazole, suggesting that an abnormal epithelial surface plays an important role in the development of PLE. After lansoprazole withdrawal, the protein leakage from the colon observed on 99mTc HSA scintigraphy and SPECT obviously diminished, and a histopathological assessment of the colon biopsy specimens indicated reduced epithelial sloughing and inflammatory cells, as well as a remarkably reduced collagen band under the mucosa. The CS findings also indicated improvements in the edematous mucosa, vascular transparency and multiple longitudinal linear lacerations of the mucosa. Simply withdrawing lansoprazole immediately alleviated the continuous watery diarrhea and generalized edema and improved the serum albumin level and hypoproteinemia in our patient. This clinical course confirmed that lansoprazole caused the CC followed by PLE.

In conclusion, we herein described the case of a patient with extremely rare CC presenting with PLE. Simply withdrawing oral lansoprazole ameliorated the diarrhea and hypoproteinemia without the need for corticosteroids. Collagenous colitis should be included in the differential diagnosis of obscure chronic diarrhea with hypoproteinemia to ensure appropriate management.

The authors state that they have no Conflict of Interest (COI).

References