Severe Diffuse Duodenitis Successfully Treated with Intravenous Tacrolimus after Colectomy for Ulcerative Colitis

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Abstract

We encountered a rare case of severe diffuse duodenitis associated with ulcerative colitis (UC). A 23-year-old man underwent total proctocolectomy with ileal J-pouch anal anastomosis for UC. He suffered from severe abdominal pain, fever and bloody diarrhea for six months after the surgery. Upper double-balloon enteroscopy disclosed severe diffuse duodenitis, of which the findings were endoscopically and histologically similar to those of colonic lesions of UC. Although the administration of prednisolone was ineffective, treatment with intravenous tacrolimus markedly improved the clinical findings. This is the first report of the successful treatment of severe UC-associated diffuse duodenitis with intravenous tacrolimus.

Key words: ulcerative colitis, proctocolectomy, duodenitis, double-balloon enteroscopy, tacrolimus

(Intern Med 53: 2477-2481, 2014)
DOI: 10.2169/internalmedicine.53.1910

Introduction

Ulcerative colitis (UC) is generally described as a superficial diffuse chronic inflammatory disease of the colon. Although UC is known to present with various concurrent extracolonic manifestations, upper gastrointestinal inflammation is considered to be a rare complication. Recently, however, some case series and case-control studies have suggested that upper gastrointestinal inflammation may be more frequent in patients with UC than previously estimated. For example, Hisabe et al. reported that 4.7% of UC patients have ulcerative gastroduodenal lesions considered to be associated with UC based on clinical and pathological features (1). In addition, Lin et al. reported that diffuse chronic duodenitis is present in 10% of UC patients who have undergone a duodenal biopsy and 40% of those treated with colectomy (2). We herein report a case of UC in a patient who suffered from severe UC-associated diffuse duodenitis that was successfully treated with the administration of intravenous tacrolimus.

Case Report

A 19-year-old man was diagnosed with pancolitis type UC. The diagnosis of UC was made based on colonoscopic findings and confirmed according to the detection of typical histological features on a colorectal biopsy. Treatment with oral mesalazine and prednisolone successfully induced remission, after which the oral mesalazine was continued as maintenance therapy. At 23 years of age, the patient’s symptoms relapsed and rapidly became severe. The administration of both prednisolone and infliximab was ineffective, while that of oral tacrolimus was partially effective, although it did not induce remission. The patient underwent total proctocolectomy with ileal J-pouch anal anastomosis and diverting
ileostomy. No evidence of Crohn’s disease was detected at the time of surgery, and the gross and microscopic features of the colectomy specimen were consistent with those of UC.

The patient subsequently developed pouchitis soon after surgery and was treated with antibiotics and an enema. The ileostomy closure surgery was postponed until the pouchitis improved. Although the pouchitis clinically improved, he was again admitted to our hospital due to vomiting, nausea and loss of appetite six months after the surgery (Fig. 1). On admission, his body temperature was 36.4°C, and the laboratory data were as follows: red blood cell count=526×10^4/μL, hemoglobin=15.8 g/dL, white blood cell count=9,700/μL and C-reactive protein (CRP)=0.4 mg/dL. The patient vomited every time he ate or drank. Based on the results of hypotonic duodenography and computed tomography (CT), a diagnosis of superior mesenteric artery (SMA) syndrome was made.

The symptoms of SMA syndrome were improved with fasting; however, severe abdominal pain with a high fever and bloody diarrhea suddenly occurred on day 17 after admission. The patient’s body temperature was 38.2°C, and the laboratory data at that time were as follows: white blood cell count=18,300/μL, CRP=10.8 mg/dL. On CT, duodenal and upper jejunal wall thickening with surrounding panniculitis was found. Treatment with antibiotics had no effect on the patient’s symptoms, and upper double-balloon enteroscopy disclosed severe edema, multiple erosions and bleeding with diffuse granular changes and friable mucosa throughout the entire duodenum (Fig. 2A). The lumen of the horizontal portion of the duodenum was narrowed by external pressure, consistent with the findings of SMA syndrome. The mucosa of the upper jejunum was edematous; however, there were no areas of erosion or diffuse granular changes. A histological analysis of the duodenal lesions revealed severe chronic inflammation with diffuse neutrophilic and lymphoplasmacytic cell infiltration and a reduction in the number of goblet cells, as well as the presence of crypt abscesses, goblet cell depletion and a reduced crypt density (Fig. 3A). Neither granulomas nor cytomegalovirus inclusion bodies were detected in any of the biopsy specimens. We therefore made a diagnosis of severe UC-associated diffuse duodenitis based on both the endoscopic and histological findings of the duodenal lesions, which were similar to those of the colonic lesions of UC.

As the patient was unable to take crushed mesalazine tablets orally due to SMA syndrome, the administration of intravenous prednisolone was initiated (40 mg/day); however, this treatment was found to be ineffective within five days. Therefore, the administration of intravenous tacrolimus was started at an initial dose of 0.02 mg/kg/day, with subsequent doses adjusted to achieve a target whole blood level of 15-20 ng/mL (3-5). This treatment markedly improved both the patient’s symptoms and laboratory data, as well as endoscopic and histological findings (Fig. 2B, 3B). The intravenous tacrolimus was subsequently converted to oral tacrolimus, and he started to take crushed mesalazine tablets (1,500 mg/d) orally, as the SMA syndrome had improved (Fig. 2C). The pouchitis had also improved in association with an improvement in the duodenitis. The patient was dis-
Figure 2. Endoscopic findings of (1) the duodenal bulb and (2) duodenal ascending portion. (A) Before treatment and at (B) two weeks and (C) three weeks after the initiation of treatment with intravenous tacrolimus. (A-1) Edema, multiple erosions and diffuse granular changes. (A-2) Severe edema, multiple erosions, bleeding and diffuse friable mucosa. (B-1) Slight edema and diffuse granular changes. (B-2) The severe edema and diffuse granular changes persisted. (C-1) Almost normal findings. (C-2) Only the edema remained.

Figure 3. Biopsy specimen of the ascending portion of the duodenum. (A: upper left) Before treatment and at (B: upper right) three weeks after the initiation of treatment with intravenous tacrolimus. (A: lower left) Severe duodenitis with diffuse plasma cells, neutrophil and lymphocyte infiltration, crypt abscesses, cryptitis, goblet cell depletion and a decrease in crypt density. (B: lower right) Mild duodenitis with slight inflammatory cell infiltration. No crypt abscesses or cryptitis were detected. The inflammation had markedly improved.
charged on day 77 after admission and continued to take crushed mesalazine tablets. His condition has remained stable, with no signs of recurrence of duodenitis or pouchitis one year after discharge.

Discussion

We herein reported a rare case of UC in a patient who suffered from severe UC-associated diffuse duodenitis that was successfully treated with the administration of intravenous tacrolimus. We made a diagnosis of UC-associated duodenitis in this case based on the findings of previous reports describing upper gastrointestinal inflammation associated with UC, of which the initial symptoms include nausea, vomiting, abdominal pain, watery diarrhea, bloody diarrhea, bloody stools and weight loss (6-12). The upper gastrointestinal inflammation associated with UC is defined as gastritis, duodenitis and/or enteritis, the lesions of which are similar to the colonic lesions of UC with respect to both endoscopic and pathological findings. In particular, diffuse duodenitis is described as a unique pattern in UC patients (2). In the present case, the endoscopic findings of the duodenum showed multiple aphthae, erosions, ulcers, granular changes and a friable mucosa. In addition, the pathological findings resembled the features of colonic lesions of UC, including chronic inflammation with diffuse lymphoplasmacytic cell infiltration, a reduction in the number of goblet cells, distortion of the crypt architecture, cryptitis and the presence of crypt abscesses. Although inflammation remains in the superficial layers of the duodenum in most patients with UC-associated duodenitis, severe cases have been reported to involve transmural wall thickness (13). Therefore, the present patient was diagnosed with a severe case of UC-associated duodenitis based on his CT findings demonstrating duodenal and upper jejunal wall thickening with panniculitis. In addition, the SMA syndrome observed in this case was not only derived from weight loss, but also severe edema throughout the enteric wall. The SMA syndrome observed in this case was not only derived from weight loss, but also severe edema throughout the enteric wall. In this case, upper double-balloon enteroscopy procedures were particularly critical for evaluating duodenjejunal lesions in this case because neither additional damage of the fragile duodenjejunal mucosa nor mucosal bleeding were avoided despite the use of repeated observations.

There is as yet no consensus regarding the treatment of upper gastrointestinal inflammation associated with UC. Previous case reports of gastroduodenitis have shown no response to proton pump inhibitors, although several reports indicated the oral intake of crushed mesalazine tablets to be effective (6, 8). In the present case, the patient was initially unable to take crushed mesalazine tablets orally due to SMA syndrome. However, he was able to resume the oral intake of crushed tablets (mesalazine: 1,500 mg/d) after the SMA syndrome improved. Corticosteroids have also been reported to be effective in most cases (7, 10-12), while some cases required a combination of corticosteroids and azathioprine (7, 11). On the other hand, some patients require surgery for complications, such as perforation (9). In our case, the intravenous administration of prednisolone was not effective, indicating that the patient’s condition was severe and steroid-resistant, whereas the administration of intravenous tacrolimus rapidly improved his symptoms as well as both the endoscopic and histological findings of the entire duodenum (Fig. 2, 3). Recently, treatment with infliximab was reported to alleviate UC-associated gastroduodenitis (9). However, we selected tacrolimus to treat the UC-associated duodenitis in the present case because it was more effective than infliximab for the treatment of UC prior to proctocolectomy. This is the first report of severe UC-associated diffuse duodenitis successfully treated with tacrolimus.

Previous reports and the present case demonstrate that the upper gastrointestinal inflammation associated with UC can be treated using a similar therapeutic strategy as that for UC. We propose the use of mesalazine as first-line induction therapy, with corticosteroids as second-line and infliximab or tacrolimus as third-line treatment. For maintenance therapy, the use of mesalazine is important, and combined therapy with an immunomodulator is considered in some cases. However, care should be taken with regard to the risk of reactivating cytomegalovirus and other infectious diseases, especially in patients treated consecutively with immunosuppressive agents.

In conclusion, we herein reported the first case of severe UC-associated diffuse duodenitis successfully treated with the administration of intravenous tacrolimus. It is important to examine the upper gastrointestinal tract in order to confirm whether UC-associated gastritis or duodenitis exists in patients with UC showing unexplained gastrointestinal symptoms after colectomy, such as upper abdominal discomfort, nausea or appetite loss.

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

References

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