

[CASE REPORT]

Usefulness of Ustekinumab for Treating a Case of Myelodysplastic Syndrome-associated Inflammatory Bowel Disease

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Abstract:

Autoimmune diseases including inflammatory bowel disease (IBD) occur in association with myelodysplastic syndrome (MDS). MDS-associated IBD frequently demonstrates a complicated course. We herein report the first case with MDS-associated IBD that was successfully treated with ustekinumab (UST), an anti-interleukin (IL) 12/23p40 monoclonal antibody. A 63-year-old man with a 7-year history of MDS was referred for examination of diarrhea, abdominal pain and fever. A blood examination revealed a marked elevation of C-reactive protein. Colonoscopy showed multiple ulcers in the terminal ileum. He was resistant to anti-tumor necrosis factor (TNF)- α antibody and azacitidine. Subsequently, UST treatment reduced colonic IL-17 and IL-6 expression and the patient currently maintains a state of remission.

Key words: MDS, IBD, Crohn's disease, Behçet's disease, ustekinumab

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Introduction

Myelodysplastic syndrome (MDS), a clonal hematologic disorder with impaired cell differentiation, is associated with dysregulated hematopoiesis, peripheral cytopenia, and a risk of leukemic progression. Increasing data support the role of innate and adaptive immune pathways in the pathogenesis and disease course of MDS (1). Inflammatory bowel disease (IBD) is a chronic inflammatory disease characterized by a dysregulated immune response. IBD including Crohn's disease (CD) and Behçet's disease (BD) has been reported to coexist with MDS (2-9). MDS-associated IBD is frequently resistant to medical treatment, such as steroids, and anti-tumor necrosis factor (TNF)- α agents. In addition, immunosuppressive therapy could result in life-threatening infections due to MDS-associated leukocytopenia. Thus, MDS-

associated IBD often demonstrates a refractory and complicated course (4, 8).

We experienced a patient with MDS-associated IBD who was successfully treated with ustekinumab (UST), an anti-interleukin (IL) 12/23 p40 monoclonal antibody. UST treatment reduced IL-17 and IL-6 expression levels in the colonic mucosa, suggesting that Th17 cells might play an important role in the pathogenesis of MDS-associated IBD.

Case Report

A 63-year-old male patient was referred in 2010 with pancytopenia and was diagnosed to have MDS, WHO subtype refractory cytopenia with multilineage dysplasia. Trisomy 8 was present in his bone marrow. Six years later, he was referred to our department due to diarrhea, abdominal pain and fever. He had a history of oral ulceration. However,

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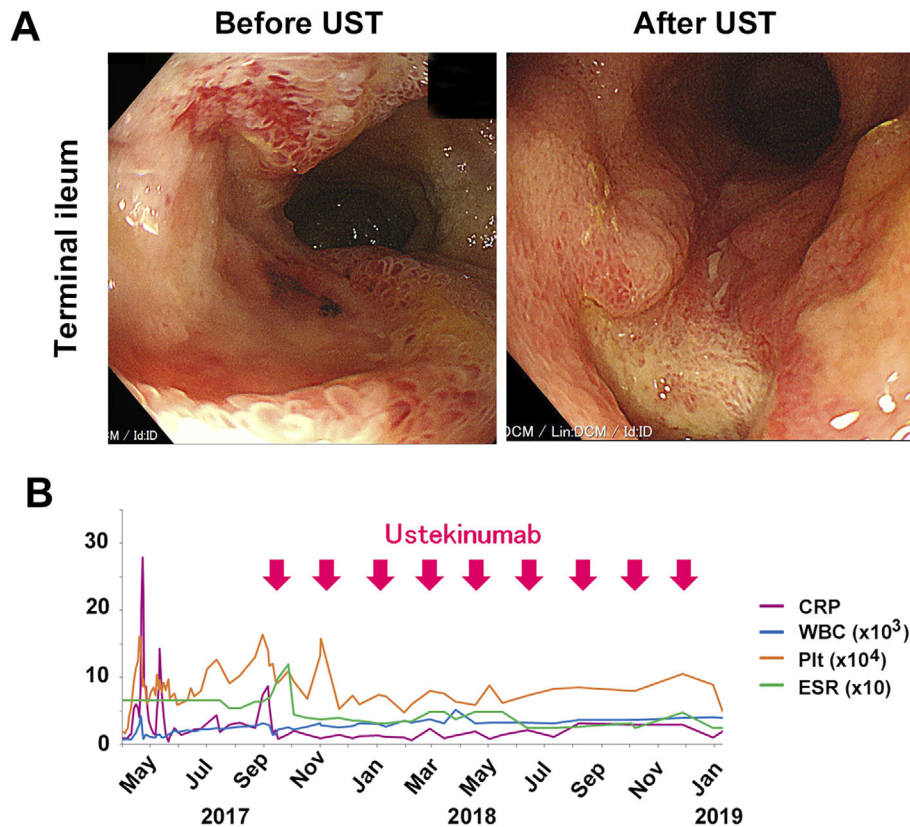


Figure 1. (A) Endoscopic image of the patient with MDS-associated IBD. A large ulcer was observed at the terminal ileum before ustekinumab (UST) treatment, and it shrank after UST treatment. The patient was successfully treated with UST. (B) The clinical course before and after UST therapy.

genital ulceration, uveitis, and skin lesions were absent. His blood tests showed a marked elevation of serum C-reactive protein (CRP, 8.7 mg/dL) and erythrocyte sedimentation rate (69 mm/h). The patient's leukocyte count was $2.9 \times 10^3/\mu\text{L}$; red blood cell count, $2.71 \times 10^6/\mu\text{L}$; hemoglobin, 8.4 g/dL; hematocrit, 27.5 %; platelet count, $11.7 \times 10^4/\mu\text{L}$. The human leukocyte antigen (HLA) B51 was positive and anti-neutrophil cytoplasmic antibody tests were negative.

Colonoscopy was performed to investigate the cause of the symptoms. We found ulcers along the mesenteric margin of the terminal ileum (Fig. 1). Continuous lesions, or diffuse mucosal edema were not seen. Neither a ulcer nor an inflamed mucosa was detected in the colon and the rectum. Enteroscopy showed no ulcers in the stomach, the duodenum and the jejunum. These colonoscopic findings suggest CD or BD rather than ulcerative colitis.

Wall thickening of the terminal ileum was detected in contrast-enhanced abdominal computed tomography scans although neither any abscess or tumor was found. Stool cultures for pathogenic micro-organisms were negative and serum level of β -D-glucan was within the normal limits. The polymerase chain reaction (PCR) for cytomegalovirus and tuberculosis using colon biopsy specimens was negative. Neither pathogenic bacteria nor ameba was found in the colonic mucosa. Thus, infection and malignancy were not likely to have caused intestinal ulcers in this case.

A pathological analysis of colon biopsy specimens exhibited a marked infiltration of inflammatory cells and the destruction of the crypt architecture. An immunohistochemical analysis showed the inflammatory cells to consist of CD68⁺ macrophages, CD4⁺ T cells, CD8⁺ T cells and myeloperoxidase⁺ neutrophils.

Considering the endoscopic findings, we diagnosed this case as CD associated with MDS. However, it may be difficult to distinguish intestinal BD from CD due to similarities in intestinal and extra-intestinal manifestations, and pathologic findings (10). We consider this case to have MDS-associated IBD. The patient was resistant to an anti-TNF- α agent, infliximab, and azacytidine treatment, and then treated with total parenteral nutrition. He relapsed when he resumed enteral feeding, which resulted in repeated hospitalization. After the initiation of UST, he was discharged in September 2017. An endoscopic examination showed the shrinkage of ulcers 6 months after UST started: an ulcer occupying one-third of the circumference decreased in size to less than 10 mm in diameter surrounded by a regenerative epithelium (Fig. 1A). A marked reduction in the serum CRP level was observed 10 months after the initiation of UST (Table). A decrease in the white blood cell and platelet counts after UST therapy led to an improvement of intestinal inflammation, while the effects of such drugs as UST could not be excluded. He has been in clinical remission for

Table. Serum Laboratory Values on before and after Administration of Ustekinumab (UST).

Laboratory test	before UST	after UST
Albumin	3.0 g/dL	3.6 g/dL
C-reactive protein	21.3 mg/dL	1.09 mg/dL
White blood cell count	6,100 / μ L	3,100 / μ L
Erythrocyte sedimentation rate	64 mm/h	26 mm/h
Red blood cell count	3.69×10^6 / μ L	3.73×10^6 / μ L
Hemoglobin	11.8 g/dL	10.9 g/dL
Hematocrit	37.1 %	34.8 %
Platelet count	17.5×10^4 /L	8.3×10^4 /L

After UST: 10 months after the initiation of UST.

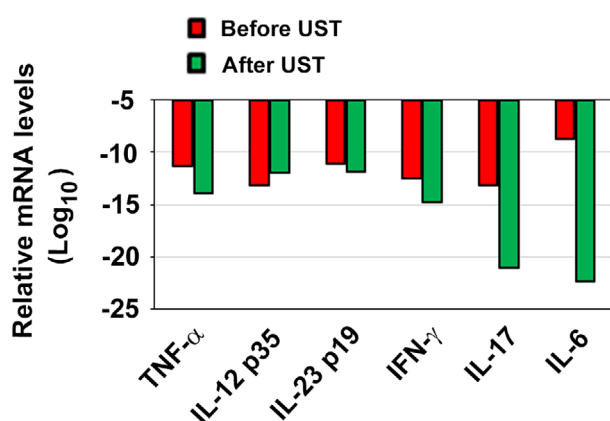


Figure 2. Cytokine profiles. mRNA was isolated from endoscopic biopsy specimens of the terminal ileum before and after ustekinumab (UST) treatment and subjected to quantitative reverse transcription polymerase chain reaction to determine the expression of TNF- α , IL-12 p35, IL-23 p19, IFN- γ , IL-17 and IL-6. The expression of these molecules was normalized by the expression of β -actin.

15 months (Fig. 1B).

We then tried to determine the molecular mechanisms underlying MDS-associated IBD. Isolated mRNA from colon biopsy specimens before and after UST treatment were subjected to a quantitative reverse transcription PCR analysis, as previously described (9, 11). UST remarkably reduced the expression of IL-17 and IL-6 in the colonic mucosa (Fig. 2). One possible mechanism explaining the decrease in proinflammatory cytokines is due to the expansion of regulatory T cells (Tregs) expressing forkhead box p3 (Foxp3) (12). The Foxp3 expression remains unchanged after UST treatment (Fig. 3).

Discussion

Immunological responses are increasingly recognized as being important in the initiation and progression of MDS (1). Indeed, autoimmune diseases occur in association with MDS, particularly in subtypes with a low risk of leukaemic transformation. Elevated IL-17 levels and IL-17-induced interferon (IFN)- γ and TNF- α overproduction may

be involved in the pathogenesis of MDS. The number of CD 3⁺ CD4⁺ IL-17 producing T cells (Th17) has been shown to markedly increase in low risk MDS. The enhanced Th17:Tregs ratio in low risk MDS may account for the high risk of autoimmune disease including IBD (13, 14). UST inhibits the IL12/23 signaling pathway, leading to reduced Th17 responses. Our findings showed that UST therapy reduced the expression of IL-17 and IL-6 in the colonic mucosa, and successfully maintained clinical remission in the patient with MDS-associated IBD. These findings suggest that Th17 might be involved in the pathogenesis of MDS-associated IBD.

CD shares many characteristics with intestinal BD, including genetic background, and clinical manifestations. Both diseases may represent an aberrant immune activity triggered by exposure to specific infectious or environmental agents in patients with an underlying genetic predisposition (10). Genome-wide association studies revealed that IL10 and IL23R variants were observed in CD patients (15). An association for BD with IL10 and the IL23R-IL12RB2 loci, although in different polymorphisms, was also reported (16, 17) suggesting that CD and BD have similar pathogeneses and genetic backgrounds. The major susceptibility gene for CD is nucleotide oligomerization domain 2/caspase-activation recruitment domain containing protein 15 (NOD2/CARD15) (18), while the common variants in NOD2 found in Caucasian patients with CD are not detected in the Japanese population (19). The only modest sensitivity and specificity of HLA-B51 for BD implies that it has limited diagnostic value (20). Thus, the differential diagnosis between CD and intestinal BD remains a challenge for clinicians because of significant clinical, and diagnostic overlap.

MDS-associated IBD frequently demonstrates a refractory and complicated course (4, 8). Consistently, this case was a primary non-responder to anti-TNF- α therapy and resistant to the administration of azacytidine. In addition, we experienced two fatal cases of MDS-associated IBD. One case with an unusual fistula connecting between the ascending colon and the cecum was resistant to anti-TNF- α therapy. In another fatal case, the administration of azacytidine transiently induced mucosal healing (9), while the patient died of sepsis after two cycles of azacytidine treatment.

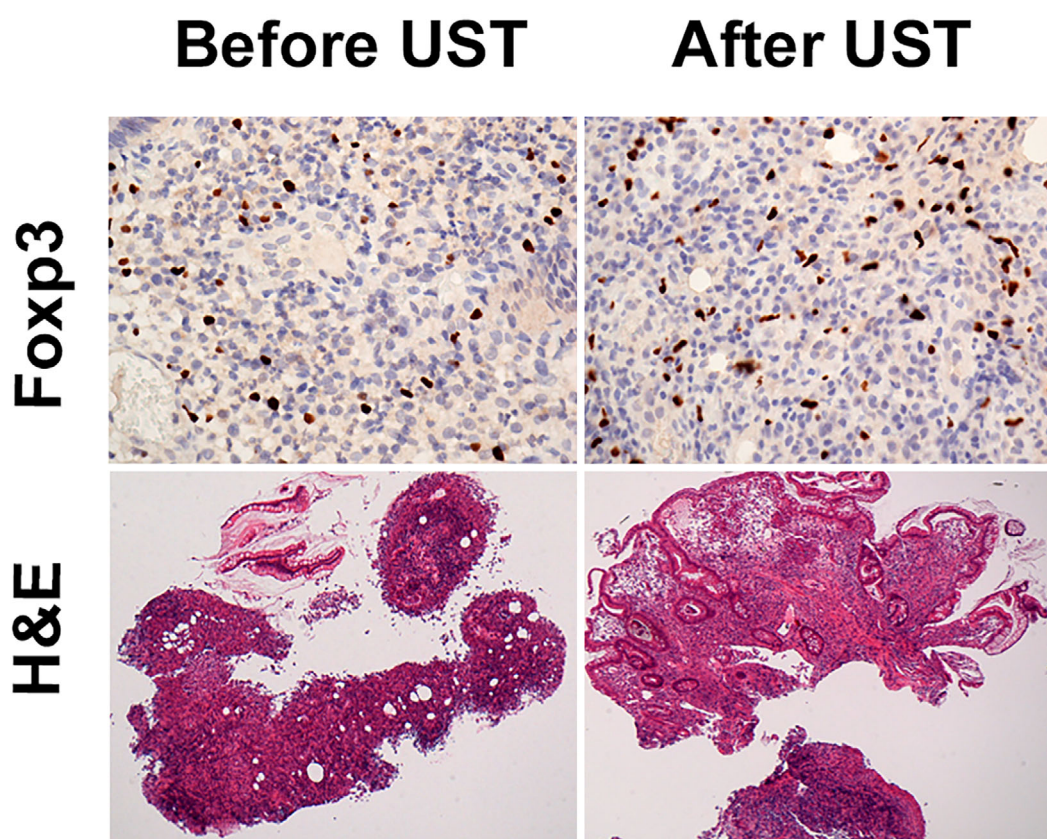


Figure 3. Pathological analysis by Hematoxylin and Eosin (H&E) staining and immunohistochemistry. Endoscopic biopsy samples obtained from the terminal ileum before and after ustekinumab (UST) treatment were fixed in 10% formalin, followed by H&E staining and an immunohistochemical analysis using anti-forkhead box p3 (Foxp3) antibody.

To the best of our knowledge, this is the first case of MDS-associated IBD successfully treated with UST. Given the low risk of serious side effects in UST therapy (21), UST treatment might be recommended for MDS-associated IBD. In CD, preceding primary non-response to anti-TNF- α agent is clinical predictor for more favorable response to UST compared with secondary non-response to anti-TNF- α therapy (21), which was consistent with the findings of our case. It should be noted, however, that confirmation of these considerations awaits future studies addressing the efficacy and safety of UST treatment in a large number of patients with MDS-associated IBD.

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

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