Successful Treatment of a Case of Late-onset Colitis after Umbilical Cord Transplantation with Metronidazole: A Case Report and Literature Review

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Abstract:
Diarrhea after hematopoietic stem cell transplantation (HSCT) can be life-threatening, and its etiology includes conditioning regimens, graft-versus-host disease (GVHD), infections, and transplantation-associated microangiopathy (iTAM). Cord colitis syndrome (CCS) has been described as a syndrome of culture-negative and antibiotic-responsive persistent watery and non-bloody diarrhea of uncertain pathogenesis and occurs in umbilical cord blood transplantation (UCBT) recipients. We encountered a case similar to CCS that developed severe watery diarrhea after UCBT without any signs of GVHD or infection and responded well to metronidazole (MNZ) treatment. Since CCS is very rare, we herein describe a case of MNZ-effective diarrhea after UCBT.

Key words: cord colitis syndrome (CCS), umbilical cord blood (UCB), metronidazole (MNZ), watery diarrhea

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Introduction
Despite the emergence of numerous novel therapies (1, 2), allogeneic hematopoietic stem cell transplantation (HSCT) remains the most effective treatment strategy for hematological malignancies in the post-remission state. In the absence of an appropriate donor, umbilical cord blood (UCB) is often selected as an alternative source. The number of patients undergoing umbilical cord blood transplantation (UCBT) has markedly increased in Japan over the past few years. Due to its improved safety profile, UCB is now regarded as an appropriate source for HSCT (3).

The risk of severe graft-versus-host disease (GVHD) is generally considered to be lower with UCBT than with other graft sources. However, previous findings have indicated that the incidence of diarrhea caused by GVHD is relatively high in patients who undergo UCBT (4). Cord colitis syndrome (CCS) was recently described as a syndrome of culture-negative and antibiotic-responsive persistent watery and non-bloody diarrhea of uncertain pathogenesis; this syndrome affects the recipients of UCBT (5). CCS shows an atypical histopathological manifestation because it typically occurs in the upper and lower gastrointestinal tract and is associated with granulomatous inflammation. Diarrhea is a common but serious complication of HSCT and is caused by various etiologies. An early and accurate diagnosis results in appropriate therapeutic approaches and better outcomes for patients.

We herein report a case of a 60-year-old man diagnosed with acute monocytic leukemia (AML M5a) who underwent UCBT and developed severe watery diarrhea without any evidence of gut GVHD, intestinal transplantation-associated microangiopathy (iTAM), or cytomegalovirus (CMV) colitis. The diarrhea responded well to treatment with metronidazole (MNZ). We herein describe the clinical course and examination findings of this case, together with a literature review.

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A 60-year-old man diagnosed with intermediate-risk AML M5a showed an increased level of Wilms tumor 1 (WT1) mRNA and elevation in the blast percentage in bone marrow 6 months after the completion of 4 courses of consolidation chemotherapy. HSCT was planned, but there were neither human leukocyte antigen (HLA)-matched siblings nor unrelated donors available. UCB was selected as an alternative donor source. The clinical course is shown in Fig. 1. The patient was treated with a reduced-intensity conditioning regimen consisting of 125 mg/m^2 fludarabine, 140 mg/m^2 melphalan and total-body irradiation (TBI) 4 Gy, followed by the infusion of a single unit of cord blood. GVHD prophylaxis consisted of tacrolimus and short-term methotrexate (MTX). The dose of MTX was 15 mg/m^2 intravenously (i.v.) on day 1, followed by 10 mg/m^2 i.v. on days 3 and 6. Neutrophil engraftment was achieved on day 19. A fever, vomiting, diarrhea, abdominal pain, and a skin rash developed on day 20. The frequency of diarrhea is shown in Fig. 1. On day 22, endoscopic biopsies of the stomach and duodenum were performed, and the pathological findings supported a diagnosis of acute GVHD. The patient was treated with 1 mg/kg of methylprednisolone (mPSL). Despite improvements in the skin rash and fever after systemic corticosteroid therapy, the diarrhea and abdominal pain remained unchanged. Morphine was administered in order to relieve the severe abdominal pain.

On day 42, computed tomography (CT) of the abdomen revealed large bowel ileus, which was attributed to the use of opioids. Therefore, opioids were slowly tapered, and a prokinetic agent was initiated. Thereafter, the abdominal pain and image findings of ileus gradually improved. However, the frequency of diarrhea remained unchanged. CT on day 72 revealed diffuse thickness of the colon wall and the retention of ascites (Fig. 2a and b). Laboratory data showed increased levels of transaminase and biliary enzymes without elevations in bilirubin. In addition, his serum albumin level markedly decreased due to its leakage into the intestine and undernutrition (Table). As an immunological study using an anti-CMV monoclonal antibody (C10, C11) demonstrated that cells were positive for CMV antigen, preemptive CMV treatment was initiated on day 42. On day 76, colonoscopy was performed and revealed that the surface of the intestine was edematous, pale, and rough, but with no signs of ulcers (Fig. 2c).

A tissue culture obtained during colonoscopy identified Enterococcus faecium, which is an enterobacterium. In addition, a stool culture was negative with no signs of clostridium toxin. A pathological examination of colonoscopy biopsies revealed that the lamina propria mucosa of the colon was edematous and showed slight invasion of lymphocytes but no signs of ulceration or nuclear inclusions (Fig. 2d and e), suggesting the absence of GVHD. Since the history of this patient was similar to the diarrheal presentation reported by Herrera et al. (5), MNZ (1.5 g daily) was administered for 14 days. After starting MNZ, his diarrhea gradually improved, as shown in Fig. 1. However, the diarrhea relapsed after the cessation of MNZ. Therefore, MNZ was administered for another 14 days. Similar to the initial administration of MNZ, the diarrhea markedly improved within a few days after restarting MNZ. The patient was discharged from the hospital on day 134. On day 139, soon af-

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**Case Report**

Figure 1. Clinical course. The frequency of diarrhea is shown as a black wave. The diarrhea responded well to treatment with MNZ. Flu: fludarabine, MEL: melphalan, TBI: total body irradiation, CBT: cord blood transplantation, MTX: methotrexate, ACV: acyclovir, GCV: ganciclovir, MNZ: metronidazole, PSL: prednisone, TAC: tacrolimus
Figure 2. Abdominal CT scan and colonoscopy findings before the MNZ treatment. (a, b) A CT scan shows the thickness of the colon wall and retention of ascites. (c) Colonoscopy performed before the MNZ treatment revealed that the mucosa of the colon was rough and pale but had no signs of ulcers. (d, e) Colonoscopy biopsy samples stained with Hematoxylin and Eosin staining indicate the retention of normal epithelium tissues and weak invasion of lymphocytes. MNZ: metronidazole

Table. Laboratory Findings before Administering MNZ.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP</td>
<td>3.0 (g/dL)</td>
</tr>
<tr>
<td>Albumin</td>
<td>1.9 (g/dL)</td>
</tr>
<tr>
<td>T-Bil</td>
<td>0.52 (mg/dL)</td>
</tr>
<tr>
<td>D-Bil</td>
<td>0.10 (mg/dL)</td>
</tr>
<tr>
<td>AST</td>
<td>83 (U/L)</td>
</tr>
<tr>
<td>ALT</td>
<td>120 (U/L)</td>
</tr>
<tr>
<td>LDH</td>
<td>238 (U/L)</td>
</tr>
<tr>
<td>ALP</td>
<td>593 (U/L)</td>
</tr>
<tr>
<td>γ-GTP</td>
<td>228 (U/L)</td>
</tr>
</tbody>
</table>


After being discharged, he presented to the outpatient clinic with watery diarrhea at a frequency of more than 10 times a day. Since this was similar to his initial presentation, a third course of MNZ was administered for 14 days. As expected, the watery diarrhea improved after restarting MNZ. CT performed after the third course of MNZ treatment showed improvements in wall thickening and the disappearance of ascites (Fig. 3). This was the last occurrence of MNZ-responsive diarrhea, with no subsequent recurrence being reported to the present date.

Discussion

The differential diagnosis of diarrhea after HSCT includes conditioning regimen toxicity, GVHD, infectious causes...
such Clostridium difficile infection, CMV reactivation, iTAM (6), drug effects, chemoradiation toxicity, and peptic ulcer disease. It is extremely important to make a precise and specific diagnosis of diarrhea after hematopoietic transplantation, as the treatment strategies differ markedly based on the cause and this complication can be life-threatening.

We herein report a case of a recipient of UCBT who developed severe but culture-negative and MNZ-responsive diarrhea. Although diarrhea relapsed several times after the discontinuation of MNZ, it was easily treated by restarting MNZ. CCS was first described by Herrera et al., and is caused by unknown pathogens, but may be treated with antibiotics, such as MNZ or fluoroquinolone. A common presentation of patients with CCS is watery and non-bloody diarrhea lasting for more than seven days. The median time of the onset of diarrhea after UCBT was reported to be 131 days and is frequently accompanied by a fever and weight loss. CT often shows diffuse thickening or an increased CT value of panniculitis of the colon wall. Erythematous mucosa is a major colonscopic finding of this syndrome. Colon biopsy findings have indicated the association of granulomas with inflammatory cell infiltration (5). Previous studies on MNZ-effective diarrhea in UCBT recipients have indicated that Bradyrhizobium enterica is a pathogen of CCS. Indeed, Bhatt et al. performed shotgun DNA sequencing and detected the genome of B. enterica in colon biopsy samples obtained from patients who underwent UCBT (7). In addition, other studies have identified Bacteroides fragilis in colon biopsy samples and proposed that this bacterium is a candidate pathogen of chronic colitis after UCBT (7). In addition to these clinical findings, B. fragilis is known to secrete an enterotoxin in animal models (8). B. fragilis is a commensal and anaerobic bacterium found in the normal flora of the human gut. It has two variations: non-enterotoxigenic (NTBF) and enterotoxigenic (ETBF) (9), with the latter regarded as a pathogen of diarrhea or colon cancer. However, the relationship between ETBF and CCS remains unclear. Based on previous findings, CCS may be related to enterococci pathogens.

A major question regarding MNZ-effective diarrhea is why it only occurs after UCBT. Herrera et al. reported that only 1 out of 381 patients who underwent non-UCBT had findings suggestive of granulomatous colitis. However, this patient’s diarrhea was related to eosinophilia and responded well to immunosuppressants. Therefore, none of the non-UCBT patients developed granulomatous colitis after hematopoietic transplantation (5). In contrast, Shimoji et al. (10) and Milano et al. (11) found that granuloma and Paneth cell metaplasia changes after chronic colitis were not always a unique feature of patients who underwent UCBT. Milano et al. also suggested that CCS might be caused by a geographically limited pathogen restricted to the northeast part of the United States. Both these and the Boston researchers who first reported CCS have advocated a multicentric study to clarify these suspicions. In addition, the Kyushu and Seattle groups asserted that this type of chronic colitis is caused by intestinal GVHD and not by infectious pathogens. Patients were treated with immunosuppressant agents rather than antibiotics in their cohort. Nevertheless, Herrera et al. also suggested a relationship between GVHD and CCS because patients with a history of grade 2 or higher GVHD were more likely to develop this type of diarrhea in their institute than those without such a history.

Another major question is why the Boston patients or our patient, who had immunotherapy-refractory diarrhea, responded well to MNZ therapy. Milano et al. made the following proposal (11): Antibiotics exert therapeutic effects against enteric organisms, which are the pathogens of CCS; the administration of MNZ modifies the microflora, which is altered due to the damage associated with acute GVHD; mycophenolate mofetil (MMF)-related colitis is often difficult to distinguish from the presentation of gut GVHD; and CCS may not consist of a simple or single etiology. MNZ is sometimes used in the treatment of chronic inflammatory bowel disease, such as Crohn’s disease or ulcerative colitis (12). Therefore, MNZ may exert immunomodulatory effects under inflammatory conditions. Magenau et al. reported that CCS is a variant type of GVHD that is accelerated by B. enterica. Therefore, MNZ is effective for late-onset diarrhea in patients after UCBT (13). In our case, the
patient was diagnosed with acute GVHD and treated with systemic corticosteroids. He may have had severe intestinal damage caused by GVHD, and his intestinal microflora may have been obliterated. Therefore, colitis was caused by bacterial translocation via the destruction of the mucosal barrier. The administration of MNZ may have altered his microflora and eventually led to the remission of diarrhea. However, there is no direct evidence to support this hypothesis because no pathogens were detected in cultures. Regarding the relapse of diarrhea, Herrera et al. reported that 45% of patients had recurrence of diarrhea within a median of 7 days after the discontinuation of MNZ, and the relapse of diarrhea was well controlled by restarting MNZ. Nevertheless, the courses and duration of MNZ treatment were not described (5). The optimum dose and course of MNZ treatment for CCS has not yet been established. CCS might be a syndrome that is triggered by various pathogens and not by a single factor alone. As discussed above, since diarrhea after HSCT can be caused by many factors, a close examination needs to be performed, and extensive efforts must be made to determine the cause of diarrhea.

**Conclusions**

This case report indicates that antibiotic-responsive colitis after UCBT needs to be considered as a possible cause of diarrhea in patients who undergo UCBT. An early and appropriate diagnosis will lead to good patient outcomes without the need for unnecessary immunosuppressant agents. Since this is a single case report, we need to accumulate similar cases of watery, non-bloody, culture-negative, and antibiotic-responsive diarrhea following hematopoietic transplantation.

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

**References**


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