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Case Report

Refractory Intestinal Behçet-Like Disease Associated with Trisomy 8 Myelodysplastic Syndrome Resolved by Parenteral Nutrition

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Keywords
Intestinal Behçet disease · Myelodysplastic syndrome · Trisomy 8 · Parenteral nutrition · Case report

Abstract
Intestinal Behçet disease (BD), associated with myelodysplastic syndrome (MDS), is often refractory to treatment. An 80-year-old man with trisomy 8 MDS (refractory anemia) developed intermittent fever. Despite investigations to exclude infectious disease, autoimmune disease, and malignancy as the cause of the fever, the etiology could not be determined. A colonoscopy revealed several shallow round ulcers in the ileocecal region and ascending colon, and the biopsy specimens showed nonspecific inflammation. Thereafter, the patient experienced abdominal pain and diarrhea. Other than an oral aphthous ulcer, the patient did not show symptoms to meet the diagnostic criteria for BD. The patient was diagnosed with intestinal ulcers (intestinal BD-like disease) with MDS and trisomy 8. After treatment failure with 5-aminosalicylic acid, steroid, colchicine, and azacitidine, cerebral infarction occurred. Eating was difficult because of the patient's impaired consciousness; hence, total parenteral nutrition (TPN) was commenced. The fever and abdominal symptoms improved with bowel rest over approximately

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1 month. Small amounts of food were orally administered to the patient following recovery from the after-effects of the cerebral infarction, but diarrhea and fever repeatedly flared up. Therefore, TPN was continued at home. The patient has not experienced any further intestinal BD symptoms for approximately 1 year with bowel rest. Nutritional therapy, including bowel rest, may be an effective treatment option for intestinal BD with MDS, and might be used as an induction therapy of remission or a supportive therapy for other treatments.

Introduction

Behçet disease (BD) is a chronic inflammatory disease of unknown etiology. Intestinal BD is a specific form of the disease that presents with ulcerated intestinal lesions. Myelodysplastic syndrome (MDS) is characterized by abnormal bone marrow hematopoietic cells and ineffective hematopoiesis. Cases of BD associated with MDS have been increasingly reported [1].

Intestinal involvement is often revealed in BD associated with MDS, and most patients have trisomy 8 [1]. Although available treatments, such as steroids, 5-aminosalicylic acid (5-ASA), immunosuppressive agents, and anti-TNFα agents [2], have been used, intestinal BD associated with MDS is often refractory to therapy [3, 4]. Herein, we report a case of trisomy 8 MDS with intestinal BD-like features, wherein remission was achieved with bowel rest by parenteral nutrition following failed treatment with steroids, 5-ASA, colchicine, and azacitidine.

Case Report

An 80-year-old man presented to our hospital with anemia. The patient was undergoing treatment for hypertension and was on no other medication. The patient developed intermittent fever >38°C and showed elevated inflammatory markers (C-reactive protein [CRP] level 13.31 mg/dL) 8 months after the first visit to the hospital. A complete blood count revealed a white blood cell count of 4,470/μL with 46.5% neutrophils, 23.5% lymphocytes, 29.5% monocytes, and 0.5% eosinophils; a red blood cell count of 239×10^4/μL; hemoglobin of 9.4 g/dL; hematocrit of 27.2%; platelet count of 9.6×10^4/μL; and a reticulocyte percentage of 2.2%. A bone marrow biopsy was performed to investigate the gradually progressing anemia. This revealed a slightly hypercellular marrow, mild dysmyelopoiesis, and dyserythropoiesis, but no megaloid changes. The proportion of myeloblasts was <5%. Chromosomal aberrations confirmed by G-band analysis showed 47, XY, +8 in 1 out of 20 cells, and fluorescence in situ hybridization analysis of the bone marrow revealed the presence of trisomy 8 in 47 of 1,000 cells. The patient was diagnosed with trisomy 8 MDS (refractory anemia) based on the abovementioned findings.

Despite investigations to exclude infectious disease, autoimmune disease, and malignancy as the cause of the fever, the etiology could not be determined. Two months after the onset of fever, lower gastrointestinal endoscopy was performed as a part of colorectal polyp follow-up. Several shallow round ulcers with punched-out margins were found in the ileocecal region and ascending colon (Fig. 1a, b). These were not present in the last colonoscopy performed 2 years ago. The biopsy specimens showed nonspecific inflammation (Fig. 1c). No pathogens were detected in the stool culture, and the polymerase chain reaction test for

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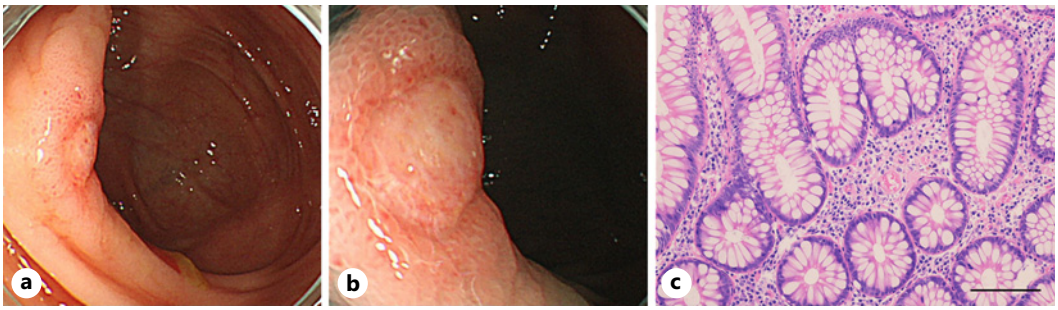

Fig. 1. Colonoscopy revealed round superficial ulcers with punched-out margins in the ileocecum and ascending colon, which had different characteristics from a typical deep ulcer of intestinal BD. Distant (**a**) and close-up (**b**) views of the ulcer in the ileocecal bulb. **c** The biopsy specimen showed nonspecific inflammation. The bar indicates 100 μm.

tuberculosis was negative. Serum β-D-glucan was within the normal range, and both serum and colonic mucosa samples were negative for the cytomegalovirus antigen. The patient experienced abdominal pain and diarrhea 1 month after the endoscopic examination. A CT scan was performed again, and we also did a fecal culture test. They did not reveal any findings that suggest a newly occurring disease.

An oral aphthous ulcer developed soon after fever onset, although no ocular lesions, genital ulcers, or skin lesions were found. The serological test was positive for the HLA-B13 and HLA-B60 alleles but negative for the HLA-B51 allele. The patient was finally diagnosed with intestinal BD-like disease with MDS and trisomy 8; 5-ASA (4 g/day), prednisolone (30 mg/day for 2 weeks), and colchicine (1 mg/day) were administered with no effect. Azacitidine therapy (120 mg/day for 1 week, followed by rest for 3 weeks) was started for MDS. However, the treatment was discontinued due to the appearance of grade 4 neutropenia. In addition, cerebral infarction occurred during the blood cell count recovery period (Fig. 2). Low-dose aspirin was administered but discontinued because massive hematochezia occurred immediately after administration. Cardiac thrombosis was suspected because of multiple cerebral infarctions, although echocardiography and Holter electrocardiogram revealed no abnormalities. Oral intake was difficult because of the patient's impaired consciousness following the cerebral infarction; therefore, total parenteral nutrition (TPN) was commenced. The fever and abdominal symptoms improved with bowel rest over approximately 1 month. Follow-up CRP levels are shown in online supplementary Figure 1 (for all online suppl. material, see https://doi.org/10.1159/000533578). The patient's general condition gradually stabilized, and he was discharged with continued TPN management. Unfortunately, colonoscopy to evaluate any improvement in the intestinal ulcers could not be performed at this stage because pretreatment for colonoscopic examination was not possible due to the patient's condition. Abdominal computed tomography revealed that intestinal wall thickness, which may be caused by inflammation, improved after bowel rest (Fig. 3). Small amounts of food were orally administered to the patient following recovery from the aftereffects of the cerebral infarction, but diarrhea and fever repeatedly flared up. Therefore, TPN was continued at home. The patient has not experienced any further intestinal BD symptoms for approximately 1 year with bowel rest, and there have been no further episodes of cerebral infarction. Baseline blood cell counts have not changed significantly since the fever onset. The MDS has remained stable, and the patient is undergoing follow-up with no specific treatment required.

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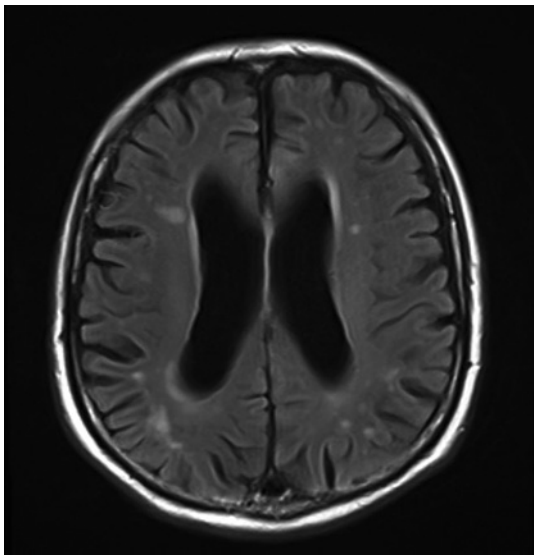

Fig. 2. High-intensity signals dominant in the right cerebral hemisphere on the diffusion-weighted image indicated acute cerebral infarctions.

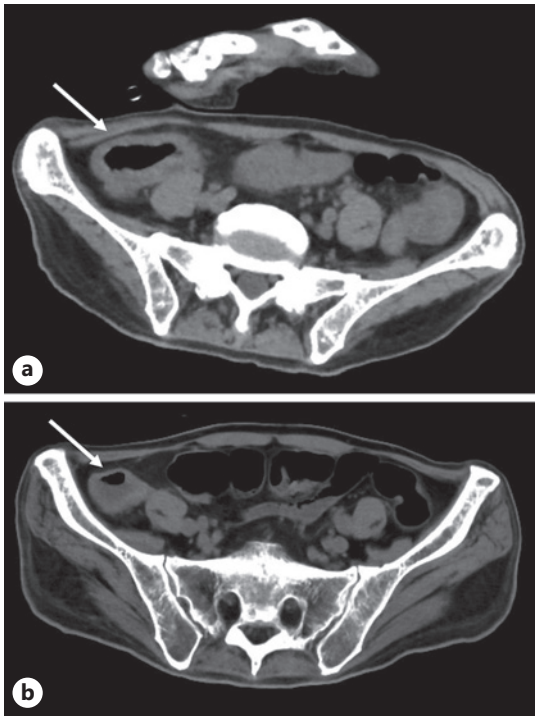

Fig. 3. Abdominal computed tomography revealed wall thickness in the cecum (**a**), which improved 4 months after bowel rest (**b**).

Discussion

The criteria for diagnosis of BD proposed by the International Study Group for Behçet's Disease are used widely [5]. This case had oral ulceration but did not have genital, eye, or skin lesions. A pathergy test was not considered necessary as the diagnostic criteria are oral ulceration along with any two of the following: eye lesions, skin lesions, genital ulcerations, and positive pathergy test. Some cases of intestinal ulcers with MDS have been reported as

having BD-like features, even though they do not meet the diagnostic criteria for BD. Hence, we used the term "intestinal BD-like disease" for this case.

Different features of BD associated with MDS have been reported. While ocular lesions were less common, the frequency of intestinal involvement was much higher compared with general BD [1, 6]. Periodic fever is a typical feature of BD with trisomy 8 MDS [6, 7]. Although features of intestinal BD associated with MDS and trisomy 8 have not been well summarized, different characteristics of ulcers compared with typical intestinal BD (single or a few deep ulcers with discrete margins in the ileocecal area) were also reported [4, 8], and multiple superficial ulcers are speculated as characteristics. This case also showed periodic fever and multiple superficial oval ulcers in the ileocecal region and ascending colon. More studies are needed to elucidate the features of intestinal BD with MDS.

Conventional therapies for intestinal BD and treatments for MDS have been reported in intestinal BD complicated by MDS [9]. Intestinal BD cases are often treated with steroids, 5-ASA, colchicine, azathioprine, and 6-mercaptopurine, but they are often ineffective [3, 4]. The present case is also refractory to 5-ASA, steroids, and colchicine. Since MDS is associated with leukopenia, 6-mercaptopurine and azathioprine require careful monitoring due to their myelosuppressive effects. There is no consensus on the efficacy of anti-TNFα agents, and many refractory cases have been reported [10]. Recently, the effectiveness of ustekinumab has been reported [11]. Conversely, MDS treatment appears to be effective and can be administered to patients who are refractory to steroid treatment [9]. Hematopoietic stem cell transplantation can achieve complete remission [3], although it is not indicated in older patients like this case because of high treatment-related mortality. Azacitidine, a drug used for MDS, has been reported to be effective [12]. Usually, the effects of azacitidine become apparent after three cycles of treatment [9]. However, in this case, treatment was discontinued because of grade 4 neutropenia and the systemic state of the patient following cerebral infarction.

In the present case, fever and abdominal symptoms were relieved by intestinal rest after failure of 5-ASA, steroid, colchicine, and azacitidine treatment. Although there is little evidence on nutritional therapy for intestinal BD, and much less on intestinal BD-associated MDS, the elemental diet therapy is recommended as a supportive therapy [2], although TPN has also been shown to be effective [13]. Usually, TPN is not sustainable due to its inconvenience and detrimental long-term toxicity. In this case, however, other therapies were ineffective, and even small amounts of food triggered symptoms. Therefore, TPN was continued unavoidably. Although cases of intestinal BD accompanied by trisomy 8 MDS are refractory to treatment, remission may be achieved by maintaining intestinal rest, as observed in the present case.

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is a newly defined acquired autoinflammatory disorder associated with MDS, characterized by systemic inflammation with multi-organ involvement [14]. However, mutations in *UBA1*, the gene responsible for VEXAS syndrome, were not investigated in this case. Although gastrointestinal lesions found in this case are not typical features of VEXAS syndrome, this should also be considered as a differential diagnosis in MDS cases with inflammatory responses of unknown etiology.

Cases of thrombosis triggered by granulocyte colony-stimulating factor (G-CSF) in trisomy 8 MDS have been reported [15]. Usually, thrombosis is rare in MDS due to a low platelet count, and although the mechanism of occurrence is unclear, trisomy 8 may be a predisposing factor for thrombosis [15]. In the present case, the underlying risk factors for multiple cerebral infarctions, such as cardiac disease, were absent; therefore, one possible reason for cerebral infarction is the thrombotic risk associated with trisomy 8 MDS.

Although aspirin was discontinued because of gastrointestinal bleeding, there was no further recurrence of cerebral infarction. Although G-CSF was not administered in this case, cerebral infarction occurred during blood cell recovery after azacitidine administration. Therefore, the sudden change in the peripheral blood cell count may have triggered thrombosis. Intestinal BD-like disease may also affect the risk of thrombosis, as BD is sometimes complicated with thrombosis. There are scarce reports of thrombosis in patients with MDS with intestinal BD-like features, and an accumulation of cases will be needed to elucidate the underlying causes.

In summary, BD-like diseases associated with MDS are often refractory to many treatments and lead to significant mortality. There are few reports on treating patients with intestinal BD with MDS effectively. Nutritional therapy, including bowel rest, may be an effective treatment option and might be used as an induction therapy of remission or supportive therapy for other treatments. Further studies are needed to elucidate the efficacy and strategy of nutritional intervention. The authors completed the CARE Checklist for this case report which is attached as online supplementary material.

Statement of Ethics

Ethical approval was not required for this case report in accordance with local and national guidelines. Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Conflict of Interest Statement

Hiroyuki Sakamoto has additional research engagements at the Project Division of ALA Advanced Medical Research, Institute for Quantitative Biosciences, The University of Tokyo, which is an endowed chair from Neopharma Japan.

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The authors declare that no funding sources are associated with this manuscript.

Author Contributions

Yasuo Matsubara, Satoshi Takahashi, Kazuaki Yokoyama, Lim Lay Ahyoung, Michiko Koga, and Hiroyuki Sakamoto were involved in the patient care. Ryo Takahashi and Yasuo Matsubara wrote the manuscript. The manuscript was reviewed by Satoshi Takahashi, Kazuaki Yokoyama, Lim Lay Ahyoung, Michiko Koga, Hiroyuki Sakamoto, Narikazu Boku, Dai Shida, and Hiroshi Yotsuyanagi. All authors have read and approved the final manuscript.

Data Availability Statement

Important data of this case are included in this manuscript. Further inquiries can be directed to the corresponding author.

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