Successful allogeneic bone marrow transplantation after massive gastrointestinal bleeding in a patient with myelodysplastic syndrome associated with intestinal Behçet-like disease

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A R T I C L E I N F O

A B S T R A C T

A 45-year-old woman was diagnosed with myelodysplastic syndrome (MDS) with trisomy 8 and Behçet-like disease (BLD) with multiple colorectal ulcers. Nonspecific inflammatory cells were infiltrated in the intestinal mucosa, whereas fluorescence in situ hybridization (FISH) analysis revealed only sporadic trisomy 8-positive cells. She presented massive lower gastrointestinal bleeding early after bone marrow transplantation but achieved long-term remission of both MDS and BLD. This is the first report of massive gastrointestinal bleeding after transplantation for MDS with BLD. Based on FISH analysis, dysregulation of systemic inflammation may be involved in BLD rather than direct invasion by trisomy 8-positive MDS clones.

1. Introduction

Myelodysplastic syndrome (MDS) is a clonal hematopoietic stem cell disorder characterized by ineffective hematopoiesis and a risk of progression to acute myeloid leukemia (AML). Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only potentially curative treatment for MDS. Behçet disease (BD) is an autoinflammatory multisystem variable vessel vasculitis of unknown etiology characterized by recurrent oral aphthae, genital ulcers, uveitis, and skin lesions. Treatment for BD is tailored to the individual patient, but corticosteroids and immunosuppressive drugs are often used [1].

BD-like symptoms with MDS have different clinical features from BD, and which have been increasingly referred to separately as Behçet-like disease (BLD) in recent years. Trisomy 8 is detected at a frequency of 76.5% in bone marrow (BM) examination of patients with MDS plus BLD compared with 7–9% in patients with MDS alone [2]. However, an etiological association between MDS and BLD has not yet been

demonstrated. Several reports have highlighted the potential efficacy of azacytidine [3], but its clinical evaluation has yet to be determined. Allo-HSCT has been reported to control both MDS and BLD in some cases [3–8]. However, there have been limited reports of complications related to allo-HSCT for MDS with BLD. Wilms' tumor gene 1 mRNA level (WT-1) is a useful molecular marker for assessing the risk of disease progression in MDS patients [9], but has not been reported in MDS with BLD

In this study, we describe the case of MDS with trisomy 8 and BLD successfully improved by bone marrow transplantation (BMT), yet which induced severe gastrointestinal (GI) bleeding in the early phase after BMT.

2. Case report

A 45-year-old woman was admitted to the hospital presenting a two-week history of fever, stomatitis, and genital ulcer. Past medical history

revealed significant patterns of endometriosis and recurrent stomatitis. The patient had not received medications, and her family history was unremarkable. On her physical examination, temperature was 38.3 °C, heart rate was 105 bpm, and all other vital signs were normal. Pallor in palpebral conjunctiva was noted. There were aphthous ulcers on the tongue, oral mucosa, and labium majus. Folliculitis-like lesions were noted in the axilla.
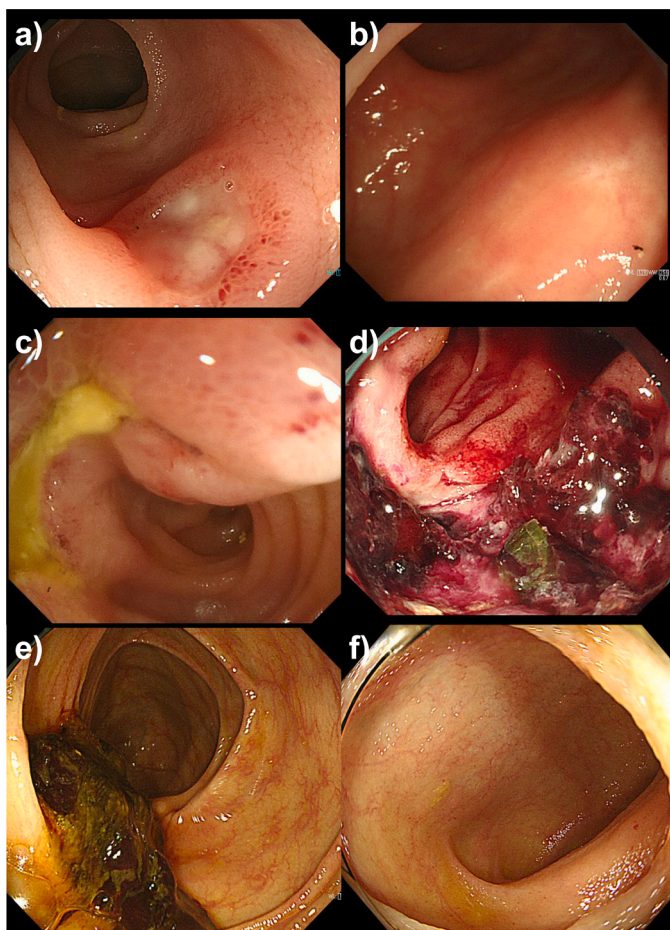
In her initial laboratory workup, the patient's white blood cell count was 7.7×10^9/L, hemoglobin concentration was 6.3 g/dL, mean corpuscular volume was 90.5 fL, and platelet count was 46×10^9/L. Peripheral blood smear showed 0.5% metamyelocytes, 33% band cells, 44.5% mature neutrophils, a few blasts, and some dysplastic cells such as giant platelets, hypersegmented neutrophils, and anisocytosis. Lactate dehydrogenase (LDH) was 400 IU/L, c-reactive protein was 14.1 mg/dL, and WT-1 in the peripheral blood were 1232 copies/μgRNA. The patient was also HLA B27 positive and B51 negative. BM examination showed hypocellularity with 2% myeloblasts, dysplastic megakaryocytes without dysplasia in erythropoiesis and myeloid lineages. The karyotype analysis revealed 47, XX, +8, -20, -21, +mar1, +mar2. A colonoscopy revealed multiple small ulcers in the entire colon, especially in the distal to ascending colon, and a part of the ulcers had pus-like deposits (Fig. 1a). Pathologic examination of the ulcer showed nonspecific inflammatory cell infiltration, mainly composed of lymphocytes and plasma cells (Fig. 2a, b). Finally, sporadic trisomy 8-

Fig. 1. Colonoscopy imaging of the cecum. (a) An ulcer with pus-like deposits in the cecum revealed by colonoscopy at BLD diagnosis. (b) An ulcer scar in the cecum after initial immunosuppressive therapies. (c) Multiple recurrent ulcers in the ileum after one cycle of azacitidine therapy. (d) A hemorrhagic ulcer in the ileum on 3 days after BMT. (e) An ulcer with blood clots in the ileum on 32 days after BMT. (f) An ulcer scar in the ileum on one year after BMT.

positive cells were noticed by fluorescence in situ hybridization (FISH) analysis (Fig. 2c). The patient was diagnosed with BD with gastrointestinal involvement by the International Study Group diagnostic criteria for BD and was finally diagnosed with MDS with multilineage dysplasia and BLD. The Revised International Prognostic Scoring System (IPSS-R) for MDS was high.
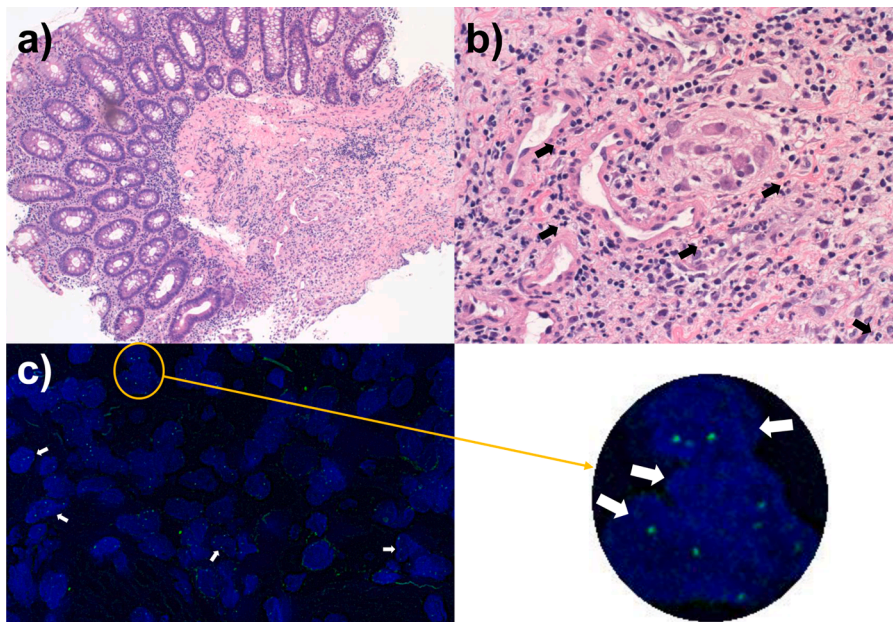
Allo-HSCT was considered for high-risk MDS after diagnosis, but her BD-like symptoms had to be alleviated first before considering a transplantation. The patient received colchicine 1 mg/body, mesalazine 3000 mg, and prednisolone (PSL) 1 mg/kg (40 mg/body) for BLD with supportive therapy for MDS. Accordingly, her fever, ulcer of the oral cavity, and cytopenias were improved, and PSL was gradually tapered until 10 mg. Her symptoms did not recur following PSL taper, and follow-up colonoscopy at 5 months after diagnosis revealed only ulcer scars (Fig. 1b). Four months after diagnosis, her cytopenias had not progressed and LDH remained mildly elevated, but 0.5% blasts appeared in the peripheral blood and WT-1 was elevated to 5891 copies/μgRNA. BM examination showed 0.4% blasts with trilineage dysplasia and the diagnosis remained MDS with multilineage dysplasia. However, immunostaining of BM revealed an increase in CD34-positive cells, followed by two or more separate occasions with 0.5% blasts in the peripheral blood. Therefore, her MDS was progressing to MDS, unclassifiable and allo-HSCT was planned for the patient.

The patient received 75 mg/m^2/day of subcutaneous AZA for 7 days while transplant coordination was conducted through the Japan Marrow Donor Program. Following one cycle of AZA, the patient developed progressive pancytopenia with need for blood transfusion and grade 4 neutropenia by Common Terminology Criteria for Adverse Events (CTCAE) followed by febrile neutropenia. A colonoscopy revealed multiple recurrent ulcers and diffusely edematous intestinal mucosa (Fig. 1c). As the recurrent BLD, the dosage of PSL was increased by 15 mg, and cyclosporine was started at a dose of 3 mg/kg orally. Following these therapies, fever and pancytopenia improved to a condition free of neutropenia and no need for transfusion support. Thereafter, we continued supportive care only, without re-administration of azacitidine.

Six months after diagnosis, the patient received BMT from an unrelated male donor with HLA 8/8 allele matched. The number of nucleated cells infused was 2.35×10^8/kg. Fludarabine (30 mg/m^2/day for 5 days) and busulfan (3.2 mg/kg/day for 4 days) were administered as the conditioning regimen. For graft-versus-host disease (GVHD) prophylaxis, methotrexate (15 mg/m^2 on day 1 and 10 mg/m^2 on days 3 and 6) was administered, and continuous intravenous cyclosporine A was started from day 1 to adjust the serum concentration level around 400 ng/mL. PSL was maintained at 15 mg/body, while mesalazine and colchicine were discontinued. On day 3 after BMT, the patient presented massive lower GI bleeding and developed hemorrhagic shock. An emergency colonoscopy identified a deep ulcer with adherent blood clots in the farther position of the ileum that had not been observed before allo-HSCT (Fig. 1d). Since hemostasis had been spontaneously achieved, no hemostatic procedure was performed. She recovered from hemorrhagic shock by circulatory management centering on transfusion (10 units of red blood cells), and the patient received conservative treatment. Platelet count was 82×10^9/L and no coagulation abnormalities were detected at the time of bleeding. Thereafter, no recurrence of lower GI bleeding was observed, and neutrophil engraftment was achieved on day 17 after BMT. On day 28 after BMT, complete hematological remission was achieved in the BM examination, and WT-1 level in peripheral blood was less than 50 copies/μgRNA. Furthermore, a colonoscopic examination on day 32 after allo-HSCT revealed an ulcer with blood clots at the same location, but no active bleeding was observed (Fig. 1e). On day 38 after allo-HSCT, acute GVHD of the skin (grade II) was developed. The topical steroid and systemic PSL (1 mg/kg) failed to control the patient's acute GVHD, and mycophenolate mofetil (MMF) (30 mg/kg) was added as the additional treatment. Thereafter, all acute GVHD symptoms were resolved, and the patient

Fig. 2. Histopathological images of ulcer lesions in the cecum at BLD diagnosis. (a ,b) Hematoxylin and eosin staining of the ulcer lesion. Nonspecific inflammatory changes with infiltration of neutrophils, lymphocytes, and plasmacytes are observed in the submucosal layer. Black arrows indicate neutrophils. A: low power magnification; B: high power magnification. (c) FISH analysis of the specimen of the ulcer lesion with DAPI staining and green-labeled chromosome 8 centromere probe. Only a few trisomy 8-positive cells are scattered in the submucosal layer. White arrows indicate trisomy 8-positive cells.

was discharged on day 75 after BMT. Colonoscopy at 1 year after BMT revealed only ulcer scars (Fig. 1f), and all BD-like symptoms had completely disappeared at that time.

3. Discussion

This is the first report of allo-HSCT recipient with BLD who experienced post-transplant life-threatening GI bleeding, to the best of our knowledge. Among the previously reported 18 cases of allo-HSCT for MDS or acute myeloid leukemia with myelodysplasia-related changes with BLD [4–8], 16 patients had GI lesions, with 10 of those patients receiving allo-HSCT with active GI lesions. Myeloablative conditioning was performed in 8 patients. No patients developed post-transplant GI bleeding.

The hemorrhagic ulcer was quite deep and extensive in the present case, even though it developed early after allo-HSCT. Although a pathological examination of the intestinal mucosa was not performed at the time of bleeding, many other differential diagnoses including bacterial enteritis and cytomegalovirus enteritis could be ruled out based on the pathology at the time of diagnosis of BLD, the result of stool surveillance culture, and negative CMV antigenemia before allo-HSCT. Taken together with the insufficient control of BLD before allo-HSCT, we suggested that the intestinal lesion of BLD, which was present before allo-HSCT, was temporarily aggravated by cytotoxic conditioning-induced mucosal injury and hypercytokinemia, resulting in life-threatening GI bleeding early after allo-HSCT. Therefore, it is necessary to carefully evaluate and control the disease status to the highest extent before allo-HSCT. However, BLD is often resistant to immunosuppressive therapy or corticosteroids [3], and may not be adequately controlled before allo-HSCT. Taken together, careful and close monitoring is necessary at the time of allo-HSCT while considering the possibility that disease control before allo-HSCT may be inadequate and that bleeding from difficult-to-evaluate sites may occur. In this case, the patient was treated with only one cycle of AZA due to pancytopenia and febrile neutropenia, delaying treatment schedules, followed by allo-HSCT. However, AZA is expected to provide clinical improvement only after 3–4 cycles, it may have been possible to avoid GI bleeding by re-administering AZA with appropriate dose modification, when necessary, before allo-HSCT. If AZA is considered inefficient, the combination with venetoclax may be an option to control MDS with BLD.

BLD have distinct clinical features, such as older age, more frequent

in women, more frequent GI lesions, and less frequent eye lesions than BD [10]. It has been reported that the onset of BD-like symptoms often precedes the diagnosis of MDS. However, the etiology of such differences and associations between MDS and BLD remains unclear. In our study, we examined trisomy 8 of GI ulcers by FISH analysis, and trisomy 8-positive cells were observed only sporadically, and the major infiltrating cells were trisomy 8-negative lymphocytes and plasma cells. Instead of considering the direct infiltration of MDS clones as the main cause of the characteristic clinical features of BLD, it would perhaps be more suitable and efficient to regard MDS clones observed sporadically as only part of the nonspecific inflammatory cell infiltration. A previous report has indicated elevated levels of various cytokines and upregulation of proinflammatory genes in patients with MDS with trisomy 8 [11]. Thus, dysregulation of systemic inflammation by trisomy 8-positive MDS may be involved in the pathogenesis of BLD.

WT-1 has been reported to be useful for risk classification and assessment of minimal residual disease (MRD) in MDS. However, it is unclear whether it is equally useful in BLD and autoimmune diseases associated with MDS. In this case, WT1 decreased after one course of AZA but was still high, and BLD was insufficiently controlled. As mentioned above, MDS may be involved in the pathogenesis of BLD, so if WT1 is high, careful evaluation of BLD activity may be necessary.

In summary, we described a case of trisomy 8-positive MDS with BLD that was successfully treated by allo-HSCT but led to severe GI bleeding during allo-HSCT. MDS with BLD can cause massive GI bleeding after allo-HSCT. It is necessary to carefully evaluate the disease status of BLD, control the disease before allo-HSCT to the greatest extend possible, and monitor closely after HSCT. In the future, further reports are needed to focus on the pathogenesis of BLD and, thus, improve the overall treatment process.

4. Authorship contributions

A.I. and S.T. wrote the manuscript; T.M. and J.I. supported pathological investigations; C.N. and E.S. reviewed and revised the manuscript; and M.Y., Y.N., S.I., K.K, Y.H, N.O―H., T.M, S.M., Y.T., N.M., C.O. and T.I. treated the patient with A.I. and S.T.

Declaration of Competing Interest

The authors declare no competing financial interests.

Acknowledgements

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