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A Case of Myelodysplastic Syndrome with Intestinal Behçet's Disease-Like Symptoms Treated by Prednisolone and Azacitidine

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 68
Final Diagnosis: Myelodysplastic Syndrome with Intestinal Behçet's Disease-Like Symptoms
Symptoms: Abdominal pain • fever • oral ulcer
Medication: —
Clinical Procedure: CT • bone marrow examination • colonoscopy
Specialty: Hematology

Objective: Rare disease

Background: Intestinal Behçet's disease-like symptoms are rare complications of myelodysplastic syndrome and are often refractory to immunosuppressive therapies. We described a case of myelodysplastic syndrome complicated by Behçet's disease-like symptoms treated with prednisolone and azacitidine.

Case Report: A 68-year-old Japanese woman was admitted to our hospital because of persistent high fever and lower abdominal pain. Oral ulcerations developed after admission, and multiple ulcers were found in her terminal ileum by endoscopic examination. She was diagnosed with myelodysplastic syndrome with trisomy 8 by bone marrow examination. Her symptoms diminished after administration of prednisolone, but relapsed afterwards. She began azacitidine therapy and her symptoms have been controlled for at least 10 months.

Conclusions: This case might suggest the possibility of azacitidine as a treatment option for myelodysplastic syndrome complicated by Behçet's disease-like symptoms.

MeSH Keywords: Azacitidine • Behçet Syndrome • Myelodysplastic Syndromes • Prednisolone

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/895431

Background

Myelodysplastic syndrome (MDS) is an acquired blood disorder characterized by varying degrees of ineffective hematopoiesis. MDS is a heterogeneous group of hematopoietic diseases and efforts to predict its prognosis are made by WHO classification system, International Prognostic Scoring system, and also recently by magnetic resonance imaging [1].

Immunological abnormalities occasionally develop in patients with MDS [2–4]. However, intestinal Behçet's disease (BD)-like symptoms are rather rare complications of MDS. Various studies have revealed the significance of trisomy 8 in the concurrent manifestation of MDS and BD with gastrointestinal ulcers [5–7]. We present a case of MDS with intestinal BD-like symptoms (oral and intestinal ulcerations) treated with prednisolone and azacitidine. We reviewed previous reports of similar cases and discuss the characteristics, possible mechanisms, and therapeutic options of this condition.

Case Report

A 68-year-old Japanese woman was admitted to our department for evaluation of a persistent high fever and lower abdominal pain. Initial laboratory tests revealed an elevated C-reactive-protein (CRP) level of 14.8 mg/dL and elevated biliary enzyme levels (alkaline phosphatase [ALP], 738 IU/L; γ-GTP, 213 IU/L). After admission, oral ulcers developed and worsened (Figure 1). High fever and abdominal pain persisted as well. Colonoscopy on day 7 revealed multiple ulcers in her terminal ileum (Figure 2). Biopsies of both lip and intestinal ulcers showed nonspecific inflammation. A computed tomography scan on day 11 revealed hepatomegaly and bowel wall thickening in the terminal ileum (Figure 3). We performed a liver biopsy, which also showed nonspecific inflammation. We did not observe any genital ulcers, eye lesions, or signs of arthritis, and she did not possess human leukocyte antigen B51 (HLA-B51). On day 13, her laboratory findings showed cytopenia (red blood cell count, 3.07×10^6; hemoglobin, 9.9 g/dL; hematocrit, 27.6%; platelet count, $6.0\times10^4/\mu L$), elevated biliary enzyme levels (total bilirubin, 2.9 mg/dL; direct bilirubin, 2.1 mg/dL; ALP, 453 IU/L; γ-GTP, 129 IU/L), enhanced inflammatory responses (CRP, 31.7 mg/dL; ferritin, 3618.0 ng/mL), and decreased prothrombin activity of 43%. At this point, we performed a bone marrow examination, which revealed granulocytic dysplasia (>10%) and a complex karyotype abnormality including trisomy 8 (Figure 4). Based on these findings, she was diagnosed with MDS (refractory cytopenia with unilineage dysplasia/refractory neutropenia). After administration of prednisolone (40 mg/day) on day 16, her symptoms promptly diminished, and her laboratory abnormalities improved. Follow-up colonoscopy on day 39 showed no intestinal ulcers (Figure 5). She was discharged on day 42. While tapering her prednisolone dose, the oral ulcers relapsed and peripheral myeloblasts were found during a blood examination. She was diagnosed with transformation to acute myelocytic leukemia and began

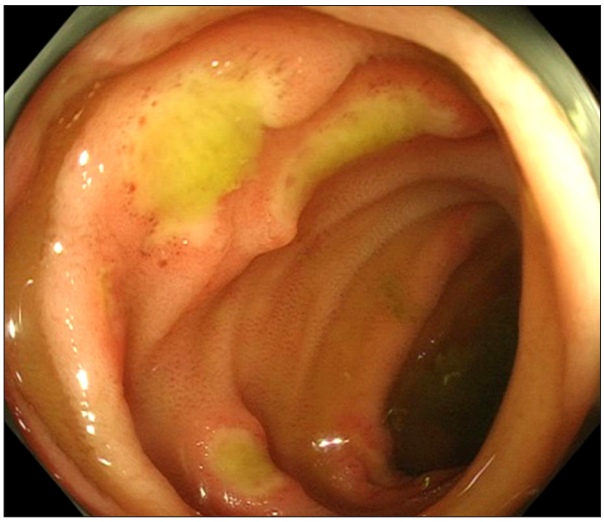

Figure 2. Colonoscopy on day 7 revealed multiple ulcers in the terminal ileum.

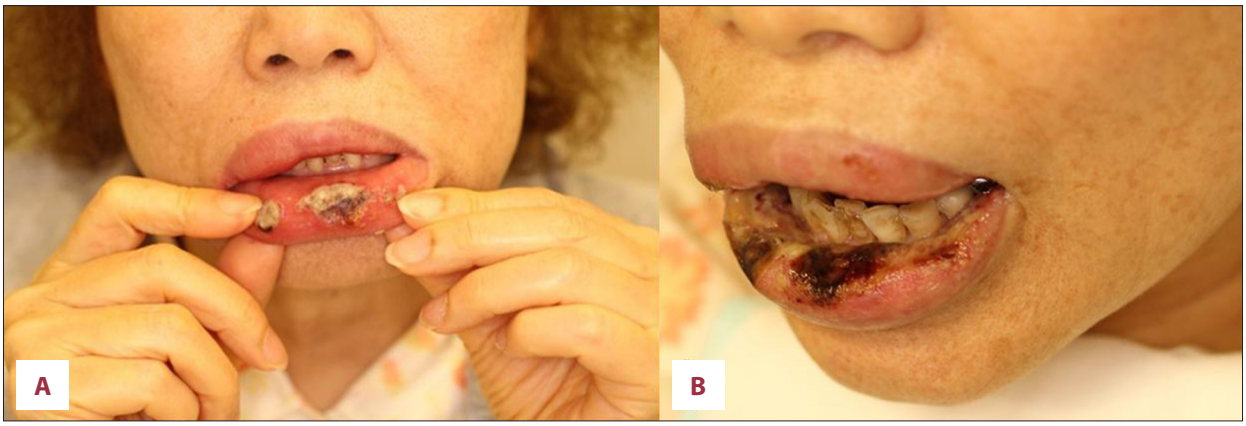

Figure 1. Oral ulcers developed and worsened (**A**: day 4, **B**: day 8).

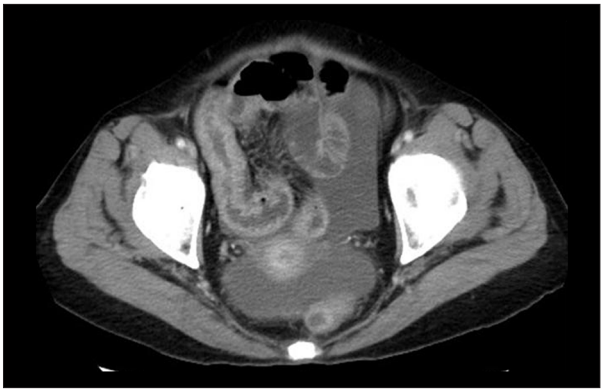

Figure 3. Computed tomography scan on day 11 revealed bowel wall thickening in the terminal ileum.

azacitidine therapy. After administration of intravenous azacitidine (75 mg/m2/day for 7 days of a 4-week cycle), oral ulcers improved and no signs of relapse, such as oral ulcers or high fever, were found at least for the next 10 months.

Discussion

Autoimmune manifestations such as fever, systemic/skin vasculitis, hemolytic anemia, Sweet's syndrome, arthritis, myositis, and neuritis develop in as many as 10% of patients with MDS [2]. These autoimmune disorders reportedly respond to immunosuppressive therapies [2–4]. However, intestinal BD-like

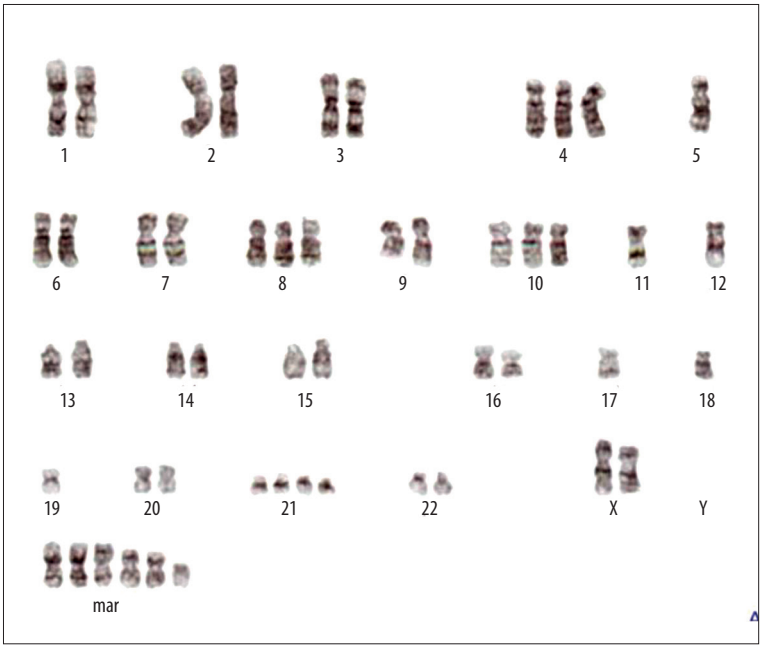

Figure 4. Bone marrow examination revealed a complex karyotype abnormality, including trisomy 8.

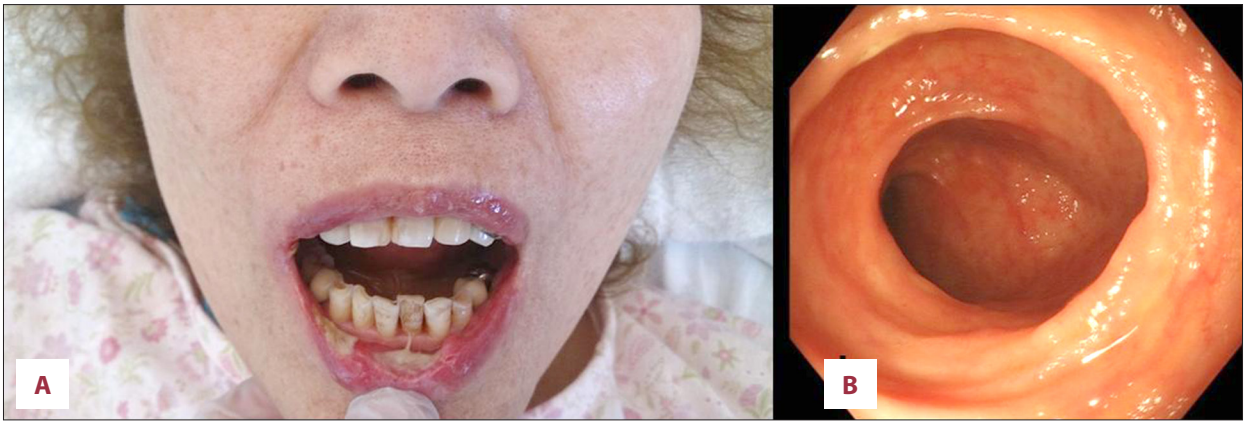

Figure 5. Oral ulcers promptly improved after administration of prednisolone (**A**: day 28), and follow-up colonoscopy (**B**: day 39) showed no intestinal ulcers.

symptoms are rather rare complications of MDS and are often refractory to such immunosuppressive therapies [5].

Approximately 40 cases of MDS complicated with BD symptoms have been reported in the literature [5]. Interestingly, most patients were Japanese and had an incomplete form of BD. Previous reports indicate that MDS complicated with BD symptoms may constitute a subset distinct from common BD or MDS [5–8]. For instance, patients with MDS with BD-like symptoms tend to have a higher prevalence of trisomy 8 than do patients with primary MDS (73.7% *vs.* 8.3–9.8%, respectively) [5,9,10]. On the other hand, compared with patients with common BD, those with MDS complicated with BD symptoms also tend to have more frequent gastrointestinal lesions (67.9% *vs.* 15.5%), less frequent eye lesions (11.1% *vs.* 69.1%), and a lower prevalence of HLA-B51 (36.7% *vs.* 54.9%) [8]. Regarding treatment, previous reports have suggested that administration of immunosuppressive agents (prednisolone, cyclosporin A, and tumor necrosis factor-alpha [TNFα] inhibitors) may have beneficial effects on BD-like symptoms in patients with MDS, but that they are not sufficient to completely control the disease activity, often resulting in relapse of symptoms or serious comorbidities such as gastrointestinal perforation and massive bleeding [5,6,11,12]. One reason for the difficulty controlling MDS complicated with intestinal BD-like symptoms appears to be that the underlying immunological abnormalities are at least partly derived from MDS itself. In fact, cases in which BD-like symptoms in patients with MDS were successfully treated by hematopoietic stem cell transplantation have been reported [12–15].

The pathogenesis of MDS with BD symptoms remains unclear. BD is a chronic inflammatory disease with recurrent acute phases or flares. Several inflammatory cytokines, including interleukin (IL)-1β, IL-6, IL-8, IL-17, IL-18, TNF-α, and interferon (IFN)-γ, have been shown to be elevated in patients with BD, especially during the active phases [16]. Similarly, inflammatory cytokines were recently reported to be involved in the pathogenesis of MDS [17]. Thus, such inflammatory cytokines may be a common factor in the pathogenesis of MDS and BD. Trisomy 8 is also assumed to be a risk factor for BD in patients with MDS [5,6,8,18] and may have an important immunological potential related to such disease activity. Chen et al. [19] analyzed various gene expression patterns in hematopoietic progenitor cells obtained from patients with MDS with monosomy 7 and with trisomy 8 using microarray analysis. Interestingly, they detected distinctively higher gene expression of several cytokines, such as transforming growth factor-β, IFN-β2, IL-6, and IL-7R, which are involved in immune activity and inflammation, in patients with trisomy 8 [19]. Watanabe et al. [20,21] found that the IL-7/IL-7R – dependent signaling pathway is involved in both the immune response in the intestinal mucosa and the development of colitis. Accordingly, patients with MDS with trisomy 8 may have the potential of developing BD-like symptoms because of increased inflammatory cytokine signaling.

In the present case, the cause of elevated biliary enzyme levels and hepatomegaly was unclear. No evidence of vasculitis or neoplastic invasion was found in liver biopsy. Since we used intravenous acetaminophen (up to 4000mg daily) for her fever and abdominal pain, this might partly be a cause of her liver damage. Prednisolone had a favorable effect on the patient's BD-like symptoms, but the effect was transient. In contrast, azacitidine has preserved its therapeutic effect for a long period of time. To our knowledge, only a single case of MDS with BD symptoms treated by azacitidine has been reported [13]. The case was a 59-year-old Japanese male, who suffered from melena, oral and genital ulcers and ulcerations in the entire colon. These symptoms were resistant to immunosuppressive therapies including prednisolone, cyclosporine A and infliximab, and occasional fever remained after the treatment with azacitidine. In contrast, symptoms completely improved by the treatment with azacitidine in our case. Reports in the literature indicate that prednisolone therapy is usually insufficient and that curative therapies for MDS itself, such as hematopoietic stem cell transplantation, are required to control MDS with BD symptoms. However, for patients who are intolerant to such therapies, azacitidine may be an effective therapeutic option.

Conclusions

This case suggests the possibility of azacitidine as treatment option for MDS complicated by Behçet's disease-like symptoms. We reviewed the characteristics of similar cases and discussed the characteristics, possible mechanisms, and therapeutic options of this clinical condition. Further studies are required to clarify the pathogenesis of this clinical condition.

Disclosure

The authors have declared no conflicts of interest.

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