

- transplantation of CD34⁺ cord blood stem cells into newborn and adult NOD/SCID mice induce differential organ engraftment. *Tissue Cell* 2012;44:80-6.
7. Navarro-Montero O, Romero-Moya D, Montes R, et al. Intrahepatic transplantation of cord blood CD34⁺ cells into newborn NOD/SCID-IL2R γ (null) mice allows efficient multi-organ and multi-lineage hematopoietic engraftment without accessory cells. *Clin Immunol* 2012;145:89-91.
 8. Choi B, Chun E, Kim M, et al. Human T cell development in the liver of humanized NOD/SCID/IL-2R γ (null)(NSG) mice generated by intrahepatic injection of CD34(+) human (h) cord blood (CB) cells. *Clin Immunol* 2011;139:321-35.
 9. Brehm MA, Shultz LD, Luban J, Greiner DL. Overcoming current limitations in humanized mouse research. *J Infect Dis* 2013;208(Suppl 2):S125-30.
 10. Ishikawa F, Yasukawa M, Lyons B, et al. Development of functional human blood and immune systems in NOD/SCID/IL2 receptor $\{\gamma\}$ chain(null) mice. *Blood* 2005;106:1565-73.
 11. McKenzie JL, Gan OI, Doedens M, Dick JE. Human short-term repopulating stem cells are efficiently detected following intrafemoral transplantation into NOD/SCID recipients depleted of CD122⁺ cells. *Blood* 2005;106:1259-61.
 12. Lavender KJ, Messer RJ, Race B, Hasenkrug KJ. Production of bone marrow, liver, thymus (BLT) humanized mice on the C57BL/6 Rag2(-/-) γ c(-/-)CD47(-/-) background. *J Immunol Methods* 2014;407:127-34.
 13. van Lent AU, Dontje W, Nagasawa M, et al. IL-7 enhances thymic human T cell development in "human immune system" Rag2-/-IL-2R γ mice without affecting peripheral T cell homeostasis. *J Immunol* 2009;183:7645-55.
 14. Chen Q, Khoury M, Chen J. Expression of human cytokines dramatically improves reconstitution of specific human-blood lineage cells in humanized mice. *Proc Natl Acad Sci U S A* 2009;106:21783-8.
 15. Drake AC, Chen Q, Chen J. Engineering humanized mice for improved hematopoietic reconstitution. *Cell Mol Immunol* 2012;9:215-24.

Successful treatment of a patient with myelodysplastic syndrome accompanied by pyoderma gangrenosum and Behçet's disease using allogeneic stem cell transplantation

TO THE EDITOR: Myelodysplastic syndrome (MDS) is a heterogeneous group of hematopoietic stem cell disorders with ineffective hematopoiesis and resulting cytopenias [1]. Approximately 10–20% of patients with MDS present with autoimmune diseases, such as vasculitis, rheumatoid arthri-

tis, and inflammatory bowel disease [2, 3]. Sometimes, patients with MDS develop skin manifestations including pyoderma gangrenosum (PG), Sweet syndrome, and skin infiltration of malignant cells. The appearance of cutaneous lesions is associated with a poor prognosis [4–6]. Traditionally, hematopoietic stem cell transplantation (HSCT) has been used for refractory autoimmune diseases [7–9] and hematological disorders. Here, we report a case of MDS associated with PG and Behçet's disease that was successfully treated with allogeneic stem cell transplantation.

A 53-year-old man was referred to our hospital in December 2011 for evaluation of pancytopenia. He had suffered from a chronic granulomatous skin lesion on the face for 2 years; there was no improvement despite treatment with methylprednisolone, methotrexate, and dapsone (Fig. 1A). Laboratory findings were as follows: white blood cell count 1,900/ μ L, neutrophils 1,010/ μ L, hemoglobin 8.5 g/dL, platelets 112,000/ μ L, and no blasts in the peripheral blood. At this time, a minimal dose of methotrexate (5 mg/week) was being administered. A bone marrow biopsy showed 4.6% myeloblasts and increased megakaryocytes with dysplastic features. We could not get cytogenetic information due to an inappropriate specimen for karyotyping.

He was diagnosed with MDS with refractory cytopenia with multilineage dysplasia (RCMD) and received a packed red blood cell transfusion every 2 months. In December 2013, he was hospitalized with fever, an aggravated skin lesion, and severe cytopenias (Fig. 1B). Lab tests revealed aggravated pancytopenia: white blood cell count 2,000/ μ L, neutrophils 240/ μ L, hemoglobin 4.9 g/dL, and platelets 32,000/ μ L.

A colonoscopy, performed to evaluate the marked anemia, showed an ulcerative lesion in the terminal ileum (Fig. 1B). A biopsy revealed a chronic ulcer with active inflammation and polymerase chain reaction tests for *Mycobacterium tuberculosis* were negative. Serological tests revealed positivity for HLA B51 and a pathergy test was positive. Based on these results, he was diagnosed with Behçet's disease (Fig. 1B). A skin biopsy of the lower lip showed ulceration with acute and chronic inflammation and focal suppurative inflammation, suggestive of pyoderma gangrenosum.

A subsequent examination of his bone marrow showed a persistent state of MDS with RCMD with a karyotype of 47, XY, dup(1)(q21q32), +8[20]. Based on the International Prognostic Scoring System (IPSS), he was categorized into the intermediate-1 risk group; based on the revised IPSS, he was categorized into the high-risk group. He received three cycles of azacitidine (75 mg/m² intravenously for 7 days, every 4 wk) bridge therapy before HSCT, which did not lead to a response. Unrelated peripheral blood HSCT with reduced-intensity conditioning (30 mg/m²/day fludarabine intravenously for 6 days; 3.2 mg/kg/day busulfan intravenously for 2 days; total 5 mg/kg anti-thymocyte immunoglobulin for graft-versus-host-disease prophylaxis) was performed in March 2014, 27 months after the diagnosis



Fig. 1. Presentation of clinical course after diagnosis of myelodysplastic syndrome (MDS). The facial granulomatous lesion at diagnosis (A), oral ulcer, suppurative ulcer on leg, and ulcerative lesion in ileum by colonoscopy (B). Improvement of the facial granulomatous lesion and leg ulcer after allogeneic stem cell transplantation (SCT) (C).

of MDS. At the time of transplantation, the PG lesion on the leg partially improved, but the facial PG lesion was still active. Neutrophil engraftment occurred on day 17, and platelet engraftment on day 27. About one year after transplantation, ulcerative skin lesions on the face and lower leg disappeared (Fig. 1C) and follow-up colonoscopy revealed no abnormal findings in the terminal ileum. Since then, up to the present, he is free of transfusions and immunosuppressants.

In this case of MDS involving trisomy 8, cutaneous manifestations (i.e., PG) preceded an overt hematological disorder and Behcet's disease. PG was refractory to several immunosuppressants but responsive to MDS treatment with allogeneic HSCT. Several case reports and series have revealed associations between various skin lesions and MDS. Farah *et al.* [5] reported that up to 10% of patients diagnosed with MDS experienced skin manifestations, including non-specific neutrophilic dermatosis, specific-lesion (neoplastic hematopoietic cell infiltration) and leukocytoclastic vasculitis. Haga *et al.* [10] demonstrated that the neutrophils in neutrophilic dermatosis originated from MDS cells. Survival analysis showed a trend of increased leukemic transformation in patients with skin lesions. Thus, it is important to recognize skin lesions in MDS patients even in the early stage, and they warrant close observation.

In patients with underlying diseases, therapy should be directed not only to autoimmune disease but also to the systemic disease. In this case, hypomethylating agent (HMA) treatment did not improve pancytopenia or the skin lesions. It is unclear whether responsiveness to HMA treatment is associated with improvements in skin manifestations. Considering the favorable clinical outcome after HSCT in this patient, an aggressive treatment strategy may be needed, if feasible, in intermediate-risk MDS patients with skin manifestations.

In conclusion, our case provides important evidence indicating that allogeneic HSCT can be a curative modality

for the treatment of MDS and associated pyoderma gangrenosum and Behcet's disease.

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Authors' Disclosures of Potential Conflicts of Interest

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REFERENCES

1. Komrokji RS, Zhang L, Bennett JM. Myelodysplastic syndromes classification and risk stratification. *Hematol Oncol Clin North Am* 2010;24:443-57.
2. Al Ustuwani O, Ford LA, Sait SJ, et al. Myelodysplastic syndromes and autoimmune diseases-case series and review of literature. *Leuk Res* 2013;37:894-9.
3. Komrokji RS, Kulasekararaj A, Al Ali NH, et al. Autoimmune diseases and myelodysplastic syndromes. *Am J Hematol* 2016;91:E280-3.
4. Hagiwara A, Fujimura T, Furudate S, et al. Generalized granulomatous dermatitis accompanied by myelodysplastic syndrome. *Acta Derm Venereol* 2014;94:223-4.

5. Farah C, Bulai Livideanu C, Jegu J, et al. Prevalence and prognostic value of cutaneous manifestations in patients with myelodysplastic syndrome. *J Eur Acad Dermatol Venereol* 2010;24:1171-5.
6. Avivi I, Rosenbaum H, Levy Y, Rowe J. Myelodysplastic syndrome and associated skin lesions: a review of the literature. *Leuk Res* 1999;23:323-30.
7. Tyndall A, Daikeler T. Autologous hematopoietic stem cell transplantation for autoimmune diseases. *Acta Haematol* 2005;114:239-47.
8. Bohgaki T, Atsumi T, Koike T. Autoimmune disease after autologous hematopoietic stem cell transplantation. *Autoimmun Rev* 2008;7:198-203.
9. Yamanaka K, Kuniyuki S, Maekawa N, Yoshida Y, Teshima H. Pyoderma gangrenosum with myelodysplastic syndrome treated with analogous bone marrow transplantation. *Acta Derm Venereol* 2009;89:105-6.
10. Haga N, Iwata H, Yamaguchi Y, et al. Mucocutaneous pyoderma gangrenosum due to trisomy 8 neutrophilic infiltrates in a patient with myelodysplastic syndrome. *Br J Dermatol* 2016;174:239-41.

Post-liver transplant myeloid maturation arrest

TO THE EDITOR: Liver transplantation (LT) has become an effective therapeutic modality for a variety of end-stage acute and chronic liver diseases. Over time, the survival rates have been steadily increasing, but complications remain common in the early and late post-transplant period, contributing to significant morbidity and mortality. Marrow suppression resulting in anemia, thrombocytopenia, and leu-

kopenia is often seen in post-LT patients [1]. However, maturational arrest of the marrow elements at a precursor stage occurs infrequently. Here we present two cases of marked myeloid maturation arrest in the post-LT period in the context of a cytomegalovirus (CMV) infection.

Case 1

A 52-year-old man had chronic liver disease (CLD) and cryptogenic cirrhosis decompensated with ascites, jaundice, acute kidney injury, and hepatic encephalopathy with eccentric portal vein thrombosis. He underwent deceased donor LT in September 2013 and was started on standard triple drug immunosuppression with tacrolimus, mycophenolate mofetil, and prednisolone. The explanted liver showed cirrhosis with an occlusive thrombus of the portal vein. In the early perioperative period, pancytopenia was diagnosed (hemoglobin [Hb], 7.3 g/dL; total leukocyte count, $0.8 \times 10^9/L$; platelet count, $10 \times 10^9/L$). The immunosuppressants and antibiotics were optimized accordingly. He later developed multiple episodes of sepsis during the post-operative period. CMV was detected in a bronchoalveolar lavage and later in plasma samples. A CMV detection assay was performed via real-time quantitative polymerase chain reaction (PCR) for the detection of CMV DNA (COBAS R, Roche Diagnostics, Branchburg, NJ, USA). The cut-off value of the CMV DNA load defining a positive result was 1,000 copies/mL. The bronchoalveolar lavage sample showed 4.60×10^6 copies/mL and the plasma sample had 8×10^3 copies/mL of CMV DNA. Multiple blood transfusions were given per clinical requirements, as was regenerative therapy in the form of granulocyte-monocyte colony stimulating factor (GM-CSF). Despite these measures, the severe pancytopenia persisted. The patient developed severe sepsis (with a multi-drug resistant organism) that led to multi-organ failure and eventually succumbed to the illness.

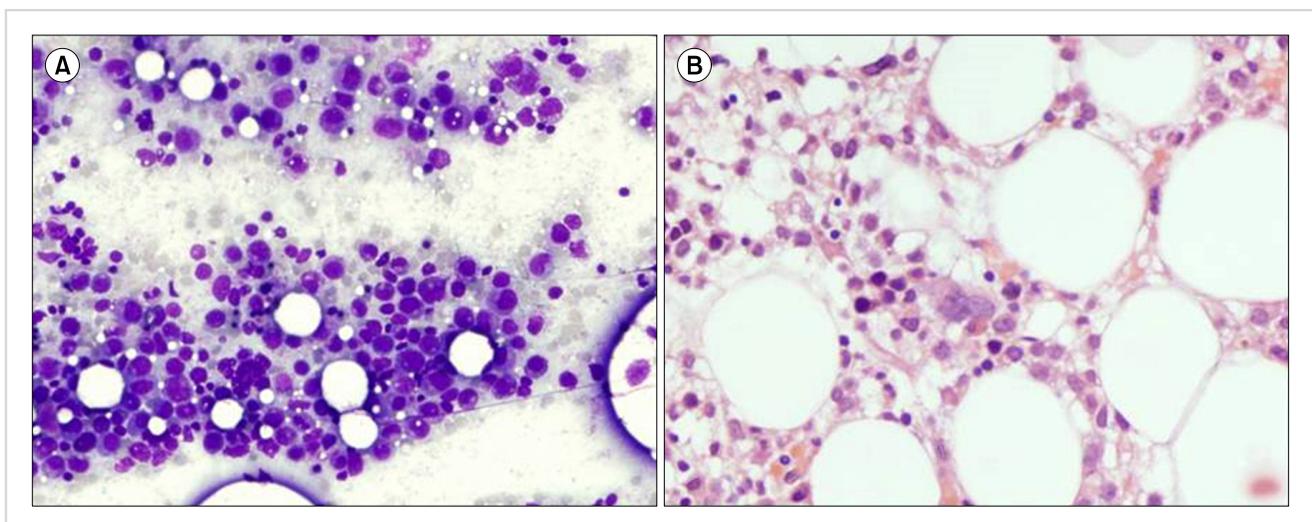


Fig. 1. Bone marrow aspirate (A, May-Grunwald Giemsa stain, $\times 400$) and biopsy (B, Haematoxylin-eosin stain, $\times 400$) of patient 1 showing myeloid maturation arrest.