Clinical Case Reports

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CASE REPORT

Successful treatment of aplastic anemia–paroxysmal nocturnal hemoglobinuria associated with eosinophilic fasciitis with matched unrelated donor allogeneic peripheral blood stem cell transplantation

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Key Clinical Message

We report the first patient case of successful treatment intervention for both eosinophilic fasciitis and aplastic anemia with allogeneic peripheral blood stem cell transplantation from a matched unrelated donor after multiple immunosuppressant failure.

Keywords

Aplastic anemia–paroxysmal nocturnal hemoglobinuria syndrome, eosinophilic fasciitis, stem cell transplantation.

Case Report

A 51-year-old man presented with progressive weight loss of 50 pounds for 6 months, persistent fatigue, worsening edema and stiffness in all four extremities, and limited range of joint motion. At presentation, a complete blood count (CBC) showed white blood cell count (WBC) of $8.8 \times 10^3/\mu L$, absolute neutrophil count of $3.7 \times 10^3/\mu L$, absolute lymphocyte count of $1.3 \times 10^3/\mu L$, absolute monocyte count of $0.6 \times 10^3/\mu L$, absolute eosinophil count of $3.1 \times 10^3/\mu L$, absolute basophil count of $0.1 \times 10^3/\mu L$, hemoglobin 8.8 g/dL, platelet count of $459 \times 10^3/\mu L$, erythrocyte sedimentation rate 108 mm/h (normal range, 0–15), C-reactive protein 4.6 mg/dL, serum lactate dehydrogenase 390 U/L (normal range, 85–227), IgE 172.9 kU/L (normal range, <150), marked polyclonal hypergammaglobulinemia 2.5 g/dL (normal range, 0.6–1.3) without paraprotein by protein electrophoresis, iron 35 μg/dL, total iron binding capacity 141 μg/dL, and ferritin 649 ng/mL. Bone marrow biopsy before immunosuppressive treatment showed hypercellular bone marrow (70–80%) with trilineage hyperplasia and prominent eosinophilia (Fig. 1A).

He was referred to our tertiary care center to evaluate for possible hypereosinophilic syndrome. Physical examination revealed tight thick skin with induration and puckering. There was no palpable lymphadenopathy or hepatosplenomegaly. Stool for ova and parasites, human immunodeficiency virus, viral hepatitis, and parasitic serologies were negative as were rheumatological workup.

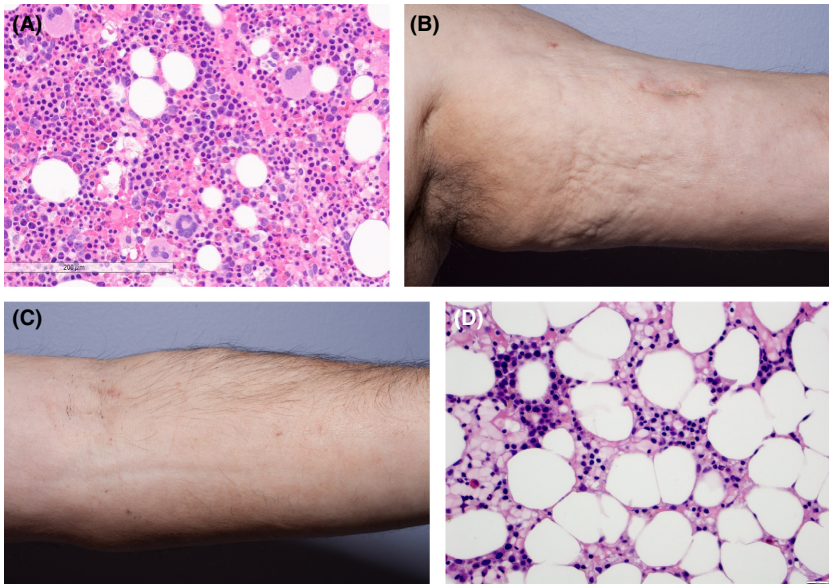

Figure 1. Clinicopathologic description of eosinophilic fasciitis-related aplastic anemia. (A) Bone marrow findings at diagnosis of eosinophilic fasciitis; hypercellular bone marrow with trilineage hyperplasia, prominent eosinophilia, and mild megakaryocytic atypia. (B) Symmetric induration with puckering of the skin consistent with peau d'orange appearance. (C) A linear depression parallel to superficial veins consistent with "groove sign." (D) Bone marrow findings at the time of diagnosis of aplastic anemia; hypocellular bone marrow (20%) with myeloid and megakaryocytic hypoplasia without fibrosis.

He was empirically treated with ivermectin, but the eosinophilia persisted. Bone marrow biopsy obtained after 2 weeks of prednisone treatment showed no morphologic or immunohistochemical evidence of an associated hematopoietic neoplasm. Bone marrow cytogenetic analysis showed normal male diploid karyotype. Qualitative nested RT-PCR for the *FIP1L1-PDGFRA* fusion transcript was not present. T-cell receptor-beta chain gene (TCRβ) rearrangement analysis showed no monoclonal TCRβ rearrangements, but detected several prominent TCRβ rearrangements (oligoclonal pattern). A next-generation sequencing-based analysis for the detection of somatic mutations in the coding sequence of a total of 28 genes was performed on the DNA extracted from the sample in our clinical laboratory improvement amendments-certified molecular diagnostics laboratory, which included *ABL1*, *ASXL1*, *BRAF*, *DNMT3A*, *EGFR*, *EZH2*, *FLT3*, *GATA1*, *GATA2*, *HRAS*, *IDH1*, *IDH2*, *IKZF2*, *JAK2*, *KIT*, *KRAS*, *MDM2*, *MLL*, *MPL*, *MYD88*, *NOTCH1*, *NPM1*, *NRAS*, *PTPN11*, *RUNX1*, *TET2*, *TP53*, and *WT1*, and did not show any evidence of molecular abnormalities. Muscle biopsy from his left biceps demonstrated several foci of CD68+, CD4+, and CD8+ cells. There were eosinophils within the epimysium, perimysium, and to a lesser degree endomysium as well as increased acid phosphatase activity with upregulation of major histocompatibility complex I, consistent with eosinophilic myofasciitis.

He was subsequently sequentially treated with the following: high-dose prednisone alone for 1 month, intravenous methylprednisolone for 1 month, oral methotrexate with prednisone for 4 months, and oral cyclophosphamide for 1 month, which resulted in no improvement of his symptoms and progressive involvement of his fasciitis to his truncal areas (Fig. 1B and C). A CBC 1 month after the last dose of oral cyclophosphamide while on prednisone 60 mg/day with frequent red blood cell and platelet transfusion showed WBC of $2.6 \times 10^3/\mu$L, absolute eosinophil count of $0.0 \times 10^3/\mu$L, hemoglobin 9.2 g/dL, and platelet count of $21 \times 10^3/\mu$L. Repeat bone marrow biopsy showed a hypocellular bone marrow (20% cellularity), and no morphologic evidence of hematopoietic neoplasm (Fig. 1D). Peripheral blood flow cytometry identified clones of glycosylphosphatidylinositol (GPI)-deficient cells among granulocytes (3.8%), monocytes (3.3%), and red blood cells (1.8%). He was diagnosed with aplastic anemia–paroxysmal nocturnal hemoglobinuria syndrome (AA-PNH) in the context of eosinophilic fasciitis.

He was found to have progressive transfusion-dependent cytopenias with WBC of $1.6 \times 10^3/\mu$L, ANC of $0.83/\mu$L, hemoglobin 7.8 g/dL, and platelet count of $40 \times 10^3/\mu$L. He was subsequently treated with horse antithymoglobulin (ATG) 40 mg/kg/day for 3 days on days 2–4, cyclosporine 5 mg/kg started on day 1 for

90 days at least, and methylprednisolone 1 mg/kg/day for 10 days on days 1–10. He responded to ATG and cyclosporine with partial improvement of CBC on day 90 of ATG therapy; WBC of 6.2 × $10^3/\mu$L, ANC of 4.75 × $10^3/\mu$L, hemoglobin 9.7 g/dL, platelet count of 21 × $10^3/\mu$L. However, he remained transfusion dependent, and continued to experience progressive debilitating symptoms related to EF. The patient had a HLA-full match donor at the allele level of HLA-A, -B, -C, -DR, and -DQ through the national bone marrow registry.

He (O Rh+ blood type) proceeded to MUD allogeneic peripheral blood stem cell transplantation from a type A Rh+ male donor with a conditioning regimen of 4 days of busulfan with a target area under the curve of 4000 μmol-min, 4 days of fludarabine 40 mg/m^2 on days −6 to −3, and rabbit ATG 0.5 mg/kg on day −3, 1.5 mg/kg on day −2, and 2 mg/kg on day −2. For graft-versus-host-disease (GVHD) prophylaxis, he received tacrolimus 0.015 mg/kg starting on day −2 and methotrexate 5 mg/m^2 on days 1, 3, 6, and 11. The infused total nucleated cells were 478 × 10^8 (5.1 × 10^8/kg) with 8.62 × 10^6/kg viable CD34-positive stem cells. He received filgrastim 5 μg/kg subcutaneously daily starting on day 7 for 5 days. CBC on day 30 showed WBC of 5.6 × $10^3/\mu$L, ANC of 1.93 × $10^3/\mu$L, hemoglobin 10.6 g/dL, platelet count of 61 × $10^3/\mu$L. Microsatellite polymorphism analysis on day 30 showed 100% donor type. As of day 297 on tacrolimus for GVHD prophylaxis, a CBC showed WBC of 5.7 × $10^3/\mu$L, ANC of 2.36 × $10^3/\mu$L, absolute eosinophil count of 0.36 × $10^3/\mu$L, hemoglobin 12.3 g/dL, platelet count of 169 × $10^3/\mu$L. He did not have significant GVHD, and was noted to have significant improvement of skin thickening with resolution of tissue eosinophilia as well as remission of aplastic anemia after engraftment.

EF [1] is characterized by collagenous thickening of the subcutaneous fascia with marked eosinophilia. Various hematological disorders are associated in up to 10% of patients with EF including AA-PNH, myeloproliferative disorders, chronic lymphocytic leukemia, myelodysplastic syndromes, lymphoma, and multiple myeloma [2]. A universal treatment strategy for EF-related AA-PNH remains unclear due to the rarity of the disease and lack of clinical trial data. Several therapeutic interventions have been reported in the literature including ATG, cyclosporine, rituximab, corticosteroids, and allogeneic stem cell transplantation from a matched related donor [3–5]. De Masson et al. summarized three cases of EF-AA treated with allogeneic stem cell transplant from a matched related donor: two of whom achieved remission; one of whom died of sepsis at day 86 of stem cell transplantation [3]. Cetkovsky et al. reported a case report of successful allogeneic bone marrow transplantation for eosinophilic fasciitis with severe aplastic anemia, and the patient achieved long-term remission of eosinophilic fasciitis as well as aplastic anemia at 34 months following bone marrow transplantation from a matched related donor [6]. In our case, the patient was previously treated with high-dose steroids, methotrexate, cyclophosphamide, and combination of ATG and cyclosporine, which failed to suppress progression of EF-related AA-PNH. We believe this may be among the first case report of successful treatment of EF-related AA-PNH with allogeneic peripheral blood stem cell transplantation from a matched unrelated donor. Further clinical studies are needed for the management of EF-related AA-PNH.

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Conflicts of Interest

All authors have nothing to disclose.

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