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Human leukocyte antigen-haploidentical hematopoietic stem cell transplant for a patient with histiocytic sarcoma

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Histiocytic sarcoma (HS) is a rare malignancy. The few favorable outcomes reported in the literature involved patients treated with hematopoietic stem cell transplant (HSCT). None of the few published case reports we found in a PubMed search used a human leukocyte antigen (HLA)-mismatched HSCT graft. We report here the outcome of a patient with HS who was treated with an HLA-haploidentical HSCT.

A 23-year-old African-American male presented with gum bleeding and epistaxis for 4 weeks without constitutional symptoms. Physical examination showed hepatosplenomegaly without lymphadenopathy, and laboratory evaluation showed pancytopenia with a hemoglobin (Hb) 6.3 g/dL (normal range [NR] 12–16 g/dL), platelet count $6 \times 10^9/L$ (NR $150\text{--}450 \times 10^9/L$) and white blood cell count (WBC) $2 \times 10^9/L$ (NR $4\text{--}11 \times 10^9/L$) with a differential of 69% neutrophils, 4% bands, 18% lymphocytes, 3% monocytes, 6% eosinophils and no blasts. Blood smear showed anisopoikilocytosis of red blood cells (RBCs) but no morphologic abnormalities of WBCs. Kidney function and liver enzymes were normal; ferritin was 1393 ng/mL (NR 10–300 ng/mL) and lactate dehydrogenase (LDH) was 135 U/L (NR 118–273 U/L). Imaging confirmed hepatosplenomegaly without lymphadenopathy. Bone marrow (BM) examination was noted for a fibrohistiocytic infiltrate with evidence of hemophagocytosis and trilineage hematopoiesis with erythroid and megakaryocytic hyperplasia [Figure 1(a)]. Immunohistochemistry was noted for increased CD68 + histiocytes but no increase in blasts. There was +3 reticulin fibrosis and abundant iron stores. The patient was transfused and treated with intravenous immunoglobulin (IVIG), high-dose steroids and etoposide for presumed hemophagocytic lymphohistiocytosis. There was no response and the patient was transferred to Johns Hopkins Hospital.

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Repeat imaging at Johns Hopkins Hospital confirmed splenomegaly (16 cm), hepatomegaly (22 cm) and numerous sclerotic lesions throughout the skeleton. Splenic core biopsy showed large CD68 + histiocytes with cytologic atypia. Hemophagocytosis was noted but was not prominent. A positron emission tomography (PET) scan showed right cervical and right para-aortic region lymph node intense activity, and multiple foci of activity throughout the skeleton, but no significant activity in liver or spleen. A right cervical lymph node biopsy was performed and showed an infiltrate of pleomorphic large cells with abundant pink cytoplasm, and varied oval to complex and hyperchromatic nuclei, but no hemophagocytosis was seen [Figure 1(b)]. By immunohistochemistry, the large cells were positive for CD163 [Figure 1(c)], CD68 and CD31, but negative for S100, Cam5.2, CD43, CD30, CD34 and SALL4, consistent with a diagnosis of HS. Combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) was administered. The patient remained red blood cell and platelet transfusion-dependent. Severe thrombocytopenia ($10 \times 10^9/L$) failed to respond to HLA-matched single donor platelet transfusions, steroids and IVIG. Etoposide was added to the regimen. Interim PET-computed tomography (CT) imaging and BM examination were consistent with a partial response. The patient received two additional chemotherapy cycles.

The patient then underwent myeloablative conditioning with oral busulfan (total dose 16 mg/kg) given on days -6 through day -3, and cyclophosphamide 50 mg/kg IV daily on days -2 and -1. He received an HLA-haploidentical T-cell replete bone marrow infusion procured from his mother (ABO-compatible, 2.4×10^8 nucleated cells/kg). This was followed by post-transplant cyclophosphamide (PT/Cy) at 50 mg/kg IV on days +3 and +4, mycophenolate mofetil (planned for day +5 through day +35) and tacrolimus (planned for day +5 through day +180) for graft-versus-host disease (GVHD) prophylaxis [1]. The post-transplant course was notable for refractory thrombocytopenia, subdural hematoma and primary graft failure (with BM examination showing marked hypocellularity, but no tumor 35 days after transplant).

Two months after the first transplant, the patient underwent a second preparative regimen with fludarabine 30 mg/m² IV and alemtuzumab 20 mg IV daily from days -6 through -2 and received a second HSCT infusion, this time with filgrastim-mobilized peripheral blood (PB) stem cells from the same donor (18.3×10^6 CD34 + cells/kg). Neutrophil engraftment to $0.5 \times 10^9/L$ neutrophils occurred on day +11. The patient developed acute respiratory failure requiring mechanical ventilation, posterior reversible encephalopathy syndrome with seizures, hemorrhagic cystitis and renal failure, managed with bilateral nephrostomy drainage and hemodialysis. Organ dysfunction resolved. At day +30 microsatellite polymerase chain reaction (PCR)-based PB chimerism analysis showed 94% donor DNA, and the platelet count had improved to $20 \times 10^9/L$. Day +60 bone marrow examination showed marked hypocellularity (5–10%) with no evidence of tumor. Day +62 chimerism analysis showed 100% donor DNA. Currently, with a follow-up of 12 months after the salvage HSCT, the patient continues to be in remission, transfusion-independent, with WBCs $4 \times 10^9/L$, Hb 9.8 g/dL and a platelet count $65 \times 10^9/L$ at his most recent visit. He is currently asymptomatic, fully functional with excellent performance status, and exhibits no clinical signs of GVHD after discontinuation of all immunosuppressive therapy.

HS is a rare malignant tumor that can occur in any organ where histiocytes are present, including nodal and extranodal sites [2,3]. As exemplified by our case, HS can be challenging to diagnose, especially in cases that arise in extranodal sites. Diagnosis requires establishing a true histiocytic lineage and distinguishing HS from other histiocytic disorders, both benign and malignant [4,5]. Indeed, improvements in immunohistochemistry showed that many previously reported cases of HS were actually misdiagnosed cases of high-grade non-Hodgkin lymphoma [2,4,6]. HS diagnosis requires histiocytic differentiation markers CD163, CD68 (KP1) and lysozyme in the absence of CD1a (Langerhans cell marker), CD21 and CD35 (dendritic cell markers) or markers indicative of other poorly differentiated large cell tumors such as melanoma or lymphoma [2,5,6].

HS is characterized by extranodal, multi-organ involvement, an aggressive clinical course, association with hemophagocytosis, and poor response to chemotherapy in most patients [2–5]. Refractory thrombocytopenia and anemia in association with hemophagocytosis, and bony involvement have been reported [2,3]. A variety of chemotherapy regimens have been used, including CHOP and CHOP-like regimens, and etoposide and thalidomide have also been used in combination [3,6,7]. The few reports of favorable outcomes have mostly been in the context of HSCT performed as consolidation after chemotherapy or as salvage after relapse [2,3,6,8,9]. Some of the reports of successful treatment predate modern immunohistochemistry, making it difficult to ascertain whether these were bona fide cases of HS [6]. HSCT with autologous cells (five cases) [2,6,8,10,11], and HLA-matched allogeneic (four cases using related and unrelated donors) HSCT have been reported [3,7,9,12]. To our knowledge, our case describes the first HLA-haploidentical HSCT for a patient with HS.

Our patient had very aggressive disease with extensive marrow involvement that precluded autologous HSCT. He was without full siblings, and timely identification of an unrelated donor for this African-American patient was unlikely. We have reported encouraging outcomes for T-cell replete allogeneic HSCT from HLA-haploidentical donors after myeloablative and non-myeloablative conditioning regimens, followed by PT/Cy for GVHD prophylaxis [1,13,14]. The use of PT/Cy is a novel approach for GVHD prophylaxis that takes advantage of the differential susceptibility of proliferating alloreactive T-cells on days +3 and +4 over non-proliferating T-cells non-reactive to high-dose cyclophosphamide [13]. Our patient had primary graft failure, and was salvaged with PB-collected T-cell replete HLA-haploidentical HSCT from the same donor using our previously described preparative regimen with fludarabine and alemtuzumab [15]. The use of HLA-haploidentical related donors may allow life-saving treatment when alternative donor options are limited.

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Figure 1.

(a) Bone marrow is remarkable for an infiltrate of cytologically bland histiocytes, many of which show hemophagocytosis. Background marrow demonstrates marked erythroid hyperplasia. (b) Core biopsy of level IV neck lymph node showing an infiltrate of pleomorphic large histiocytes with hyperchromatic nuclei that vary from oval to complex. Most neoplastic histiocytes have abundant pink cytoplasm. No areas of hemophagocytosis

are identified. (c) Immunostain for histiocyte marker CD163 in neck lymph node biopsy showing diffuse positivity.