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Case report

Treatment of severe Evans syndrome with an allogeneic cord blood transplant

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Summary:

Immunosuppressive therapy is commonly used in the management of autoimmune disorders. As marrow-derived lymphocytes appear to play a key role in these diseases, lymphoid ablation followed by replacement with autologous or allogeneic stem cells may be a therapeutic option. We report a 5-year-old boy with severe Evans syndrome which consists of immune thrombocytopenia and Coombs-positive hemolytic anemia. He was rendered into complete remission with marrow ablation followed by rescue with an HLA-identical sibling cord blood transplant. He unexpectedly died 9 months following transplant from acute hepatic failure of unknown etiology.

Keywords: cord blood transplant; Evans syndrome; autoimmune disease

Utah Unique Patient No. 263 was the product of a normal pregnancy, labor and delivery. He was apparently healthy until 5 months of age when he presented with Coombs-positive hemolytic anemia and thrombocytopenia. Bone marrow evaluation revealed a hypercellular marrow with normal myeloid and erythroid elements, but increased megakaryocytes. No viral infection could be identified. The diagnosis of Evans syndrome was made, and he was subsequently treated with prednisone, intravenous immune globulin, 6-mercaptopurine and danazol, all with poor response. Because of refractory thrombocytopenia, he underwent splenectomy at 9 months of age, with a transient rise in his platelet count to greater than 100×10^9/l but with a rapid fall to less than 20×10^9/l. Over the next 4 years, he was treated with cyclosporine, azathioprine, combination chemotherapy, anti-Rh antibody (anti-D) and 28-day cycles of pulse methylprednisolone, vincristine, and intravenous immune globulin. The pulse therapy was most successful, as it transiently increased his platelet count to greater than 50×10^9/l for 1 to 2 weeks.

Despite frequent platelet counts of less than 20×10^9/l, he remained clinically stable until age 4 years, when he began experiencing increased difficulty with mucosal bleeding, which prompted frequent platelet transfusions. At $4\frac{1}{2}$ years, he had a major gastrointestinal bleed, followed 1 month later by an intracranial hemorrhage. He required transient ventilator support, but eventually regained full neurologic function. Direct (DAT) and indirect (IAT) Coombs evaluations were always 3+ positive. Due to the severe and refractory nature of his disease, the option of novel therapy with bone marrow transplantation was pursued.

HLA typing of the family, and a search of the unrelated marrow donor registries, did not identify an appropriate donor, but DNA-based typing for HLA-A, -B, -DRB1 of the amniotic fluid of a sibling fetus, of 6 months gestational age, revealed a complete HLA match. Cord blood was harvested and cryopreserved at delivery, and the patient was started on myelo- and immuno-ablation 13 days later with TBI 225 cGy once daily for 6 days (total dose 1350 cGy), then cyclophosphamide 60 mg/kg once daily i.v. for 2 days (total dose 120 mg/kg), followed by cord blood thawing and infusion (0.385×10^8 nucleated cells/kg patient, 0.096×10^6 $CD34^+$ cells/kg patient). Acute graft-versus-host disease (GVHD) prophylaxis was with cyclosporine, with G-CSF initiated on day +1. The patient engrafted with an ANC greater than 0.5×10^9/l on day +16. On day +17, he developed symptoms of acute GVHD, with temperatures of up to 40°C, skin rash that on biopsy was consistent with GVHD, and severe pulmonary insufficiency. He was intubated for 2 days and treated with high-dose steroids, with rapid resolution of symptoms. Platelet engraftment was delayed, with sustained platelets greater than 30×10^9/l by day +170. He was platelet-independent from day +240, and RBC independent from +210. Re-evaluation of his RBC antibody status revealed a DAT that was only microscopically positive by day +20, and negative on day +286. Antiplatelet antibodies were negative on day +115, and day +176. Figure 1 illustrates his transfusion requirements for the 9-month period just prior to, and following BMT.

On day +286, the patient was admitted to the hospital with acute onset of fulminant hepatic failure and coma following a 2 day history of streptococcal pharyngitis, vomiting and malaise. Medications at the time of admission were amoxicillin, prophylactic trimethoprim-sulfamethoxazole and deferoxamine mesylate for transfusional iron overload. The patient additionally had received two therapeutic doses of acetaminophen in the preceding 48 h. Upon admission,

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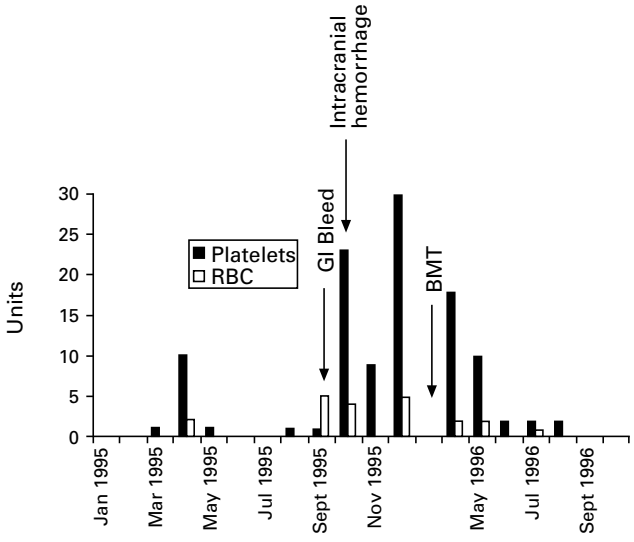

Figure 1 Platelet and red cell use from 9 months prior to transplant until 8 months post-transplant.

the patient's hepatic transminases were markedly elevated with serum aspartate aminotransferase (AST) of 410 IU/l and alanine aminotransferase (ALT) of 589 IU/l. Plasma ammonia, prothrombin time and partial thromboplastin times were also elevated with values of 263 μmol/l, 20.7 s and $>$100 s, respectively, further reflecting severe hepatocellular injury. Gamma-glutamyltranspeptidase (GGT), total bilirubin and alkaline phosphatase were normal. The patient had no known history of antecedent liver disease, and values for hepatic aminotransferases were normal in the preceding month.

An infectious or toxic etiology for this patient's liver failure was suspected, however all cultures for viral, bacterial and fungal pathogens were negative during his hospitalization. Toxicology screening was also negative. As no clear etiology was present, liver biopsy was planned and the patient was considered for liver transplantation. His coma deepened however, and he developed multisystem organ failure. Life support was withdrawn, and the patient died 289 days following transplant.

At autopsy, the patient's liver biopsy was nondiagnostic. Patchy portal inflammation, focal centrilobular hemorrhage and necrosis, and moderate steatosis were present. There was minimal siderosis. Further, hepatic tissue showed no evidence of specific toxins nor human herpes virus 6, cytomegalovirus, herpes simplex virus, adenovirus, bacteria or fungus. After the patient's death, total antibody for hepatitis A virus was reactive, however IgG and IgM levels were not determined. It therefore cannot be concluded if an acute hepatitis A virus infection was present, or if IgG was acquired from prior transfusions or intravenous immunoglobulin.

Discussion

Evans syndrome is often difficult to treat due to its chronic course characterized by remissions and exacerbations.[1] Often, the response to corticosteroids and splenectomy is transient, and additional treatment is required. Further, there is a high risk of development of other autoimmune disorders. Our patient experienced life-threatening bleeding despite aggressive medical therapy and chronic transfusion support. The severity of his disease, and its poor response to treatment, prompted our novel therapeutic approach: immuno- and myelo-ablation followed by infusion of HLA-matched sibling cord blood.

The rationale for stem cell transplantation as treatment for autoimmune diseases comes from both animal models of human diseases and anecdotal human experience. The animal models have demonstrated prevention, transfer and cure of autoimmune diseases following immunoablation and hematopoietic stem cell infusion, supporting the theory that these diseases represent disorders of hematopoietic stem cells or their progeny.[2]

There are several anecdotal reports of the resolution of autoimmune diseases following allogeneic BMT in humans.[3–9] Many of these transplants were done in individuals with rheumatoid arthritis (RA) who developed treatment-related severe aplastic anemia (SAA).[3–5] Three of four patients from these early anecdotes died from transplant-related complications.[3] Results from more recent series have been more encouraging, with several reports of sustained remissions of underlying autoimmune diseases following allogenic BMT.[4–8] McAllister *et al*[9] from our institution reported a patient with multiple sclerosis (MS) who received an HLA-matched sibling transplant for the treatment of chronic myelogenous leukemia. Her MS symptoms improved, and the MRI of her brain is stable to improved 1 year following transplant. Lowenthal *et al*[4] have suggested that the preparative regimen of BMT may induce disease remission, and that this remission may be sustained due to clonal elimination of effector cells.

The etiology of this patient's fulminant hepatic necrosis is unknown. Further, the observed liver histology does not explain his clinical course. Although an infectious or toxic etiology is suspected, this has not been confirmed. Autoimmune diseases including chronic active hepatitis have been associated with Evans syndrome.[1] This patient however did not have serologic or histologic evidence of autoimmune hepatic disease. A multifactorial etiology for this patient's hepatic failure is more likely. Perhaps it was due to an acute infection in the face of previously undetected hepatic compromise from iron overload, total parenteral nutrition and medications.

Although this patient died unexpectedly, the cord blood transplantation appeared successful in the treatment of his refractory Evans syndrome. Cyclosporine has been successfully used to treat autoimmune diseases including Evans syndrome in small series of patients.[10] This may have contributed to this patient's remission. However, he had no evidence of response with cyclosporine pretransplant, and no evidence of disease recurrence 2 months after discontinuation of cyclosporine, and 4 months after discontinuation of prednisone. At the time of death, the patient was off all immunosuppression, and had complete resolution of his autoimmune disease. Platelet engraftment was delayed, but the patient was able to maintain an unsupported platelet count of 80×10^9/l from day +240, and antiplatelet antibodies were negative. The IAT became negative by day

+16, and the DAT changed from 3+ pretransplant to only microscopically positive with IgG by day +20, and negative at the time of this patient's death. At autopsy, a bone marrow biopsy showed 20–50% cellularity with trilineage engraftment, and chimerism studies showed 100% donor reconstitution. Although follow-up was limited, this patient achieved a complete remission of severe Evans syndrome following HLA-identical sibling cord blood transplant.

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