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Case report

Bone marrow transplantation in Shwachman–Diamond syndrome: report of two cases and review of the literature

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Summary:

Patients with Shwachman–Diamond syndrome (SDS) have an increased frequency of myelodysplasia and leukemic transformation. We described two patients who received allogeneic stem cell transplantation and developed multiple complications, including seizure, hyperglycemia and renal tubular acidosis. A review of the literature showed that patients with SDS appeared to have an increased incidence of various transplant-associated problems. These patients frequently have underlying organ dysfunction and should be managed with extreme caution when treated with allogeneic stem cell transplantation.
Keywords: Shwachman–Diamond syndrome; myelodysplasia; leukemia; BMT; complications

Shwachman–Diamond syndrome (SDS) is a rare autosomal recessive disorder characterized by exocrine insufficiency, short stature, skeletal abnormalities and bone marrow dysfunction. There is an increased risk of marrow aplasia and leukemic transformation, the latter often preceded by a phase of myelodysplasia (MDS).[1,2]

Allogeneic stem cell transplantation offers potentially curative treatment for MDS, leukemia and marrow failure syndromes. Few patients with SDS have undergone BMT. We report our experience of allogeneic BMT in two SDS patients who developed MDS and monosomy 7 abnormality. Severe complications were encountered in both cases. We reviewed the outcome of allotransplantation in other patients published in the literature and noticed a significant number of post-transplant problems.

Case 1

An 8-year-old boy with MDS/monosomy 7 had a past history of short stature, growth hormone deficiency, recurrent diarrhea and loss of mineralization of distal femora. CT scan of the abdomen showed a fatty pancreas and serum amylase and lipase activity were virtually absent. He received a CD5, CD8 T cell-depleted (Applied Immune Sciences, Santa Clara, CA, USA), unrelated donor (micromismatched at 1 HLA-DR locus) BMT after conditioning with thiotepa 5 mg/kg i.v. on day −7, CY 60 mg/kg i.v. on day −6, −5 and TBI 3 Gy/day on days −4 to −1. GVHD prophylaxis included CsA, short Mtx and MP. The post-BMT course was complicated by several episodes of seizure of unknown etiology. Later on he developed severe electrolyte wasting as the result of renal tubular acidosis. He had grade IV GVHD that failed to respond to MP, antithymocyte globulin and hydroxychloroquine therapy. He became severely hyperglycemic (blood sugar $>$1000 mg%) and hypernatremic after pulse MP therapy. This responded slowly to insulin and hydration. He died on day 93 of pulmonary hemorrhage. An autopsy was not performed. His ANC exceeded 500/mm^3 on day 18 but he remained platelet and red cell transfusion-dependent. A bone marrow examination on day 31 showed 1.2% blasts and normal cytogenetics.

Case 2

A 9-year-old child with a history of short stature, growth hormone deficiency, and metaphyseal chondroplasia developed marrow hypoplasia. Bone marrow examination 2 years later revealed myelofibrosis, with monosomy 7 and + i(7q) cytogenetic abnormalities. A MRI of the abdomen showed hemosiderosis of the liver and fatty replacement of the pancreas. Serum lipase and amylase were at the low normal range. The patient received a T cell-depleted (by Cellpro Ceprate selection device, Bothell, WA, USA) BMT supplemented with CD34$^+$ selected peripheral blood stem cells from his mother who was HLA-A, B disparate, DR identical, and MLC non-reactive. Conditioning for BMT and GVHD prophylaxis were similar to case 1. Status epilepticus developed 3 weeks post-BMT; CT scan of the brain, CSF, serum glucose, electrolytes calcium, magnesium and CsA levels were normal. The patient also had grade IV acute GVHD, renal failure, steroid-associated hyperglycemia and pulmonary hemorrhage. He died on day 32 after BMT. An autopsy was not performed. Bone marrow examination was not repeated after transplant but there was evidence of myeloid recovery and the patient was platelet transfusion independent until the onset of pulmonary hemorrhage 3 days before death.

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Table 1 BMT in patients with Shwachman–Diamond syndrome

Age (years)	*Diagnosis*	*Cytogenetics*	*BMT type*	*BMT regimen*	*Complications*	*Outcome*	*Ref.*
10	Marrow aplasia	N/A	MSD	BUCY	Congestive heart failure	Death day +23	3
38	Marrow aplasia Post-AML therapy	−18, t(21;?)(q22;?) dic(22;?)(p11;?)	MUD	BUCY	None	Disease-free 5 years	4
24	AML (M4)	inv 9	MSD	BUCY	Mucositis gr III Cardiac, renal, CNS gr II GVHD gr III Delayed engraftment	Relapse 9 months, Died of CMV IP 10 months	5
17	Marrow aplasia	N/A	MSD	CY/TLI	GVHD gr I Hyperglycemia	Disease-free 9 months	6
5	AML (M5a)	del(7), t(4;?) (?q31;q11)	MUD	CY/TBI	Graft rejection	Relapse, Death 1 year	7
?	Marrow aplasia	N/A	HLA-A mismatched sibling	Ara-C/CY/TBI	VOD Liver transplant	Disease-free 10 months	8
8	MDS (RAEB)	−7	MUD	Tt/CY/TBI	CNS gr IV GVHD gr III RTA, IP Hyperglycemia	Death day 93	Case 1
9	MDS (RA)	−7 i(7q)	2-antigen mismatched parent	Tt/CY/TBI	CNS gr IV GVHD gr IV Pulmonary hemorrhage	Death day 31	Case 2

MSD = matched sibling donor; MUD = matched unrelated donor; RTA = renal tubular acidosis; IP = interstitial pneumonia; MDS = myelodysplastic syndrome; TLI = total lymphoid irradiation; Tt = thiotepa; RA = refractory anemia, RAEB = refractory anemia; with excessive blasts.

Discussion

SDS patients have a predilection for developing marrow failure and leukemic transformation; the risk of the latter phenomenon has been reported to range from 5–33%.[1,2] A total of 19 cases of leukemia and MDS have been reported. Cytogenetic analysis was performed on 15 patients; seven had an abnormality involving chromosome 7.

Including this report, eight cases of allogeneic BMT have been reported on SDS patients (see Table 1).[3–8] Severe to fatal complications were encountered in six patients post-transplant. A patient with aplastic anemia died of cyclophosphamide-associated cardiomyopathy.[3] Myocardial fibrosis and cardiomegaly have been described in SDS patients.[9] Two patients had poor engraftment and a third had delayed marrow recovery from prior antileukemic chemotherapy. A young child developed severe hepatic VOD requiring a liver transplant.[8] Both of our patients developed seizure after BMT. Although neurologic complications may be due to medication or coexisting morbidity (such as sepsis or electrolyte imbalance after transplant), none were clearly responsible for the seizures encountered in our cases. Patients with SDS have been reported to have nonspecific CNS abnormalities including hypotonia, optic atrophy, retinitis pigmentosa, ataxia and EEG changes.[2] Conceivably, these changes may render SDS patients susceptible to seizures. Our first patient developed Fanconi-type renal tubular acidosis. This complication may be related to the administration of CsA and amphotericin. However, renal tubular dysfunction has been described in SDS patients who did not receive BMT.[10] Both of our patients also had hyperglycemia after steroid therapy; one went on to develop non-ketotic diabetic acidosis 36 h from start of treatment. It is noteworthy that impaired glucose tolerance has also been reported in other patients with SDS,[11] as well as in one other BMT case.[6]

A number of factors may have contributed to the high complication rate seen in the SDS patients. Underlying hematologic abnormalities may have placed these patients at higher risk of toxicities. Divergent and nonspecific organ malfunctions have been observed in patients with this syndrome.[1] The use of alternative marrow donors is associated with more frequent transplant-related complications. There were reports of increased chromosome fragility in several patients with SDS,[12] but breakage studies were found to be normal in both of our patients.

With improving supportive care, a larger number of SDS patients may survive to develop serious marrow abnormalities requiring allogeneic stem cell transplantation. These patients will require extensive evaluation prior to treatment and should be considered high-risk for post-BMT complications.

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