

Letter to the Editor

In DOCK8 deficiency donor cell engraftment post-genoidental hematopoietic stem cell transplantation is possible without conditioning

To the Editor:

DOCK8 deficiency is an autosomal-recessive combined immunodeficiency with a high incidence of cutaneous viral infections and malignancy.¹ Hematopoietic stem cell transplantation (HSCT) has proven efficacy in treating the disease. Six cases have been reported so far to have successful HSCT.¹⁻⁵ Most of the reported cases received myeloablative conditioning prior to stem cell transplantation.¹⁻⁵ Full donor chimerism and DOCK8 deficiency correction had been recently reported by using reduced intensity conditioning.⁶ Here, we report 1 case with DOCK8 deficiency who showed evidence of donor cell engraftment following genoidental unconditioned HSCT.

The patient presented at 6 years of age with a history of early-onset eczema and recurrent pneumonia since 3 years of age that was complicated by bronchiectasis. He also had food and drug allergy. Significant eosinophilia (2600/mm³) and elevated serum IgE level (28,180 KU/L) were found. Although he had a normal serum IgM level, his serum IgG level was high while the IgA level was undetectable. His absolute CD3 T-cell count was 1682/mm³ with low natural killer cells but normal B cell number. *In vitro* lymphocyte proliferative response to mitogens was severely depressed (Table I). Screening for known genetic mutations underlying severe combined immunodeficiency was negative. He was diagnosed as suffering from autosomal-recessive hyper-IgE syndrome. Monthly intravenous immunoglobulins and cotrimoxazole prophylaxis were commenced. He developed severe chronic diarrhea caused by cryptosporidial infection with secondary sclerosing cholangitis. He also acquired persistent cytomegalovirus and EBV infection and finally was admitted to the intensive care unit with clinical sepsis, severe dehydration, and electrolyte imbalance.

Although the definitive diagnosis was not established at that time, we decided to rescue him with HSCT. He underwent an unconditioned bone marrow transplantation from genoidental HLA-matched sibling at age 8 years. CD34⁺ stem cells (4.1 × 10⁶/kg) were infused. No graft versus host disease (GVHD) prophylaxis was given. Donor cell chimerism as assessed by short tandem repeat typing with a sensitivity of 3% showed evidence of sustained engraftment from the first month until 1 year posttransplant as shown in Table II. Donor cell engraftment resulted in the control of his viral and cryptosporidial infections with decreased IgE level to 330 IU/L. At fourth week post-HSCT, he developed severe diarrhea and skin rash secondary to acute gut and skin GVHD that were proved by appropriate tissue biopsies from skin and gut with poor response to immunosuppressive medications including high-dose steroid, cyclosporine, mycophenolate mofetil, daclizumab, and last antithymocyte globulin. The patient was hospital dependent and unfortunately 1 year post-HSCT he succumbed to severe uncontrolled chronic GVHD and sepsis. He was labeled DOCK8 deficient few years posttransplant when his younger sibling presented with a similar illness, and they were both found through 2.7M Cytogenetic Microarray to carry a large deletion involving the *DOCK8* gene (chr9: g. 209,111,338,227 del 129,1160) with no DOCK8 protein

TABLE I. Immunologic workup pre- and post-HSCT

	Time			Normal range
	6 y of age	8 y of age pre-HSCT	1 y post-HSCT	
CD3 (/mm ³)	1,682	609	562	1,700-1,900
CD4 (/mm ³)	1,033	171	261	800-1,700
CD8 (/mm ³)	384	329	240	700-1,000
CD19 (/mm ³)	601	402	<7	400-800
CD16/56 (/mm ³)	72	24	117	200-400
DR (%)	29	53	35	—
Eosinophil (/L)	2.6	1.24	0.1	0.04-0.4 × 10 ⁹
IgG (g/L)	26.1	20	5.4	2.5-9.1
IgA (g/L)	<0.25	<0.25	<0.25	0.2-1.2
IgM (g/L)	0.35	0.45	0.32	0.2-1.5
IgE (KU/L)	28,180	11,800	520	1.6-30
PHA (CPM)	9,155	ND	ND	94,935-171,149

ND, Not determined.

TABLE II. Donor chimerism post-HSCT

Months post-HSCT	Lymphocytes (%)	Myeloid (%)
1	9.9	0
2	8.7	4.8
3	15.6	13
6	6.8	10.1
12	13.2	26.1

expression as assessed by western blot analysis (Fig 1). His brother presented with eczema, warts, recurrent skin abscesses, varicella, and brucellosis and at age 7 years developed severe aortic aneurysmal dilatation involving the ascending, arch, and descending aorta that required major surgical reconstruction. He was offered HSCT, but the family was reluctant.

This is the first reported case of HSCT done for a DOCK8-deficient patient without conditioning. Although the patient died 1 year posttransplantation precluding further follow-up of clinical status and immune reconstitution, the fact that he was able to clear viral infections (cytomegalovirus and EBV) and cryptosporidiosis attests to a partial recovery of functional immunity. The sustained donor cell engraftment and GVHD development in spite of no chemotherapy conditioning usage indicate severe T-cell dysfunction and impaired ability to reject grafts in DOCK8 deficiency as seen in severe combined immunodeficiency disease. This finding opens the door to discuss the role and the intensity of chemotherapy conditioning used in transplant in such patients. Reduced intensity conditioning regimen might be a reasonable option for most patients, and unconditioned HSCT can be offered for critically ill patients with disseminated infections and end-organ damage. Further studies and long-term follow-up are required to determine the appropriate conditioning regimen.

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Western Blot of DOCK8 Expression

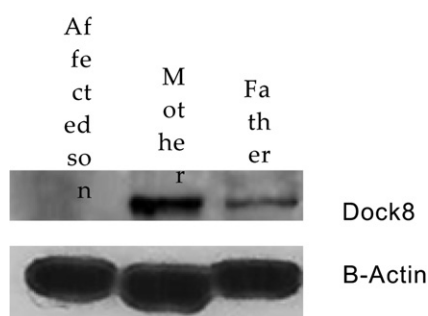


FIG 1. Western blot for DOCK8 protein for patient and parents.

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