

Letter to the Editor

Successful engraftment of donor marrow after allogeneic hematopoietic cell transplantation in autosomal-recessive hyper-IgE syndrome caused by *dedicator of cytokinesis 8* deficiency

To the Editor:

The hyper-IgE syndromes are rare combined immune deficiencies associated with marked elevations in plasma IgE levels and eosinophilia. An autosomal-dominant form of hyper-IgE syndrome caused by mutations in *signal transducer and activator of transcription 3* is characterized by elevated IgE, eosinophilia, eczema, recurrent skin and pulmonary infections, and skeletal abnormalities.¹ Recently, an autosomal recessive form of hyper-IgE syndrome caused by mutations in the *dedicator of cytokinesis 8* (*DOCK8*) gene has been identified and is characterized by elevated IgE levels, eosinophilia, atopic dermatitis, asthma, food allergies, recurrent upper and lower respiratory tract infections, and unusual susceptibility to infections with herpesvirus family members (herpes simplex virus, human papilloma virus) and molluscum contagiosum.^{2,3} Cutaneous infections with human papilloma virus have progressed to squamous cell carcinomas in some cases. Immunologic evaluation of *DOCK8*-deficient patients has revealed T-cell lymphopenia with impaired proliferative responses of both CD4⁺ and CD8⁺ T cells as well as impaired differentiation of T_H17 T cells.²⁻⁴

We report a case of an 8-year-old girl, born to first-degree cousins, who initially presented with pneumococcal meningitis at 11 months of age, complicated by chorda tendineae rupture and flail mitral valve. Isolated asplenia was noted during imaging. She later began to have recurrent episodes of upper and lower respiratory tract infections, pneumococcal bacteremia, giardiasis, and cutaneous infections with herpes simplex virus and *Staphylococcus aureus*. She also developed flat warts thought to be a result of human papilloma virus infection. Complete blood count revealed hypereosinophilia that ranged from 11,020 to 49,700 cells/ μ L (Table I) for which she was treated with corticosteroids because of concerns of possible cardiac involvement. Bone marrow examination ruled out a leukemic process. The patient developed moderate persistent asthma and mild eczema. She had multiple food allergies, elevated total IgE (Table I), and positive specific IgE to milk, egg, fish, peanuts, and tree nuts. The patient had received immunization with tetanus toxoid and 23-valent pneumococcal polysaccharide vaccine (Pneumovax, Merck, Whitehouse Station, NJ) and had protective antibody titers to tetanus toxoid and to 6 of 14 pneumococcal serotypes tested. However, titers waned by age 5 years 6 months, and she failed to respond to Pneumovax booster given at age 6 years (see this article's Table E1 in the Online Repository at www.jacionline.org). Her T-cell numbers decreased over time, whereas her B-cell numbers were elevated (see this article's Table E2 in the Online Repository at www.jacionline.org). T-cell proliferation to mitogens and antigens was mildly diminished (see this article's Table E3 in the Online Repository at www.jacionline.org). Serum IgG levels fell over time, and the patient was started on intravenous immunoglobulin replacement therapy at age 7 years. Her clinical presentation prompted an evaluation for *DOCK8* deficiency. Western blot of lysates from PBMCs and an EBV-immortalized B-cell line revealed absence

TABLE I. Eosinophil counts and IgE levels

Age	Absolute eosinophil count (cells/ μ L)	IgE (U/mL)
10 mo	1,020	ND
2 y 7 mo	49,700	ND
3 y 8 mo	22,390	ND
4 y	21,710	930
6 y 8 mo	22,450	1,340
7 y 1 mo	13,340	574
7 y 10 mo	20,730	1,287

ND, Not determined.

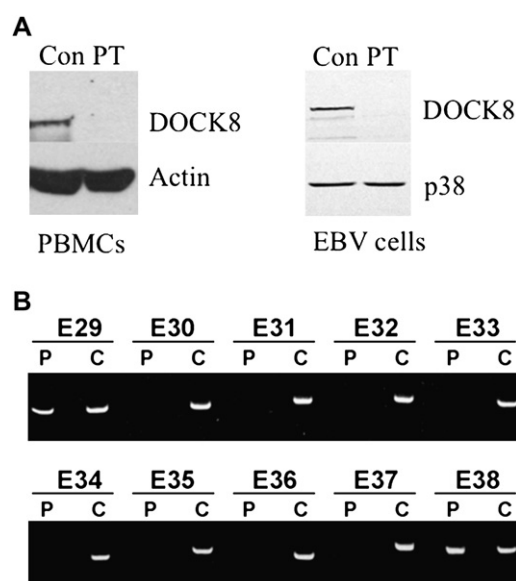


FIG 1. A, Absent DOCK8 expression in patient PBMCs and EBV-immortalized B-cell line (EBV-B cells). Western blot of lysates from control (C) and patient (P) PBMCs and EBV-B cell probed with anti-DOCK8 antibody and antibodies to actin and p38 mitogen-activated protein kinase (p38) for loading controls. B, Deletion of exons 29 through 36 of the *DOCK8* gene in patient genomic DNA. PCR amplifying individual exons of the *DOCK8* gene (exon 28 [E28] through exon 37 [E37]) using patient (P) or control (C) genomic DNA from EBV-B cells.

of DOCK8 protein (Fig 1, A). PCR amplifying genomic DNA revealed a deletion of exons 28 to 35 of the *DOCK8* gene (Fig 1, B).

Although experience with *DOCK8* deficiency is limited, its long-term prognosis is poor. Many *DOCK8*-deficient patients have disfiguring molluscum or human papilloma virus infections or die from fatal infections, squamous cell cancers, or lymphoma.² Therefore, the decision was made to perform allogeneic hematopoietic cell transplantation (HCT) for definitive correction of her combined immune deficiency. The patient was conditioned with 16 doses of busulfan intravenously adjusted to achieve levels of 800 to 1200 μ mol/min on days -9 to -6 and 4 doses of cyclophosphamide 50 mg/kg intravenously on days -4 to -1 without incident. She received unmanipulated bone marrow containing 10×10^6 /kg CD34⁺ cells from her fully matched unaffected younger brother. Cyclosporine A and short-course

TABLE II. Posttransplant T-cell and B-cell subsets

Posttransplant day	Day +37
CD3 ⁺ absolute	706
CD3 ⁺ /CD4 ⁺ absolute	520
CD3 ⁺ /CD8 ⁺ absolute	142
CD56 ⁺ absolute	175
CD19 ⁺ absolute	2
CD3 ⁺ /CD4 ⁺ /CD45RA ⁺ %	4.4
CD3 ⁺ /CD4 ⁺ /CD45RO ⁺ %	95.6
CD3 ⁺ /CD8 ⁺ /CD45RA ⁺ %	29.9
CD3 ⁺ /CD8 ⁺ /CD45RO ⁺ %	70.1

methotrexate were given for graft-versus-host disease prophylaxis, and she received standard antiviral and antifungal prophylaxis. Neutrophil engraftment occurred on day +16 followed by a rapid rise in lymphocyte count to 4490 cells/ μ L on day +21. She was febrile and tachypneic with evidence of pulmonary edema with no organisms recovered from nasal secretions or sputum. Cell type-specific chimerism studies on day +21 post-HCT revealed that 100% of CD3⁺ cells (3536 cells/ μ L) and 100% of CD15⁺ cells (6210 cells/ μ L) were of donor origin. Elevated numbers of lymphocytes were attributed to the response of normal donor cells to occult infection present before the transplant. Fevers and tachypnea resolved, and she was discharged on day +35 post-HCT on cyclosporine A with no signs of acute graft-versus-host disease. Repeat analysis of T and B lymphocyte subsets on day +37 post-HCT revealed continued T-cell engraftment and evidence of emerging naive CD4⁺ and CD8⁺ T cells (Table II). T-cell proliferation was not evaluated because the patient continued to receive immune suppression with cyclosporine A. She had neither bacterial nor viral skin infections post-HCT. She presented day +58 post-HCT to the emergency department of her local hospital with high fever, and blood cultures were taken. She was started on antibiotics of appropriate coverage and referred to our institution, where she was found to have septic shock. She died 6 hours later of overwhelming *Klebsiella pneumoniae* bacteremia. Congenital asplenia may have contributed to the patient's susceptibility to *Klebsiella*, as has been previously reported.⁵

In summary, we report a child with *DOCK8* deficiency who underwent allogeneic HCT after myeloablative conditioning and demonstrated full donor chimerism early after transplant. These results suggest that HCT may be a viable option to treat *DOCK8* deficiency. Unfortunately, the death of the patient precluded further follow-up of immune function and clinical status.

This experience demonstrates that HCT with conventional myeloablative conditioning may be potentially curative in *DOCK8* deficiency, although more experience is clearly required

to assess clinical outcomes. Furthermore, early diagnosis of this newly discovered immune deficiency before repeated infectious injury will likely optimize clinical outcomes after HCT. Because *DOCK8* is expressed in both hematopoietic and nonhematopoietic tissues, further experience and long-term follow-up will be needed to determine whether correction of the hematopoietic compartment is sufficient to protect *DOCK8*-deficient patients from infection and cancer. As this letter was being prepared, Gatz et al reported successful HCT on two patients with autosomal recessive hyper-IgE syndrome found to be due to *DOCK8* deficiency after transplant.⁶

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TABLE E1. Antigen-specific antibody titers to vaccines

Antigen	Serotype	Antibody titer		
		4 y*	5 y 6 mo	6 y*
Tetanus (IU/mL)	ND	2.9		
Pneumococcus (μg/mL)	1	1.09	0.03	0.11
	3	24.75	1.31	0.23
	4	5.38	0.94	0.41
	5	0.57	0.02	0.01
	6B	48.48	5.71	1.81
	7F	4.17	0.14	0.14
	8	11.48	0.49	0.11
	9N	0.26	0.01	0.0
	9V	9.37	0.27	0.32
	12F	0.18	0.03	0.01
	14	77.53	2.32	2.87
	18C	19.19	1.66	0.8
	19F	27.78	11.65	3.37
	23F	28.79	1.45	1.03

*More than 1 month after booster of 23-valent pneumococcal vaccine.

ND, Not determined.

TABLE E2. Lymphocyte counts

		Age at testing				Normal value
		4 y	7 y	8 y	8 y 7 mo	
Lymphocyte counts (cells/ μ L)	CD3 ⁺ cells	1172	924	693	750	1000-2600
	CD4 ⁺ cells	824	409	408	530	530-1500
	CD8 ⁺ cells	173	408	278	191	330-1100
	CD56 ⁺ cells	347	176	198	83	70-480
	CD19 ⁺ cells	2560	1309	1570	2798	270-860

TABLE E3. Proliferation of PBMCs to mitogens and antigens (cpm of ^3H -thymidine incorporation into DNA)

Stimulus	Patient	Control
Medium day 3	885	566
Concavalin A	33,753	67,764
Phytohemagglutinin	19,527	33,148
Pokeweed mitogen	106,935	67,937
Medium day 6	818	534
Tetanus toxoid	4,189	9,310
Diphtheria toxoid	4,352	11,920

Assay was performed on the same day using PBMCs from the patient and a healthy control.