Resolution of food-induced anaphylaxis in DOCK8-deficient patients following bone marrow transplantation

Fatih Azık[1], Dilek Azkur[2], Zekai Avcı[1], Emine Vezir[2], Pamir Işık[1], Bahattin Tunç[1], Can N. Kocabaş[2]

[1]Department of Pediatric Hematology and Oncology and [2]Department of Pediatric Allergy and Immunology, Ankara Children's Hematology and Oncology Training and Research Hospital, Ankara, Turkey.
E mail:cankocabas@yahoo.com
Received: 29 January 2015, Revised: 19 February 2015, Accepted: 3 March 2015

To the Editor,

We present a report on the resolution of food induced-anaphylaxis in three children with DOCK8 deficiency following bone marrow transplantation (BMT). The patients had autosomal-recessive DOCK8 deficiency and food anaphylaxis and were successfully treated with BMT. This study presents the long-term outcome of food allergy in these patients. After BMT, food anaphylaxis in two of the patients was resolved. The third patient could tolerate the cooked form of the food in question, although tolerance to the raw product remained unknown, since the parents denied this form of the food to the child due to fear of anaphylaxis.

The patients, who were diagnosed as autosomal-recessive DOCK8 deficiency, presented with severe dermatitis of neonatal onset, severe food allergies, recurrent and severe bouts of pneumonia and high peripheral eosinophilia and serum IgE. All of the patients had a history of food anaphylaxis and had clearly positive skin tests with the foods responsible. Following BMT, the patients underwent periodic evaluation of skin prick tests and specific IgE (Fig. 1). On the basis of their detailed clinical evaluations and test results, the patients subsequently underwent open oral provocation tests with the foods responsible for their allergies.

DOCK8 deficiency is an autosomal recessive primary immunodeficiency (PID) disease caused by loss-of-function mutations in the *DOCK8* gene. It affects cell signaling and reorganization of the cytoskeleton[1]. DOCK8 is expressed within the immune system, and patients with this deficiency have multiple abnormalities of the immune function, including defective T-cell function, impairment of the humoral immune system, high IgE levels, eosinophilia and impaired production of antigen-specific antibodies. These lead to the clinical features of DOCK8 deficiency. The clinical presentation is characterized by atopic dermatitis, asthma, food allergies, recurrent respiratory tract infections, unusual susceptibility to viral infections with herpesvirus family members (herpes simplex virus, human papilloma virus and molluscum contagiosum) and development of malignancies in late childhood or early adulthood[1].

There have been recent reports about DOCK8-deficient patients being treated successfully

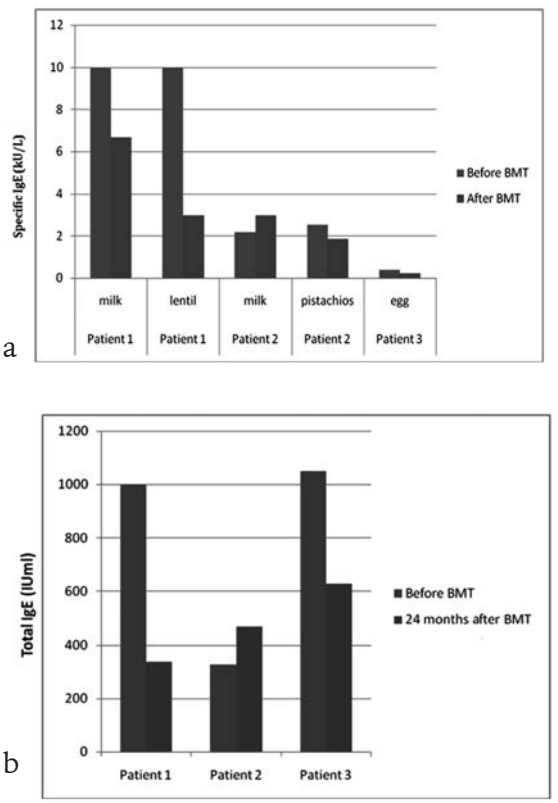

Fig. 1. Total IgE (a) and food specific IgE (b) level of the patients before and after BMT.

with BMT[2-7]. However, reports on the course of food allergy after BMT in patients with DOCK-8 deficiency are few and controversial. Although most of these patients were reported to have had food allergies before transplantation, it was not clear whether the allergies continued or subsided following BMT. In studies concerning the course of food allergy after transplantation, some patients reportedly overcame their allergies, while others continued to display a reaction following consumption of the allergy-triggering food [3-7].

Here, we report complete resolution of food allergies in two of the three DOCK8-deficient children and amelioration of symptoms in the

Table I. Demographic and Clinical Features of DOCK8-Deficient Patients

	Patient 1	Patient 2	Patient 3
Age at diagnosis (years)	3.5	7	8
Gender	female	male	male
Age at onset of symptoms of food allergy	1 month	12 months	6 months
Consanguinity of parents	First cousins	First cousins	First cousins
Recurrent respiratory tract infections	yes	yes	yes
Viral infections HSV1 HPV	 - -	 - Epidermodisplasia verruciformis	 + Epidermodisplasia verruciformis
Allergies Atopic dermatitis Food allergy	 yes lentils, milk	 yes milk, pistachios	 yes eggs
Malignancy	-	Squamous cell carcinoma	-
Age at HCT	14	4.5	11
GVHD	Acute grade II GVHD of the skin	none	none
Chimerism	Full	Full	Full
Follow-up duration	34 months	27 months	24 months

Table II. Lymphocyte Subsets and Percentage of Eosinophils in DOCK8-Deficient Patients before and after BMT

	Patient 1		Patient 2		Patient 3	
	BMT		BMT		BMT	
	Before	After	Before	After	Before	After
Lymphocyte subsets						
CD3 (%)	28.0	67.0	74.0	53.0	48.0	44.0
CD4 (%)	16.0	35.0	18.0	27.0	15.0	23.0
CD8 (%)	18.0	30.0	52.0	29.0	28.0	19.0
CD19 (%)	60.0	30.0	14.0	33.0	37.0	50.0
CD4/CD8	0.9	1.1	0.34	1.18	0.6	1.35
CD16+56 (%)	6.0	2.0	13.0	14.0	9.0	6.0
Lymphocytes (%)	5.0	2.3	14.0	41.0	20	51.0
Eosinophils (%)	59.5	8.7	3.5	2.2	12.7	1.9
Count	11,900	600	300	100	600	100

third child following treatment with BMT. Demographic and clinical features of the patients are presented in Table I. All patients were born to consanguineous parents (first-degree cousins). One patient was diagnosed early in life because of family history. All three patients were treated with intravenous immunoglobulin (IVIG) replacement and prophylactic antibiotics prior to BMT. All three received a fully matched BMT and achieved good immune reconstitution. Eczematous lesions healed completely following BMT, and severe infections resolved. Furthermore, IgE levels and specific IgE levels were reduced (Fig, 1) and eosinophil and lymphocyte counts normalized (Table II). The patients required no further treatment and displayed stable engraftment at 24-37 months following BMT.

The first patient (7-year-old female), had experienced anaphylactic reactions to milk and lentils; after BMT she could consume these foods on a frequent basis without any reactions. The second patient (16-year-old male) had had anaphylaxis in response to ingestion of milk and pistachios. Following BMT, he could tolerate cooked milk-containing products, including cakes, cookies and ice cream, consuming them without any reactions. His response to pistachios remained undetermined, as his family refused a provocation test with milk and pistachios. Our third patient (13-year-old male) had had anaphylaxis in response to ingestion of eggs. At the 4th post-BMT month, an oral challenge with eggs was performed, resulting in urticaria. At the 21th post-BMT month, however, the oral challenge had negative results. Since then, he has remained tolerant of eggs and consumes them on a regular basis without any adverse reactions.

Resolution of food allergy following BMT may show that the defect resulting in abnormal IgE production in response to food and the basis of T-cell memory lie within the hematopoietic stem cells. DOCK8-deficient patients have impaired production of Th1-type cytokines such as IL-2, IFNg and TNFa, and this Th2 bias is suspected to be the reason for susceptibility to atopy[4]. Bone marrow transplantation may help to build up the balance between Th1 and Th2 lymphocytes, and this may lessen allergic manifestations[3,7]. Related articles in this area have reported that eczema has resolved following BMT. Although food allergy is a frequent finding in DOCK8-deficient patients, detailed information has usually not been provided. The fate of food allergy after BMT has not been reported in most studies. Among the reports that do offer such information, there are conflicting results. In accordance with our results, Barlogis et al.[6] reported a 9-year-old girl who had multiple food allergies, including strawberry anaphylaxis; reintroduction of diversified foods did not reveal any allergies following BMT. A 12-year-old boy with a peanut allergy[3] and a 3-year-old girl with cow's milk, egg and citrus fruit allergies[5] were also reported to tolerate the foods to which they had previously been susceptible, following BMT for DOCK8 deficiency.

In contrast to these results, other patients with DOCK8 deficiency and food allergies continued to have allergic symptoms after BMT upon consumption of the foods in question. Bittner et al.[7] reported a 7-year-old patient who continued to have reactions to allergy-triggering foods 6 years after BMT, but the symptoms were less severe. The patient had a reduced intensity conditioning regimen, and the authors argued that incomplete chimerism, especially in B cells and the myeloid compartment, might allow for the preservation of allergic sensitization, possibly through the long-term survival of IgE-secreting plasma cells. Al-Herz et al.[4] reported two patients who did not outgrow their food allergies after BMT. Both of these patients were reported to have had good immune reconstruction, but the conditioning regimen and level of chimerism were not specified.

How DOCK8 deficiency leads to the development of high serum IgE and allergic disease has not yet been explained. It will be interesting to determine whether patients treated with BMT will outgrow their eczema and food allergies. Allergic disorders constitute a form of immune deviation, and after BMT they can resolve. The cases presented in this report may provide an insight into the basic mechanism(s) involved in food allergy.

Key words: anaphylaxis, bone marrow transplantation, children, DOCK8 deficiency, food allergy

REFERENCES

1. Rezaei N, Hedayet M, Aghamohammadi A, Nichols KE. Primary immunodeficiency diseases associated with increased susceptibility to viral infections and malignancies. J Allergy Clin Immunol 2011; 127: 1329-1341.
2. Metin A, Tavil B, Azık F, et al. Successful bone marrow transplantation for DOCK8 deficient hyper IgE syndrome. Pediatr Transplant 2012; 16: 398-399.
3. Hourihane JO, Rhodes HL, Jones AM, Veys P, Connett GJ. Resolution of peanut allergy following bone marrow transplantation for primary immunodeficiency. Allergy 2005; 60: 536-537.
4. Al-Herz W, Ragupathy R, Massaad MJ, et al. Clinical, immunologic and genetic profiles of DOCK8-deficient patients in Kuwait. Clinical Immunol 2012; 143: 266-272.
5. Boztug H, Karitnig-Weiß C, Ausserer B, et al. Clinical and immunological correction of DOCK8 deficiency by allogeneic hematopoietic stem cell transplantation following a reduced toxicity conditioning regimen. Pediatr Hematol Oncol 2012; 29: 585-594.
6. Barlogis V, Galambrun C, Chambost H, et al. Successful allogeneic hematopoietic stem cell transplantation for DOCK8 deficiency. J Allergy Clin Immunol 2011; 128: 420-422.
7. Bittner TC, Pannicke U, Renner ED, et al. Successful long-term correction of autosomal recessive hyper-IgE syndrome due to DOCK8 deficiency by hematopoietic stem cell transplantation. Klin Padiatr 2010; 222: 351-355.