

A Case of *DOCK8* Deficient Hyper-IgE Syndrome Presenting Primarily With Eczema, Food Allergy, and Asthma

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Dedicator of cytokinesis 8 (*DOCK8*) deficiency is a rare and recently described immunodeficiency, which is characterized with cutaneous viral and sinopulmonary infections, eczema, and high IgE levels. A *DOCK8* deficient patient who had been followed up for severe atopic dermatitis, multiple food allergies, and asthma for several years is reported and clues are given for the diagnosis of *DOCK8* deficiency. A 7-year-old girl was referred due to refractory eosinophilia and eczema. She had angioedema of the lips and increase in eczematous lesions during infancy after milk and egg ingestion and during childhood after fish, hazelnut, and wheat-containing food ingestion. She had episodic wheezing attacks since she was 1-year-old, and she had recurrent pneumonia and acute otitis media in the following years. She was hospitalized for pyoderma after a zona zoster infection. Laboratory findings suggested *DOCK8* deficiency and mutational analysis verified. She had stem cell transplantation from a matched unrelated donor but unfortunately she died due to pneumonia 3 months after transplantation. Even though infants have food allergy and recurrent wheezing attacks, the presence of refractory eczema should be carefully followed up by pediatricians for the presence of recurrent cutaneous infections to exclude the diagnosis of *DOCK8* deficiency in which stem cell transplantation is the only option and must be done as soon as possible.

Introduction

HYPER-IGE SYNDROME IS one of the primary immunodeficiencies with aberrant IgE production in which recurrent sinopulmonary infections, eczema, high IgE levels, and eosinophilia are seen. It is associated with a negative dominant mutation in the signal transducer and activator of transcription 3 (*STAT3*) gene, which was historically named as *Job Syndrome*¹ and with a newly described recessive mutation in the dedicator of cytokinesis 8 (*DOCK8*) gene. *DOCK8* deficiency is differentiated from *STAT3* deficiency by the occurrence of cutaneous viral infections including especially molluscum contagiosum, herpes viruses. The coexistence of allergic diseases that is, asthma, food allergy, and airborne allergies and the absence of skeletal and dental abnormalities and pneumatocoles are the other distinctive features of *DOCK8* deficiency. It was first described in 11 patients followed by 21 patients described 1 month later in 2009 who had homozygous and compound heterozygous loss of function mutations in chromosome 9p af-

fecting *DOCK8* protein.^{2,3} *DOCK8* is a signal transducer protein that plays a role in the regulation of cell movement, adhesion, growth, and morphology, mainly in lymphocytes. *DOCK8* deficiency gives rise to disrupted proliferative responses in both CD4+ and CD8+ T cells. The interruption of the proliferative responses in T cells results in diminished T cell activation and function and disorganized production of functional antibodies by B cells leading up to a kind of combined immunodeficiency.

It is estimated that more than 100 patients have been diagnosed with *DOCK8* deficiency worldwide.⁴ The largest case series, reported by Zhang and Engelhardt et al. showed that almost all patients (100% and 95%, respectively) had atopic dermatitis, 82% had food and 48% had environmental allergies including anaphylaxis, and 54% and 48% of the patients respectively had asthma or reactive airway disease. The majority of the patients (100% and 91%, respectively) had cutaneous viral infections especially with herpes simplex and human papilloma virus and sinopulmonary infections (91% and 100%, respectively).⁵

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Herein, a child with initial complaints related to eczema, multiple food allergies, and asthma and during follow-up diagnosed as *DOCK8* deficiency is reported to describe the clues for suspicion of *DOCK8* deficiency.

Case Presentation

A 7-year-old girl was referred to our hospital due to refractory eosinophilia. She had lesions of atopic dermatitis since neonatal period. She had a history of increase in lesions and angioedema of the lips after ingestion of egg and cow's milk-containing food in infancy. In the following years, she had similar symptoms with the ingestion of hazelnut, fish, and wheat-containing food, all of which were eliminated from her diet. She had had episodic wheezing attacks since she was 1-year-old and she had been treated on inhaled corticosteroid, montelukast daily and inhaled salbutamol on demand. Her past medical history was remarkable for recurrent pneumonia, acute otitis media, and a few herpes labialis infections, and she had been recently hospitalized for pyoderma after zona zoster infection. She also had eosinophilia ranging between 700–6,800/ μ L, which was noticed during the last 3 years.

On physical examination her height and weight were below third percentile for her age, and her skin was pale and dry. She had diffuse and severe atopic dermatitis, lichenification on both antecubital fossae, and vesicles and brownish crusts forming a linear pattern on both sides of anterior and posterior thoracic wall reminiscent of varicella zoster virus infection (Fig. 1).

Laboratory findings (Table 1) showed low IgM, very high IgE levels, and eosinophilia. The antibody titers against Hepatitis B vaccine and isohemagglutinin levels were low. Moreover, decreased percentages of CD3+ and CD4+ lymphocytes were determined on flow cytometer analysis. Even though the ratio of CD4+ to CD8+ lymphocytes were inverted abnormally, the absolute numbers of T cell subsets were in normal ranges. Beyond these, B cell percentage and absolute number were higher than normal. Lymphocyte proliferation test showed half of the control's levels after stimulation with concanavalin A and phytohemagglutinin. Her skin prick tests for the evaluation of allergy showed positive reaction against milk, hen's egg, soy, wheat, pistachio, hazelnut, and codfish. The specific IgE levels for these allergens were higher than 0.35 kU/L, as well. The thoracic computed tomography showed ground glass appearance in the upper lobes and upper segments of lower lobes of both lungs, and focal air trapped areas in between areas of ground glass appearance. The bronchoalveolar lavage culture was positive for *Candida albicans*, *Aspergillus flavus* complex, and

TABLE 1. ABNORMAL LABORATORY FINDINGS OF THE PATIENT

Laboratory tests	Findings
Peripheral blood smear	30% eosinophil, 26% neutrophil, 28% lymphocyte, 8% band, 8% monocyte Absolute lymphocyte number: 3948/ μ L
Immunoglobulins ^{16,a}	IgA: 166 mg/dL (70–303) IgM: 21.4 mg/dL (69–387) IgG: 1350 (864–2134) IgE: 4663 kU/L (<100)
Specific antibody response	Antibody titers against Hepatitis B antigen: 0.78 IU/mL (>10 IU/mL)
Isohemagglutinins	Anti B: 1/8
Lymphocyte subsets ^{17,a}	CD3: 37% (55–78) 1460/ μ L (700–4200) CD4: 12% (27–53) 470/ μ L (300–2000) CD8: 24% (19–34) 940/ μ L (300–1800) CD19: 48% (10–31) 1900/ μ L (200–1600) CD16 + 56: 11% (4–26) 430/ μ L (90–900)
Lymphocyte proliferation test	Patient's control's
SI concanavalin A	$\frac{42441}{6755} = 6.28$ $\frac{92405}{4335} = 21.31$
SI phytohemagglutinin	$\frac{109538}{6755} = 16.21$ $\frac{206893}{4335} = 47.72$

^aThe normal values of immunoglobulins and lymphocyte subsets are given in the references.

SI, stimulation index.

Moraxella catarrhalis. With these findings, diagnosis of autosomal recessive hyper-IgE syndrome caused by *DOCK8* mutation was suspected, and the homozygous mutation was established by sequence analysis. A large deletion was found in *DOCK8* gene between exons 1 to 9. A matched related donor screening revealed none but matched unrelated donor was found. The hematopoietic stem cell transplantation was successfully performed 2 months ago. But unfortunately on the third month after transplantation she died due to pneumonia when she was on immunosuppressive treatment at the same time.

Discussion

Recurrent viral cutaneous infections, asthma, food/airborne allergies, and changes in immunoglobulin and T cell levels are the distinctive features of *DOCK8* deficiency that distinguishes it from *STAT3* deficiency. Our patient was first diagnosed with atopic dermatitis and food allergy, later in infancy wheezing episodes were added to the clinical picture. During childhood, after 2 and a half years of age, she was hospitalized several times for pneumonia, she had a few episodes of herpes simplex stomatitis that were not remarkable. Before admission to our department she had pyoderma after a zona zoster infection. So the occurrence of

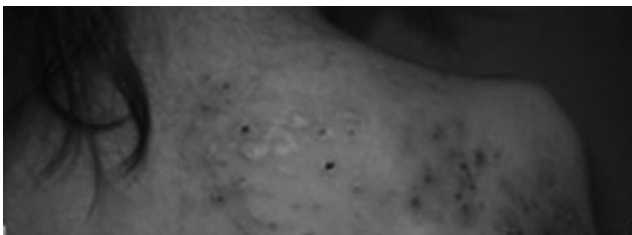


FIG. 1. The vesicles and brownish crusts forming a linear pattern caused by zona zoster on the posterior thoracic wall.

a few cutaneous viral infections with the presence of neonatal-onset recalcitrant eczema and food allergy highlighted the presence of *DOCK8* deficiency.

The other features that are common for *STAT3* deficiency and *DOCK8* deficiency such as atopic dermatitis, bacterial/fungal sinopulmonary infections, high IgE, and eosinophilia were present at our case. The first symptom presented at our patient was atopic dermatitis, which was first diagnosed after the neonatal period. The culture of her bronchoalveolar lavage was positive for *Candida albicans* and *Aspergillus flavus* that supported the diagnosis of an immunodeficiency.

The awareness of autosomal recessive hyper-IgE syndrome caused by *DOCK8* deficiency must be increased in atopic patients with asthma, food allergy, eczema, high IgE levels, and eosinophilia if recurrent viral cutaneous infections with human papilloma virus, herpes simplex virus, and molluscum contagiosum virus and bacterial or fungal sinopulmonary infections occur concomitantly. The patients with severe atopic dermatitis are not only at risk for viral and bacterial cutaneous superinfections due to excoriations, but also they have high IgE levels and eosinophilia.⁶ Some of patients with atopic dermatitis are prone to infections with herpes simplex virus or smallpox virus, which are known as eczema herpeticum and eczema vaccinatum.⁷ So, the presence of recurrent sinopulmonary infections besides atopic dermatitis differentiates *DOCK8* deficient ones from non-deficient ones.

The allergic reactions in *DOCK8* deficient patients are rather frequent. In the case series reported by Zhang et al., 9 of the 11 patients had food allergies with multiple sensitizations, 7 had environmental allergies including Bermuda grass, mold, pets, and dust, and 6 had drug allergy. All of them had atopic dermatitis and 5 had asthma.² From the other 21 patients with *DOCK8* mutation reported by Engelhardt et al., (3 of which were the same ones with Zhang's cases) all of them had eczema, 11 had multiple food allergies, 7 had asthma, 2 had dust mite and latex allergy, 2 had animal hair and environmental allergy, and 1 had drug allergy.³ Our patient also had multiple food allergy, asthma, and atopic dermatitis but no history of drug allergy and environmental allergy.

It is already known that *DOCK8* protein also act as a tumor suppressor protein and has a role in the increased carcinogenesis rate in *DOCK8* deficient patients.⁵ Homozygous deletion of *DOCK8* was found in a lung cancer cell line and *DOCK8* expression was decreased in primary lung cancers⁸ and hepatocellular carcinoma.⁹ Additionally, *DOCK8* gene was 1 of the 3 tumor suppressor genes involved in pathophysiology of squamous type of lung cancer in which *DOCK8* protein was underexpressed.¹⁰ In *DOCK8*, immunodeficiency, defective T cell immunity, and chronic HPV infections are contributing factors to the increased risk of lymphomas and squamous cell carcinomas.⁵ Stem cell transplantation is the only treatment modality in autosomal recessive hyper-IgE syndrome. Stem cell transplantation must be done before the emergence of a malignant disease, though it is not proven yet if it prevents malignancy occurrence or not. Transplantation is also helpful in the healing of eczematous lesions and food allergy¹¹ and our patient could also be evaluated for these, but unfortunately she died 3 months after transplantation.

The index case had no lymphopenia but low lymphocyte proliferation response to stimulants suggested diagnosis of combined immunodeficiency. The percentage of CD3+ and CD4+ lymphocytes were low but the absolute numbers of

them were in normal ranges, in contrast to the majority of the patients with low total T cells and CD4+ T cells reported previously.¹² Additionally, the ratio of CD4+ to CD8+ lymphocytes was inverted in our patient in contrast to the data reported by Zhang et al.² B cell level was higher than normal in our patient and that is why the absolute lymphocyte number was found to be in normal ranges. Increase in B cell number was also found in half of the patients reported by Engelhardt et al.³ Besides this, low IgM level with the lack of specific antibody production was consistent with *DOCK8* deficiency in this patient as it is the case in the majority but not all the patients.⁵

Atopic dermatitis is a common disease with high prevalence rates in different parts of the world.¹³ There are several reports showing an increase in the prevalence of food allergy and anaphylaxis in the last decade.^{14,15} In addition to her food allergy and asthma, recurrent cutaneous infections, short stature, neonatal onset recalcitrant atopic dermatitis, eosinophilia, high IgE, and low IgM levels were clues for the correct diagnosis of *DOCK8* deficiency in this patient. In conclusion, in children with atopic dermatitis, asthma, and food allergy, occurrence of cutaneous viral diseases and sinopulmonary infections must be thoroughly questioned by the pediatricians. Even though autosomal recessive hyper-IgE syndrome caused by *DOCK8* deficiency is a rare kind of immunodeficiency as an underlying defect seen in atopic patients, this syndrome must be overviewed in children with allergy, recurrent viral infections, and low IgM levels. Stem cell transplantation must be done as soon as possible, since it is the only treatment modality for recurrent infections, eczema, and maybe for food allergy.

Acknowledgment

We thank Helen Su for mutational analysis.

Author Disclosure Statement

The authors declare that they have no conflict of interest.

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Received for publication July 11, 2012; accepted after revision October 3, 2012.