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Case Report

DOCK8 deficiency with hypereosinophilia and the syndrome of inappropriate antidiuretic hormone secretion during herpes infection

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ABSTRACT

Background. Hyperimmunoglobulin E syndrome (HIES) due to dedicator of cytokinesis8 (DOCK8) deficiency may present in infancy and childhood with different clinical features involving recurrent infections, allergic dysregulation, and autoimmunity.

Case. In this report, we describe a patient who first presented with severe hypereosinophilia and went on to develop the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in the context of a severe herpes infection. Investigation revealed the presence of underlying DOCK8 deficiency presenting with atypical clinical features.

Conclusions. Distinct inflammatory features associated with infections may be seen in the course of primary immunodeficiency diseases, and early functional and molecular genetic tests will aid the proper management.

Key words: dedicator of cytokinesis (DOCK8) deficiency, syndrome of inappropriate antidiuretic hormone secretion (SIADH), interferon response.

Hyperimmunoglobulin E syndrome (HIES) is a form of primary immunodeficiency characterized by elevated serum IgE, rash, and recurrent skin and sinopulmonary bacterial infections.[1] Heterozygous mutations in the *STAT3* gene cause autosomal dominant (AD) HIES[2,3] and biallelic mutations in the dedicator of cytokinesis8 (*DOCK8*) gene cause autosomal recessive (AR) form of HIES, which was first described in 2009.[4,5]

Patients with AR-HIES, caused by the defects in the *DOCK8*, *PGM3*, *ERBIN*, and *ZNF341* genes, do not generally fulfill the criteria described for AD-HIES caused by *STAT3* gene defect.[5-7] DOCK8 deficiency presents with recurrent viral cutaneous infections, asthma, food/airborne allergies, and changes in immunoglobulin and T cell levels that are typical features for differentiation of DOCK8 deficiency from other AR-HIES. In a large case series of DOCK8 deficiency, eczema was detected in 99% of patients whereas, recurrent respiratory and persistent viral infections occurred in 91 and 80% of cases, respectively.[8] Allergies were observed in 71% of patients and were mostly caused by food allergens and abscesses (60%). Pneumonia, sepsis, and cerebral infections were common life-threatening infections, respectively experienced in 32%, 29%, and 22% of patients, in this study.[8]

Herein, we present a child with severe hypereosinophilia, cow milk allergy, recurrent herpetic skin lesions, and syndrome of inappropriate antidiuretic hormone secretion (SIADH) in the presence of DOCK8 deficiency.

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Case Report

A 4-month-old girl, the first child of parents from the same village, had severe eosinophilia (30%) on admission to the emergency department with fever. There was no evidence of dysplasia in the bone marrow smear. Platelet-derived growth factor receptor alpha polypeptide (*PDGFRA1*) gene defect responsible for the myeloproliferative variant of hypereosinophilic syndrome was negative. Evaluation of eosinophilia revealed cow milk protein allergy in the patient, and the elimination of cow milk led to the regression of eosinophilia. At 9 months of age, she had an urticarial rash after ingesting cow milk, which regressed following oral antihistamines. She was hospitalized for severe oral lesions, possibly due to herpetic gingivostomatitis. A week later, widespread vesicular lesions on the face and hands and ear discharge developed, and she was admitted to our center. On physical examination, her weight was 8.5 kg (25-50 percentile), height was 70 cm (25th percentile), and head circumference was 44 cm (<3 percentile). She had a widespread herpes infection affecting the right hemifacial region, mouth, and hands. Complete blood count showed anemia, leukocytosis with mild neutropenia, and severe eosinophilia (Table I). Erythrocyte sedimentation rate was 76 mm/hr (normal range [NR]: 0-20); C-reactive protein (CRP) was 2.07 mg/dL (NR: 0-0.8). Sulbactam-ampicillin and acyclovir treatment were started for the herpes infection. Combined immunodeficiency was considered due to the severe and recurrent viral skin infection, food allergy, eosinophilia, and elevated serum IgE. Monthly intravenous immunoglobulin (IVIG) was started together with antibacterial and antifungal prophylaxis. Abdominal ultrasonography (USG) and echocardiography

Table I. Laboratory findings of the patient.

	First admission	Second month of the assessment	References
White blood cells, mm^3	15900	17500	6400-13000
Absolute lymphocyte count, mm^3	6100	7800	3400-9000
Absolute neutrophil count, mm^3	1400	2600	1500-8500
Absolute eosinophil count, mm^3	1500	5600	0-500
IgA (mg/dL)	13.6	19.9	17-69
IgG (mg/dL)	820	939	463-1006
IgM (mg/dL)	114	132	46-159
Total IgE (IU/mL)	14	511	(0.76-7.31)
Lymphocyte subsets, % (/mm^3)			
CD3	42% (2226)	28% (2128)	53-75% (3600-8900)
CD4	22% (1166)	16% (1216)	32-51% (1300-3400)
CD8	18% (954)	14% (1064)	14-30% (620-2000)
CD16/56	3% (159)	2% (152)	3-15% (180-920)
CD19	49% (2597)	66% (5016)	16-35% (2100-6200)
Lymphocyte proliferation test, SI (P/C)			
PHA	50/60		
Con A	39/48		
PMA/Ion	8/2		

Con A: concanavalin A, Ig: mmunoglobulin, P/C: patient/control, PHA: phytohemaglutinin, PMA/Ion: PMA/ionomycin, SI: stimulation index

were normal. There were few eosinophils in microscopy of the bronchoalveolar lavage (BAL) fluid of the patient, who had ground glass changes on thoracal computerized tomography (CT). CMV PCR was 496426 copies/mL in BAL fluid. Gancyclovir, and due to severe hypereosinophilia, methylprednisolone (2 mg/kg/day) was added to the therapy. Eosinophilia resolved, and the patient was discharged with steroids after 6 weeks of hospitalization. In the *DOCK8* gene analysis, a homozygous large deletion was detected, and the DOCK8 protein expression was absent (Fig. 1).

One week after her discharge, the patient developed blurred consciousness, and severe hyponatremia was detected without any signs of dehydration. Her vital signs were normal. No edema and hepatomegaly were present on physical examination. Laboratory tests showed hyponatraemia (114 mEq/L), hypochloremia (86 mEq/L), and normokalemia (5.17 mEq/L) with low plasma osmolality (245 mOsm/kg, NR: 275-295) and inappropriately high urinary osmolality (451 mOsm/kg). Urinary sodium (112 mEq/L, NR: 15-267 mEq/L), and β-2 microglobulin levels (192 ng/mL, NR: 0-300 ng/mL) were normal. Serum glucose and lipid profile were within normal limits, whereas serum uric acid was very low (0.7 mg/dL, NR: 1.8-5.0 mg/dL), and serum blood urea nitrogen (8.04 mg/dL, NR: 5-15) and creatinine levels (0.18 mg/dL, NR: 0.03-0.5) were normal. Blood gas analysis, thyroid function tests (free T4: 11.8 pmol/L, NR: 9.0-25.7; TSH: 0.53 mIU/mL, NR: 0.5-4.5 mIU/ml) were normal. Plasma renin and aldosterone concentrations were in the low-normal range showing a lack of dehydration (7.31 pg/mL, NR: 2.71-16.51; and 36 pg/mL, NR: 30.7-275 respectively). Regarding severe hyponatremia, plasma ADH level was inappropriately high (1.78 pmol/L), suggesting a lack of ADH secretion suppression. These confirmed the diagnosis of SIADH. Magnetic resonance imaging of the brain and hypophysis of the patient revealed normal brain and anterior pituitary gland with the absence of a bright spot of the neurohypophysis. Acyclovir was given for the recurrent herpetic lesions around the mouth, and fluid restriction was commenced for the SIADH management. Oral salt and loop-diuretics were applied, as fluid restriction was not possible. SIADH resolved in a four-month period.

The interferon response to stimulation with various nucleic acids (immune-stimulatory DNA (ISD), polydA:dT, polyI:C, D type CpG ODN) and cyclic dinucleotide cGAMP was tested in the patient's peripheral blood mononuclear cells during the hospitalization for herpes infection. The analysis revealed a markedly reduced type I interferon response compared to healthy controls (Fig. 2). The defective interferon (IFN) response was not only restricted to stimulation with the plasmacytoid dendritic cell targeting toll-like receptor 9 (TLR9) ligand D35 as previously

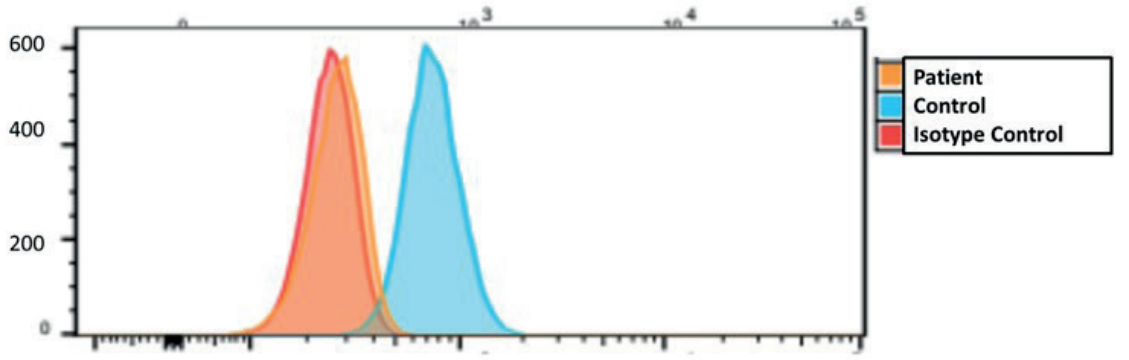

Fig. 1. DOCK8 expression was absent in the patient

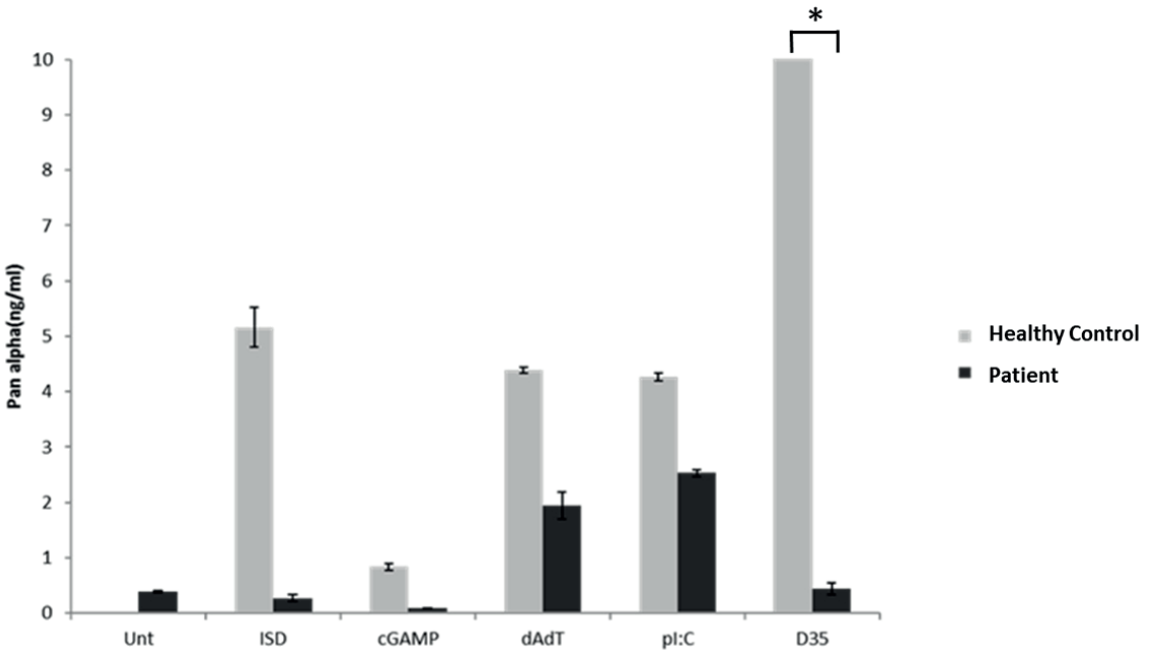

Fig. 2. Interferon response to several stimulating agents were low compared to healthy controls. Experiments were performed at least three times and each reaction was run in triplicate. cGAMP: cyclic dinucleotide guanosine monophosphate – adenine monophosphate, D35: D type CpG ODN, dAdT: polydA:dT, ISD: immune stimulatory DNA, Pan alpha: pan-specific interferon-α, pI:C: polyC, Unt: Untreated. *Statistically significant ($p<0.05$).

reported[9] but was also pronounced when cyclic GMP-AMP synthase (cGAS) and STING (Stimulator of Interferon Genes) ligands ISD and cGAMP were employed. The patient was discharged at 13 months of age and underwent stem cell transplantation in another center one year later.

Informed consent was obtained from the family for the publication of the case report.

Discussion

When eosinophilia accompanies recurrent viral infections and allergic symptoms (asthma, food/airborne allergies), the DOCK8 deficiency should be in the differential diagnosis. Since there is a high risk of mortality and malignancy, prompt diagnosis and evaluation for bone marrow transplantation as well as confirmation of the diagnosis using molecular genetic analysis are critically important for immediate and proper management.[10] Although our case had distinctive clinical features, a prompt diagnosis was achieved within a short time, and bone marrow transplantation was performed.

Another important finding in our patient was the low level of IgE when she presented firstly. We also observed that the IgE level may be low[8] in the early course of the disease and increases progressively in other patients with the *DOCK8* gene defect.

The skin is one of the major affected organs in patients with DOCK8 deficiency. Recurrent herpes infections, as in our patient, molluscum contagiosum infection, mucocutaneous candidiasis, and malignancies have been reported.[8] In a multicenter study, cutaneous viral infections have been reported in 68% of cases (n=40).[10] It is difficult to manage the viral cutaneous infections in DOCK8-deficient patients.[3] Recurrent herpetic infections in our patient caused poor oral intake of the patient and required intravenous antiviral therapy.

Hyponatremia due to SIADH is a presenting feature of several diseases, such as pulmonary infections, malignancies, or CNS infections.[11] A localized herpes infection in the patient was associated with the SIADH. Severe infections of Epstein –Barr virus (EBV), cytomegalovirus (CMV), varicella-zoster virus (VZV) may also cause SIADH.[12,13] Although SIADH due to disseminated herpes infections due to CNS involvement has been well described[13], SIADH associated with localized herpes has been rarely reported. It has been first reported in two adult patients with localized herpes zoster ophthalmic infection. In this study, it is reported that SIADH was treated with fluid restriction and a high salt diet, and lasted for 3 to 4 months.[12] As SIADH may be associated with central nervous system pathologies[13], we suggest that these patients and our patient who has infections around the head region may have yet asymptomatic central nervous system involvement, which may have regressed due to antiviral therapies.

Inadequate IFN-α production and plasmocytoid dendritic cell deficiency have been reported in DOCK8 deficiency. A patient diagnosed with refractory warts in addition to DOCK8 deficiency was reported to have benefited from IFN- α 2b treatment.[9] During SIADH, which seems to occur due to asymptomatic central nervous system involvement, the patients may benefit from IFN-α 2b treatment.

The expression of IFN-γ was known to be decreased in DOCK8 deficiency while interleukin 4 and interleukin 5 are increased leading to T helper-2 response and hypereosinophilia respectively. In a DOCK8 defective patient, IFN-γ is measured as about half of the values in the healthy control.[14] We planned to test the IFN-α response in the patient during hospitalization for severe herpes infection before the test for DOCK8 protein expression and molecular genetic analysis. A benefit of functional studies is the definition of the new findings in a known disease. It is known that low IFN-α response is seen in DOCK8 deficiency. However, it is reported previously that the defective IFN-α response was due to stimulation with the plasmacytoid dendritic cell targeting TLR9 ligand D35.[9] The novel finding in our report is that the IFN-α response is also low when cGAS and STING ligands ISD and cGAMP were employed. The defective interferon alpha response is not only mediated with TLR9, but also mediated with cGAS and STING.

The presentation of the present patient with DOCK8 deficiency was diverse. The absence of IgE elevation at presentation and the SIADH in the course of the disease were important findings. Low interferon response and low DOCK8 protein expression helped the early diagnosis of the patient.

Uncontrolled herpes infection in the present patient likely triggered the SIADH. Distinct inflammatory features associated with infections may be seen in the course of primary immunodeficiencies, and early functional and molecular genetic tests will aid the proper management.

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Ethical approval

Informed consent was obtained from the family for the publication of the case report.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: AMY, DC; data generation and collection: AMY, DC, MG, BK, EG; analysis and interpretation of results: AMY, DC, MG, İT, NG, AÖ, İT, MG, DÇ; draft manuscript preparation: AMY, DÇ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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