DOCK8 deficiency in a boy who presented with a giant aortic aneurysm between aortic root and iliac bifurcation

DOCK8 eksikliği olan bir olguda aort kökü ile iliyak bifurkasyon arasında dev aort anevrizması

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Summary– Dedicator of cytokinesis 8 protein (DOCK8) deficiency is an autosomal recessive, inherited form of hyper-immunoglobulin E (hyper-IgE) syndrome, characterized by persistent cutaneous viral infections, elevated IgE, eosinophilia, and allergic manifestations. The case of a 10-year-old boy who presented with giant aortic aneurysm between the aortic root and iliac bifurcation is described in the present report. Aortic aneurysm of this size has not yet been reported.

CASE REPORT

A 10-year-old boy was born the third child of consanguineous parents. Symptoms began at approximately 3 months in the form of severe atopic dermatitis. He had multiple food allergies (cow’s milk, egg, and lentil) and severe recurrent pneumonia; before the age of...
he was hospitalized 4–5 times. Excessive xerosis, recurrent urticarial lesions, eosinophilia, and increased IgE levels were observed after the age of 5. Immunological evaluation at the age of 6, was: absolute lymphocyte count: 1600 (normal range [NR]: 1500–7600/mm³); CD3: 960 (NR: 1000–4900/mm³); CD4: 200 (NR: 500–2700/mm³); CD8: 760 (NR: 300–2100/mm³); CD19: 400 (NR: 200–2200/mm³); natural killer cells: 150 (NR: 200–900/mm³); total eosinophil: 1890/mm³; immunoglobulin G: 1240 (NR: 528–1490 mg/dL); immunoglobulin A: 66 (NR: 23–205 mg/dL), immunoglobulin M: 15 (NR: 33–207 mg/dL); IgE: 6970 (NR: 0–100 IU/mL) (Table 1). At age 7, the patient experienced severe herpetic cutaneous lesion in the right external auditory canal, confirmed by a positive Tzanck smear (Figure 1). Given clinical manifestations and immunological evaluation, DOCK8 deficiency was suspected. Genetic testing revealed a large homozygous deletion with starting exons 18–48 in the DOCK8 gene. After the age of 7, the patient was not brought to the clinic and contact was not sought. At the age of 10, he was referred to pediatric emergency services with suspicion of aortic aneurysm based on outpatient transthoracic echocardiogram and presence of chest pain. Written informed consent was obtained. Transthoracic echocardiogram showed giant aortic aneurysm with severely dilated ascending and descending aorta. Thoracic computed tomography revealed aneurysm with maximal aortic diameter 80×76×64 mm between the aortic root and iliac bifurcation (Figure 2a, b). Cardiovascular surgery team deemed patient inoperable due to high risk of complication.

### DISCUSSION

DOCK8 protein activates Rho GTPases, which act as a type of guanine exchange factor. These GT-
Pases regulate several important cellular functions, particularly in lymphocytes, such as actin cytoskeletal organization, cell cycle progression, and gene expression. DOCK8 deficiency leads to combined immunodeficiency with an AR pattern of inheritance, characterized by eosinophilia, recurrent cutaneous viral infections, a wide range of allergic symptoms, and typically elevated IgE.

Several hematologic or epithelial malignancies, and various autoimmune events such as vasculitis, autoimmune hemolytic anemia, and nephropathy have been reported in follow-up of DOCK8-deficient patients. Skin manifestations including newborn rash, severe eczema, skin abscess, and various severe cutaneous infections, including herpes simplex virus, Varicella-zoster virus, human papillomavirus, Molluscum contagiosum virus, and mucocutaneous candidiasis have been reported in DOCK8-deficient patients. Of these manifestations, recurrent cutaneous herpetic infection in the right external auditory canal and severe eczema were observed in the present case. Allergic symptoms that have been reported in DOCK8-deficient patients include food allergies, asthma, allergic rhinitis, anaphylaxis, drug allergies, and urticarial lesions.

Cow’s milk, egg, and lentil allergies, atopic dermatitis, and urticarial lesions were observed in the present case. Neurologic manifestations have also been reported in DOCK8-deficient patients, including encephalitis, meningitis, encephalopathy, lymphoma, abscess, cerebral infarct/stroke, hemiparesis, and diplegia. None of these were observed in the present case. While vascular abnormalities including aneurysms, dilation, arterial tortuosity, and lacunar infarctions have been reported in STAT3-deficient patients, similar vascular abnormalities are less commonly reported in those with DOCK8 deficiency.

Aydin et al. reported 2 cases of cerebral vascular aneurysm out of 136 DOCK8-deficient patients. Al Mutairi et al. reported the case of a child with giant aortic aneurysm between the aortic root and descending aorta. Giant aortic aneurysm between the aortic root and iliac bifurcation was also a feature of the present case, and an aortic aneurysm of its size has never before been reported. It has been speculated that the pathogenesis of vascular abnormalities may relate to matrix metalloproteinases or transforming growth factor β dysregulation in hyper-IgE syndrome patients. Matrix metalloproteinases regulate tissue remodeling. Abnormalities of transforming growth factor β have also been identified in syndromes such as Marfan and Loeys-Dietz, which include vascular abnormalities similar to those of hyper-IgE syndrome.

In conclusion, early diagnosis and stem-cell transplantation are highly important in DOCK8-deficiency treatment, due to poor prognosis. The present report emphasizes that vascular pathologies such as giant aortic aneurysm, which may significantly contribute to morbidity and mortality, are extremely important aspects of DOCK8-deficient patient follow-up.

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REFERENCES


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