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# DOCK 8 IMMUNODEFICIENCY

**Anaesthesiology**

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## ABSTRACT

Autosomal recessive (AR) DOCK8 deficiency is a well-known actinopathy, a combined primary immune deficiency with impaired actin polymerization that results in altered cell mobility and immune synapse. DOCK8-deficient patients present early in life with eczema, viral cutaneous infections, chronic mucocutaneous candidiasis, bacterial pneumonia and abscesses, together with eosinophilia, thrombocytosis, lymphopenia, and variable dysgammaglobulinemia that usually includes Hyper-IgE. In fact, before its genetic aetiology was known, patients were described as having a form of Hyper-IgE syndrome, a name now deprecated in favour of genetic defects. We describe a school-age female patient with a clinical picture suggestive of DOCK8 deficiency, except for high serum IgE or a family history: early onset, failure to thrive, oral fungating lesion, generalized maculopapular rashes, bronchiolitis, pneumonia, recurrent otitis media, bronchiectasis, candidiasis, leucocytosis, eosinophilia, high IgA, low IgG and low CD4+ T cells. We were able to confirm the diagnosis through protein expression and whole-exome sequencing. We review the clinical, laboratory, and genetic features of 200 DOCK8-deficient patients. Despite this, the constellation of signs, symptoms, and findings allow the suspicion of DOCK8 deficiency and other actinopathies.

## KEYWORDS

DOCK8, Hyper-IgE, Autosomal recessive.

## INTRODUCTION

An estimated 7,000 individually rare diseases together afflict about 1 in every 17 humans (1). Individuals with rare diseases endure a diagnostic odyssey in which they consult an average of more than seven physicians for more than 6 years before someone suspects their correct diagnosis (2). Diagnostic errors are an important source of waste, complaints, complications, and deaths (3). Inborn errors of immunity (IEIs) are a group of congenital rare diseases with increased susceptibility to infection, autoimmunity, inflammation, allergy and cancer (4)

Combined immune deficiencies (CIDs), which stunt the numbers or responses of lymphocytes are among the most severe IEIs (5). They manifest themselves since very early in life with adverse reactions to live vaccines, severe eczema, variety of skin lesions with or without fever, chronic diarrhoea, atopic and/or bleeding diatheses, failure to thrive and opportunistic infections, as well as a life-long risk of autoimmune disease and malignancy. Depending on the lesions and clinical presentation from the time of onset probably because of misdiagnosis or delay in referral due inadequate attempt to perform required diagnostic strategies, most often patients present to referral centres with complicated clinical situations, where patient can have failure to thrive due to inadequate intake of various reasons, inability to sleep due to anxiety in addition to apparent morphology, hesitance towards medical practice as parents had been made aware as rare clinical presentations in very few of patients and pessimism of outcome negating parents or relatives' support to patient. But most of Actinopathies are CIDs that prevent the polymerization of actin, thus impairing cell mobility and the immune synapse of hematopoietic cells (6). Autosomal recessive (AR) DOCK8 deficiency is one of the better-known actinopathies.

The dedicator of cytokinesis 8 is a large protein that activates the small GTPase CDC42, which is essential for the reorganization of actin (7). DOCK8 also interacts with the WIP-WASp complex, regulates STAT3 and promotes a Th17 CD4+ differentiation (8, 9). The defective actin accumulates in natural killer (NK) cells and cripple their cytotoxicity function (10). Although , DOCK8 deficient patients were first described as suffering from a type of Hyper-IgE syndrome (11), it soon became clear that this is a distinct entity of graver prognosis (12). Here, we describe the case of a DOCK8-deficient school-age girl with high IgE serum levels, who nevertheless had other signs and findings that allowed suspecting the diagnosis.

### Case Report

A 6-year-old female patient was referred to our care for a history of Oro-facial lesion since 2 years which started as isolated lesion and ended up with fungating mass involving both upper and lower lip including oral mucosa, respiratory infections, and mucocutaneous involvement of perioral region. The mass is granulomatous in nature with overlying crust and pus, which bleeds easily and causes pain to touch. Patient had drooling of saliva from oral cavity, difficulty in swallowing in addition to chocking episodes while eating soft diet, inability to lie down due to fear of choking and collection of saliva in oral cavity.

Most commonly she has been sitting with forward flexion of head so to facilitate passive drainage of saliva. She also has generalised maculopapular rash with eruptions which improves with antibiotics and reappears when antibiotic is stopped. There is no sweating or abnormal movement noted. History taking from Mother revealed that patient has history of recurrent infections at the age of 11 months which required ICU admission.

She has prominent history of recurrent ear infection. Born from a non-consanguineous family from ( citizen of South Asia) she is vaccinated as per age and mother states that the patient tolerated the Bacille Calmette-Guérin (BCG) vaccine shortly after birth and her family history was significant only for one spontaneous abortion of unknown cause .

In early stages of life when patient 11 months old , she had extensive rashes attributed to recurrent infections. Later, the patient also developed one episode of bronchiolitis, three episodes of pneumonia and at least 8-10 times a year of otitis media with effusion In addition she had intermittent diarrhoea twice-a-month and mucocutaneous candidiasis as well.

On physical examination, low weight, short stature, absent tonsils, a dry skin with extensive maculopapular rashes and mild hepato splenomegaly were noted. Discoloured skin patches were corroborated in the forehead, trunk, hands and soles, as well as some skin lesions in feet.
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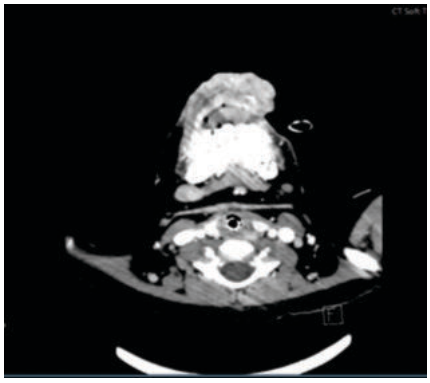
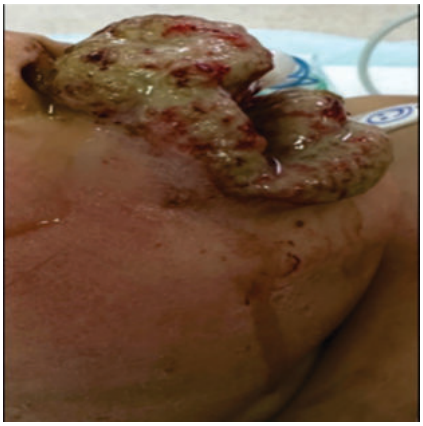
High-resolution CT of the chest revealed lung lesion probably air space opacification and loss of lung volume and CT of Head and neck identified as Thicken lip upper more than lower one



**(Fig:1) (CT SCAN IMAGE)**

associated with possible skin lesion , multiple lymphadenopathies in cervical region and small volume in thoracic region.

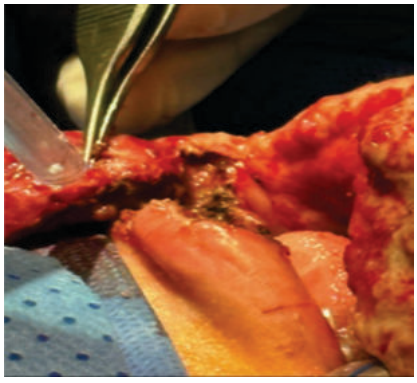
Blood counts reported leucocytosis (11000 cells/mm3) and hyper-eosinophilia 1800/mm3), with Hb. 96 g/dL, neutrophils 5505, lymphocytes 2700 , monocytes 1290, and 866,000/mm3 platelets. Serum immunoglobulin for IgA: 550, IgG: 400 mg/dl. In addition total serum IgE was very high at 13505 IU/mL(Normal < 90IU/ml). CD4+ T cells were a low at 19.020, with the rest of lymphocyte subsets within the normal range (CD3+ 1,346, CD8+ 530, CD19+ 863, CD4/8 815 cells/mm3). Serologies for HIV: Neg, EBV: Neg, and CMV: Positive. A provisional diagnosis of CID (Combined immune deficiency was given. Alternative diagnoses we entertained for this patient were as follows: Wiskott–Aldrich syndrome (WAS), HIV/AIDS (CD4+ lymphopenia) and leukaemia (hyper eosinophilia). However, a bone marrow aspirate and a CGL myeloid mutation panel were reported as normal. As per serum immunoglobin assay with very high serum IgE and high serum IgA with low IgG ; DOCK8 deficiency was included in the differential diagnosis, considering the constellation of early onset, failure to thrive, skin lesions of different morphology, bronchiolitis, pneumonia, recurrent otitis media, bronchiectasis, candidiasis, and leucocytosis .



**(Fig 2)**

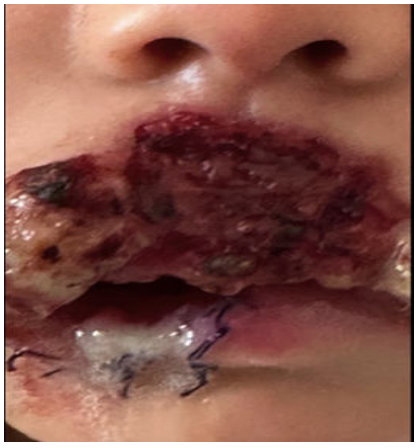
The patient is currently stable underwent surgical excision of Oral lesion for biopsy and cosmetic purpose. In pre-anesthesia evaluation , difficult air way was anticipated and all the preparations of difficult airway management were done involving Fibreoptic bronchoscope and Glide scope. During induction for surgery after preparing the Operation theatre for anticipated difficulties, with the backup of surgical (ENT Team), IV induction was done with Propofol, Fentanyl and Rocuronium.

As the mask holding was difficult, the lesion was covered with gauze piece and large size mask as per appropriate age was selected to ventilate the patient. Glide scope was used to visualize the vocal cord for tracheal intubation in view of potential bleeding oral lesion. Precautions were taken not to disrupt the lesion and 5.0 ETT (Fig.2 ) was placed after visualization of cord. Lesion was excised partially and some cosmetic reconstruction ( Fig. 3) was done to make sure to facilitate oral intake by patient. Some loose teeth also were extracted as were loose due to mucous involvement of oral cavity. Biopsy samples were sent. Patient was extubated with back up of difficult extubation due to extensive surgery considering anticipated airway oedema.



**(Fig 3)**

Result came as positive for HSV, CMV, EBV, oral prophylactic antibiotics (TMP/SMZ+ Piperacillin + tazobactam1700 mg TID 4 Days, Clindamycin and Valacyclovir 250 mg Ganciclovir IV 125 mg IV BD, Fluconazole oral liquid, Topical steroid (Dexpentenol) and Immunoglobin therapy IVIG 10 gm once. She is awaiting hematopoietic stem cell transplantation (HSCT). The patient is doing well after 1 month of continuous treatment and follow up. Lesions on perioral region (Fig.4) shows significant improvement. Oral Intake has significantly improved. Child is more active as routine part of her life and awaits for discharge after complete recovery.



**(Fig 4)**

**DISCUSSION:**

Primary immune-deficiencies (PIDs) are becoming more widely recognized due to improvements in genetic screening and identification of these diseases, which have shown a surprisingly wide range of possible clinical manifestations. It is now understood that PID manifests itself in a variety of ways, including atopic disease, autoimmunity, cancer and viral susceptibility (13). This paradigm is illustrated by the combined immunodeficiency dedicator of Cytokinesis 8 (DOCK8) deficiency. DOCK8 deficiency was discovered to be the underlying defect in the majority of patients with autosomal recessive hyper IgE syndrome (AR-HIES) as first reported in 2009 by Englhart et al. (14)

Davis initially described the Hyper IgE Syndrome (HIES), often referred to as Job Syndrome, in 1966 (15). HIES is an uncommon immunodeficiency illness and the chief clinical symptoms are recurrent Eczema-like rash, skin and lung abscesses, as well as elevated serum IgE levels. The prevalence of this illness is less than 1/100,000 and it typically affects young children and newborns without regard to a person's gender or race. The DOCK protein is crucial for cytoskeletal organization and influences dendritic cell movement. Lack of DOCK8 causes early T cell apoptosis, reduced toxicity of natural killer (NK) cells and the persistence of germinal centre B cells. Cellular and/or humoral immunity are involved in the aetiology of AR-HIE patients due to DOCK8 gene mutations. Significantly fewer T cells are present than usual and memory B cell numbers may also be declining (16).

The present case report describes a 6 year old female patient with oro - facial lesion since 2 years , which started as isolated lesion and ended

up with fungating mass involving both upper and lower lip including oral mucosa and mucocutaneous involvement of perioral region along with respiratory infections.

In addition, she has history of mild hepatosplenomegaly, failure to thrive, bronchiectasis, bronchiolitis, pneumonia, recurrent otitis media, candidiasis, hyper-eosinophilia, leukocytosis, multiple lymphadenopathies and CD4+lymphopenia. Her total serum IgE was very high at 13787 IU and serology was positive for Cytomegalovirus. Above clinical pictures suggest to have provisional diagnosis of CID (Combined immune deficiency) was made. High serum IgE, IgA and low IgG along with the presenting clinical signs and symptoms suggesting to have DOCK8 deficiency with other differential diagnosis as Wiskott–Aldrich syndrome, HIV/AIDS (CD4+ lymphopenia), and leukaemia (hyper eosinophilia).

More than 250 DOCK8-deficient patients have been identified to date, and 98% of them exhibited elevated serum IgE levels. In 2016, Kienzler et al. (17) identified a female patient with DOCK8 deficiency who didn't have significant serum IgE levels. Only three of the 136 patients in Aydin et al.'s study had blood IgE levels that were within the normal range (twelve more had IgE that was high but not "hyper": less than 1,000 IU/mL) (18). A case of a 3-year-old who came with widespread sheets of molluscum over the trunk, vaginal area, ears, and eyelids along with occipital and submandibular lymphadenopathy was described by Purcell Claire et al (19). Investigations revealed peripheral eosinophilia, elevated IgE, low IgM, and lymphopenia with aberrant T-cell subsets. The instance of a school-age boy with a DOCK8 deficiency and normal IgE serum levels is described by Edna Venegas-Montoya , who nevertheless had other signs and findings that allowed suspecting the diagnosis (20). The case of a 7-year-old child who was referred to their hospital due to improper walking posture was described by Jing Yang and Yan Liu (21).

The patient's clinical symptoms included an irregular walk, an eczema-like dermatitis, an abscess on a fingertip, excessive muscular tone and facial paralysis. Serum IgE levels and blood eosinophil levels both significantly increased, and T lymphocyte subsets showed a reduction. By using whole exome sequencing, two new compound heterozygous variants in the DOCK8 gene (c.1868 + 2 T > C and c.5962-2A > G) were found. The DOCK8 gene has been documented to contain more than 130 mutations to date, with extensive deletions accounting for the majority of these. Chinese patients with autosomal recessive high IgE had 11 distinct DOCK8 gene variants.

When IgE was identified and proven to be noticeably high in the serum of the initially described patients, whose trait was inherited in an autosomal dominant pattern, the Hyper-IgE syndrome was renamed from "Job syndrome" to that term. Eventually, a collection of autosomal recessive patients who shared a little similar phenotype (i.e., a high serum) emerged (22). Between 2009 and 2018, IgE, eosinophilia, abscesses, and skin lesions) were characterised and their genetic causes were discovered. When compared to STAT3 loss of function, DOCK8 deficiency has a very different prognosis and course of treatment since it is categorised and comprehended as a combined immunological dysfunction(23). One common mistake is to believe that all Hyper-IgE disorders are identical, while having various etiologies. The most common clinical presentations include eczema, food allergy, molluscum/plain warts, abscesses, candidiasis, pneumonia, hyper- IgE (98%), eosinophilia (96%), low IgM, and low T cell in DOCK8-deficient patients. Hematopoietic stem cell transplantation (HSCT) is the sole recommended treatment since it has the only chance of being curative for patients with DOCK8 deficiency. These patients have a lifelong cumulative risk of acquiring aneurysms, malignancies and deadly infections(24).

Patients with DOCK8 deficiency may not have high total serum IgE levels, yet the astute clinician will maintain a differential diagnosis based on early onset eczema, food allergy, unusual infection, abscess, autoimmunity, eosinophilia, dysgammaglobulinemia, and CD3+ lymphopenia.

## CONCLUSION:

To conclude, patients with DOCK8 deficiency may or may not have high total serum IgE levels. DOCK8 deficiency leads to a combined immunodeficiency with broad and devastating clinical sequelae. Our case highlights the unique presentation of oro-facial lesion associated with DOCK8-deficient patients.

This report has no conflict of interest.

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