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Case report

A 17-year old patient with DOCK8 deficiency, severe oral HSV-1 and aggressive periodontitis – A case of virally induced periodontitis?

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ABSTRACT

We present a 17-year old girl with DOCK-8 deficiency, severe untreated oral HSV-1 infection and associated aggressive periodontitis. DOCK-8 deficiency is a primary immunodeficiency, caused by biallelicloss-of-function mutations in the DOCK8 gene, often leading to severe viral and fungal mucocutaneous infections. Nevertheless, to date DOCK8 has not been associated with severe periodontitis and inflammatory bone loss around teeth. Understanding whether DOCK8 deficiency or severe HSV-1 infection underlies susceptibility to periodontitis is central to this case and may provide insights into susceptibility factors for periodontitis in the general population. Our clinical and microbiological data suggest that severe HSV-1 infection is the driver of periodontal inflammation in this case.

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1. Why this case is important

Periodontitis is a common inflammatory disease, in which an exaggerated immune response to microbial signals becomes tissue-destructive, resulting in loss of tooth supporting structures (connective tissue and bone) [1–3]. However, which factors are the most crucial for disease susceptibility and progression is not fully understood [4–6]. In the quest to understand complex inflammatory diseases, the study of extreme phenotypes in patients with monogenic immune defects provides critical opportunities to evaluate disease susceptibility.

Here, we present a case of DOCK8 deficiency, severe oral Herpes Simplex Virus-1 (HSV-1) infection and aggressive periodontitis. DOCK8 deficiency is an autosomal recessive primary immunodeficiency disease (PID) caused by loss-of-function mutations in the *DOCK8* gene [7,8]. DOCK8 deficiency belongs to the group of hyper-IgE syndromes (HIES) and shares many clinical features with Job's syndrome but also exhibits distinct clinical features. A distinctive feature of DOCK8 deficiency that helps to distinguish it from other hyper IgE disorders is the increased susceptibility to mucocutaneous viral infections; typically caused by herpes simplex virus (HSV), human papillomavirus (HPV), molluscum contagiosum virus (MCV), and varicella zoster virus (VZV) [9]. Viral susceptibility in these patients has been attributed to a progressive T and B cell lymphopenia as well as defects in $CD8^+$ T cell survival and function, NK cell function, B cell activation and defective generation of antigen specific responses [8].

2. Case description

This is a case of a 17-year old Lebanese girl with DOCK8 deficiency [7,8]. DOCK8 deficiency is an autosomal recessive primary immunodeficiency caused by loss-of-function mutations in the *DOCK8* gene [7,8]. Patients with DOCK8 deficiency have a decreased number of T and B cells, elevated serum IgE, eosinophilia and present with persistent cutaneous viral infections, recurrent sinopulmonary infections and mucocutaneous candidiasis [9].

The patient presented with a chief complaint of severe generalized oral pain, difficulty opening her mouth and eating. She was on a soft diet and liquids. Her medical history included recurrent mucocutaneous fungal and viral infections and recurrent

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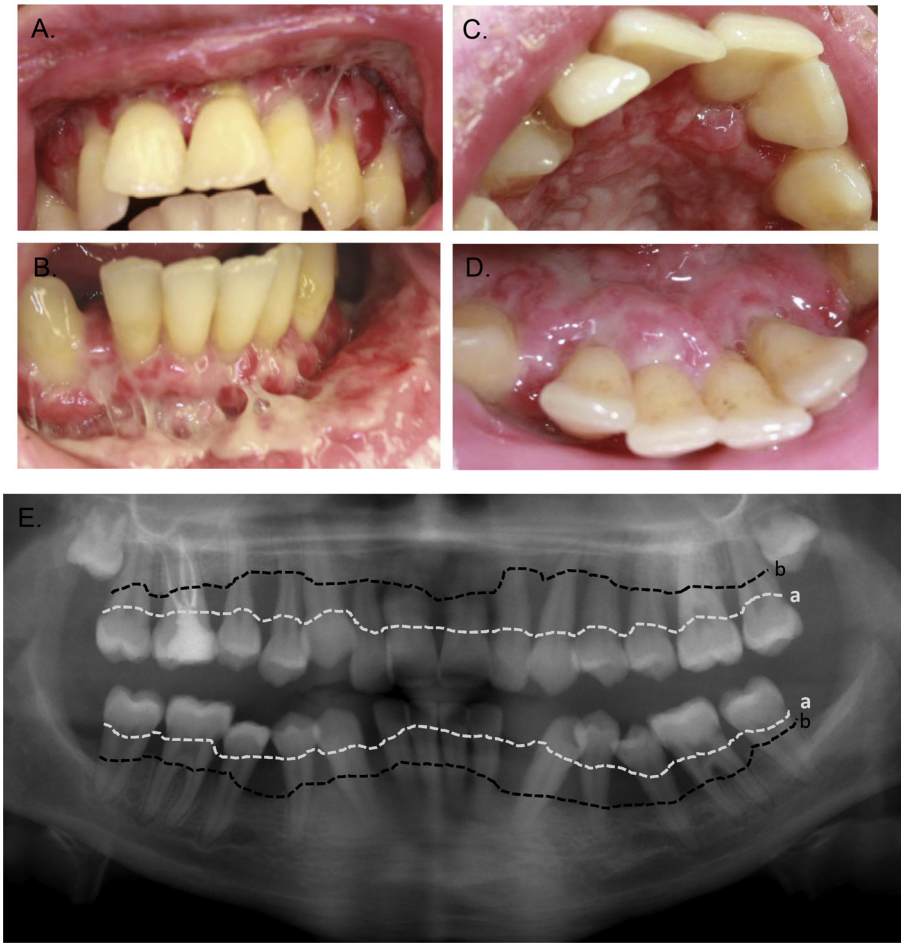

Fig. 1. Initial clinical oral presentation and diagnostic radiographs. (A–D) Intraoral photography of widespread HSV-1 intraoral lesions. Ginigiva appear erythematous, edematous and necrotic. White coating is covering the majority of mucosa areas, indicative of sloughling necrotic epithelia. Areas shown are: facial surface of maxilla (A) and mandible (B) palatal (C) and lingual surfaces (D). (E) Panoramic radiograph. Severe bone loss is indicated by the two drawn lines. The white line represents the expected physiological bone level (a) and the black line (b) the actual bone level.

pneumonias. Weight/height were below the 3rd percentile. Immunological findings were consistent with a DOCK8 diagnosis including low CD4/CD8 T cells, high serum IgE and eosinophilia. NK and neutrophils were within range. A novel homozygous deletion of exons 28–35 in the DOCK8 gene was identified in this patient.

Examination revealed submandibular/sublingual lymph adenopathy and limited oral opening (21 mm). Intraoral findings were significant with dramatic generalized necrotic oral lesions (Fig. 1A–D). Oral radiographs showed a complete adult dentition but with generalized bone loss around teeth, suggestive of severe periodontitis (Fig. 1E), a rare finding in a young patient. To diagnose the etiology of the oral/mucosal necrotizing disease and related severe periodontitis, samples were obtained for microbiology and histopathology.

2.1. Microbiological findings

Intraoral swabs were PCR positive for HSV-1 with crossing threshold (Ct) values strongly suggestive of active HSV-1 infection. EBV PCR was negative. HSV-1 was recovered in cell culture from oral swabs and *in vitro* susceptibility testing confirmed sensitivity to both acyclovir and foscarnet. Gram stain was negative for yeast/fungal elements. Fungal cultures did not grow (Fig. 2A). Patient was seropositive for HSV-1 but negative for HSV-2.

Tooth-associated microbial samples (subgingival plaque), were all strongly PCR positive for HSV-1. Microbial characterization (with a microarray for 300 oral bacterial species [10]), showed a mixed community of oral commensals, with a dominance of *Capnocytophaga* species. A few organisms associated with chronic periodontitis (*Porphyromonas gingivalis* and *Treponema denticola*) [4] were detected but not *Aggregatibacter actinomycetemcomitans* [10] an organism associated with aggressive periodontitis (Fig. 2B).

2.2. Oral pathology

A persistent ulcerated lesion on the soft palate was biopsied. Pathology showed no malignant changes, but marked inflammation with dominance of neutrophils, eosinophils and granulation tissue (Fig. 3A). Numerous giant cells at the base of the ulcer showed cytopathic effects (Fig. 3B) and were positive by immunohistochemistry for HSV-1 (Fig. 3C). Special staining for mycobacteria, fungi and CMV were negative.

2.3. Patient management

Patient was placed on oral Valacyclovir 750 mg three times daily for her HSV-1 infection and was advised to seek periodontal treatment. When she returned to the hospital one year later for hematopoietic stem cell transplant (HSCT), her oral lesions had improved significantly with only a few necrotic areas still visible (Fig. 4A). Oral opening was 31 mm and eating was improved. Nevertheless, she had not received periodontal treatment. Oral swabs