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# 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.

### Keywords

DOCK8 deficiency; oral HSV-1; aggressive periodontitis

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The authors declare no competing interests

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## 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)[123]. However, which factors are the most crucial for disease susceptibility and progressionis not fully understood[456]. In the quest tounderstand 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 exibits 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 simplexvirus (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].

## Case Description

This is a case of a17-year old Lebanese girl with DOCK8 deficiency[78]. 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 pneumonias. Weight/height were below the 3$^{rd}$ 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 lymphadenopathy and limited oral opening (21mm). Intraoral findings were significant with dramatic generalized necrotic oral lesions (Figure 1A–D). Oral radiographs showed a complete adult dentition but with generalized bone loss around teeth, suggestive of severe periodontitis (Figure 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.

## Micobiological Findings

Intraoral swabs were PCR positive for HSV-1 with a 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 (Figure 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 (Figure 2B).

## 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 (Figure 3A). Numerous giant cells at the base of the ulcer showed cytopathic effects (Figure 3B) and were positive by immunohistochemistry for HSV-1 (Figure 3C). Special staining for mycobacteria, fungi and CMV were negative.

## 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 (Figure 4A). Oral opening was 31mm and eating was improved. Nevertheless, she had not received periodontal treatment. Oral swabs remained positive for HSV-1 but the obtained Ct values suggested a decreased viral load. Biopsies of a remaining oral lesion showed only very sparse HSV positive cells now localized to the superficial layer of the squamous mucosa (indicative of viral shedding). Comprehensive periodontal evaluation[11] showed generalized severe bone loss (probing depths-PD>5mm in 30% of sites). Bleeding on probing (inflammation) was also generalized. We treated her with deep dentalcleanings (Scaling and Root Planning) to reduce tooth-associated microbial load. The patient responded to the combination of antiviral therapy and periodontal treatment with visible changesin gingival architecture, swelling and erythema within two weeks. At the conclusion of this combined treatment of antiviral and periodontal therapy the majority or oral lesions and significant areas of gingival inflammation had resolved.

In preperation for transplantation the patient received immunosuppressive and myeloblative agents (busulfan IV, fludarabine and keratinocyte growth factor) and antibiotics (amoxicillin/clavulanate). Five days into this regimen she responded with complete resolution of remaining oral lesions and gingival inflammation (Figure 4B).

During and after transplant she had minimal oral issues. She received biweekly superficial cleanings and daily chlorhexidine. At 100 days post-HSCT there were no remaining oral lesions and HSV-1 testing was negative, reflecting immune reconstitution. Periodontal tissues were free of visible gingival inflammation and with significant reduction in periodontal depths secondary to tissue shrinkage (Figure 4C–D).

## Discussion and Evaluation of Similar Cases

This case provides a unique opportunity to witness unprecedented oral HSV-1 and associated aggressive periodontitis in a young patient with DOCK8 deficiency.

To investigate etiology of periodontitis in this case, we evaluated the contribution of known risk factors. Severe disease at a young age is extremely rare and typically assocated with neutrophil defects[1213] or with *A. actinomycetemcomitans*[1014]. Neutrophil dysfuction is not considered part of DOCK8 and our patient's neutrophil counts were normal with extensive neutrophil infiltration in biopsied lesions. *A. actinomycetemcomitans* was alsonot detected.

The clinical presentation combined with microbiological evidence and observations is response to antiviral treatment point to the role of HSV infection-not as a sole etiology- but as an important factor contributing to the aggressive nature of the disease in this case. Our patient developed periodontitis in the setting of severe-untreatedoral HSV-1 and the virus was detectable at periodontitis sites. Herpes-viruses have been previously associated with aggressive periodontitis[151617]. Periodontitis generally represents microbe-stimulated inflammation[1] therefore it is conceivable that severe viral infection may become a driving force potentially exaggerating microbial stimulation leading to destructive periodontal inflammation. Whether DOCK8 provides a unique setting for excessive pro-inflammatory responses to HSV-1 cannot be ruled out.

Further supporting the role of HSV-1 is the clinical response to treatment. Our patient received antiviral and local periodontal therapy and responded within weeks with reduction in gingival inflammation. Complete resolution in this case occurred following the combined antibiotic and immunosuppressive regimen in preparation for HCST, consistent with the microbe-stimulated inflammatory nature of periodontitis.

In conclusion, the current case demonstrates an impressive presentation of HSV-1 oral disease and periodontitis and may provide insights into the pathogenesis of periodontal diseases.

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## Highlights

- We present a case of severe oral HSV-1 infection in a patient with DOCK8 deficiency
- We document severe periodontitis and bone loss in this young patient
- HSV-1 infection appears exacerbate periodontal destruction in this patient

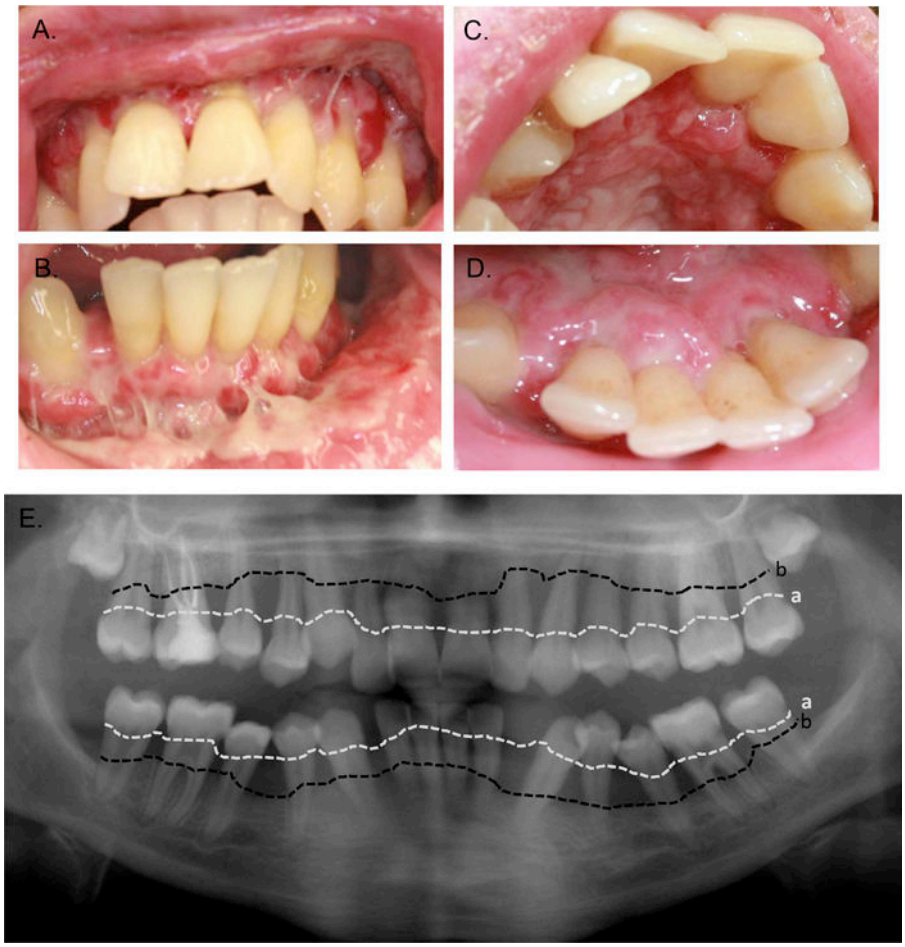


**Figure 1. Initial Clinical Oral Presentation and Diagnostic Radiographs**

(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.

A.

CLINICAL MICROBIOLOGY

| | Oral Swab | Dental Plaque |
|---|---|---|
| **HSV PCR** | Positive | Positive |
| **EBV PCR** | Negative | NA |
| **Fungal Culture** | No Growth | NA |
| **HSV-1 Culture** | Recovered in cell culture | NA |
| **Gram Stain** | Mixed oropharyngeal flora/ No Fungi | Mixed oropharyngeal flora/ No Fungi |
| **16S Microarray** | NA | Mixed Commensals (Positive for Periodontitis-related species) |

B.

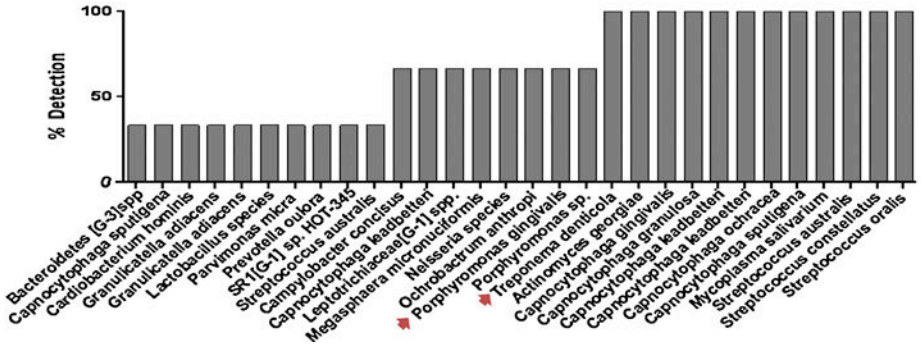


**Figure 2. Oral Microbiology**

(A) Diagnostic Microbiology on oral swabs and dental plaque. (B) 16S microarray for approximately 300 oral species (HOMIM) was performed on subgingival dental plaque samples (Percentage of detection throughout all teeth sampled). Classic periodontitis-related species indicated with red arrows.

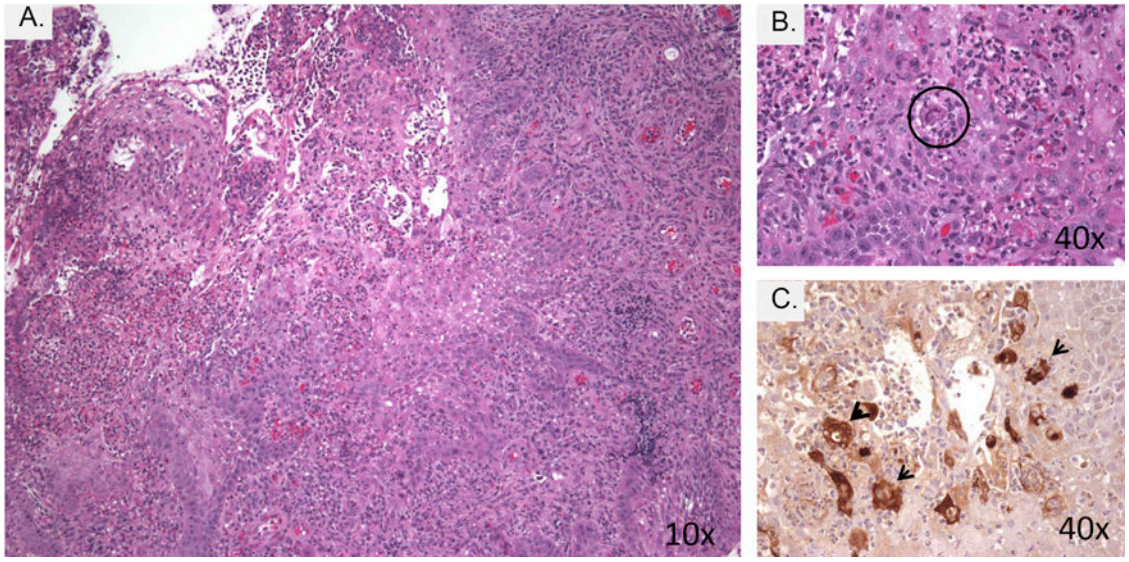


**Figure 3. Oral Pathology**

Histological evaluation of an ulcerated oral lesion. (A) H&E staining reveals ulcerated squamous mucosa with marked acute and chronic inflammation, granulation tissue and scattered multinucleated giant cells. (B) Multinucleated cells with cytopathic changes shown at higher magnfication (circled) and are positive for HSV-1 by immunohistochemistry (C, brown staining indicated by arrows). Original magnifications shown.

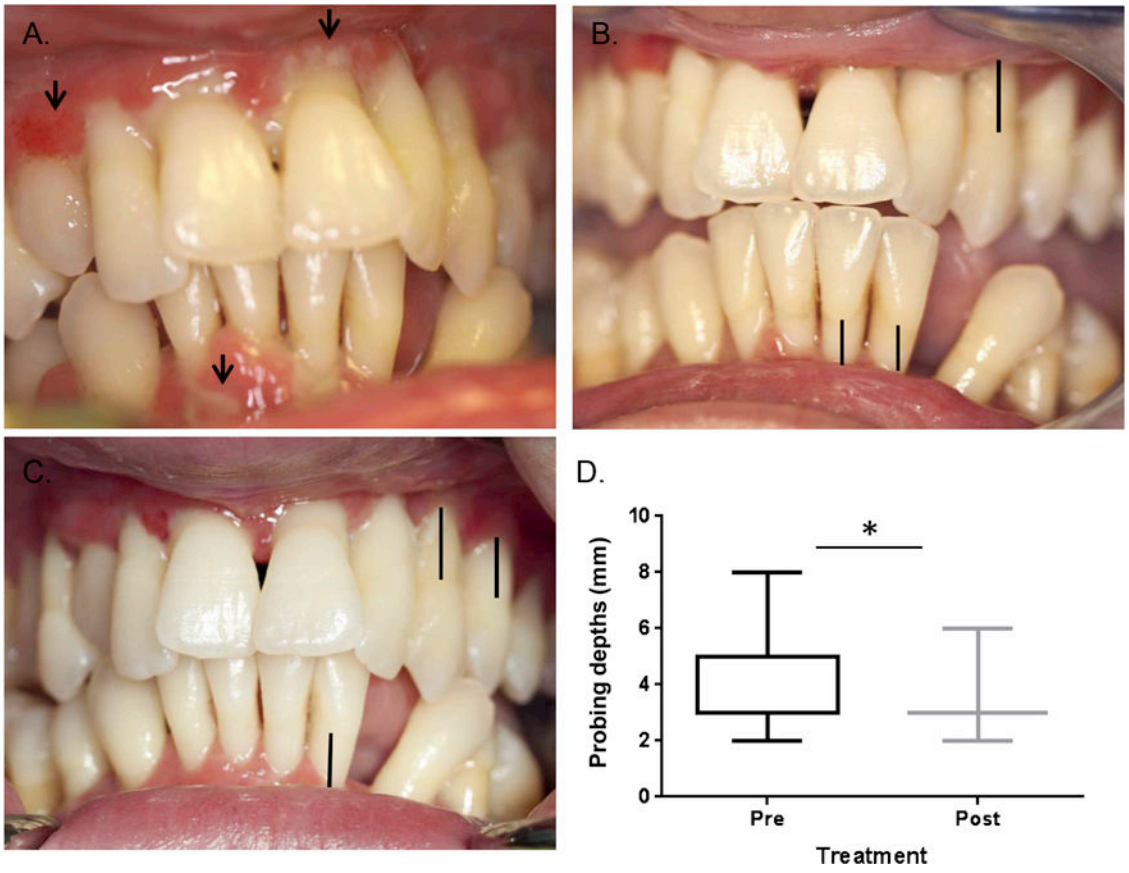


**Figure 4. Clinical course of Disease**

Intraoral photography at various time points of treatment (A–C). (A) Patient had received one year of Valacyclovir and was two weeks post periodontal treatment. Arrows indicate remaining areas of necrosis and erythema. (B) Following 5 days of immunosuppressive conditioning prior to transplant. Images (A) and (B) are taken 7 days apart. (C) 100 days post HCT. Black lines on teeth indicate areas tissue shrinkage (recession) resulting from inflammatory resolution. D. Full mouth probing depths in mm before periodontal treatment (pre) and at the end of the follow up period (post). Mean ± SE and range shown, *=$p<0.01$.