# Acyclovir-Resistant Cutaneous Herpes Simplex Virus in *DOCK8* Deficiency

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## PRACTICE **POINTS**

- Patients with dedicator of cytokinesis 8 (*DOCK8*) deficiency are susceptible to development of severe recalcitrant viral cutaneous infections, including herpes simplex virus (HSV).
- Dermatologists should be aware that prophylactic acyclovir may not be sufficient for HSV suppression in the setting of severe immunodeficiency.
- Viral culture should be performed on suspicious lesions in *DOCK8*-deficient patients despite acyclovir prophylaxis, and the threshold for HSV resistance testing should be low.
- Acyclovir-resistant cutaneous HSV lesions require escalation of therapy, which may include addition of foscarnet, cidofovir, or subcutaneous pegylated interferon alfa-2b to the therapeutic regimen.

Patients with dedicator of cytokinesis 8 (*DOCK8*) deficiency are susceptible to development of severe viral cutaneous infections, including herpes simplex virus (HSV). We report a 32-month-old girl with homozygous *DOCK8* deficiency who developed a posterior auricular cutaneous lesion that was culture positive for HSV despite acyclovir prophylaxis. Resolution of this lesion was only observed after addition of foscarnet to the treatment regimen. Prophylactic acyclovir may be insufficient for suppression of cutaneous HSV in patients with *DOCK8* deficiency, and a high index of suspicion for viral resistance is necessary for prompt initiation of appropriate antiviral treatment in these patients.

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Dedicator of cytokinesis 8 (*DOCK8*) deficiency is the major cause of autosomal-recessive hyper-IgEsyndrome.[1] Characteristic clinical features including eosinophilia, eczema, and recurrent *Staphylococcus aureus* cutaneous and respiratory tract infections are common in *DOCK8* deficiency, similar to the autosomal-dominant form of hyper-IgE syndrome that is due to deficiency of signal transducer and activation of transcription 3 (*STAT-3*).[1] In addition, patients with *DOCK8* deficiency are particularly susceptible to asthma; food allergies; lymphomas; and severe cutaneous viral infections, including herpes simplex virus (HSV), molluscum contagiosum, varicella-zoster virus, and human papillomavirus. Since the discovery of the *DOCK8* gene in 2009, various studies have sought to elucidate the mechanistic contribution of *DOCK8* to the dermatologic immune environment.[2] Although cutaneous viral infections such as those caused by HSV typically are short lived and self-limiting in immunocompetent hosts, they have proven to be severe and recalcitrant in the setting of *DOCK8* deficiency.[1] Herein, we report the case of a 32-month-old girl with homozygous *DOCK8* deficiency who developed acyclovir-resistant cutaneous HSV.

## Case Report

A 32-month-old girl presented with an approximately 2-cm linear erosion along the left posterior auricular sulcus at month 9 of a hospital stay for recurrent infections. Her medical history was notable for multiple upper respiratory tract infections, diffuse eczema, and food allergies. She had presented to an outside hospital at 14 months of age with herpetic gingivostomatitis and eczema herpeticum that was successfully treated with acyclovir. She was readmitted at 20 months of age due to *Pneumocystis jiroveci* pneumonia, pancytopenia, and disseminated histoplasmosis. Prophylactic oral acyclovir (20 mg/kg twice daily) was started, given her history of HSV infection. Because of recurrent infections, she underwent an immunodeficiency workup. Whole exome sequencing analysis revealed a homozygous deletion c.(528+1_529−1)_(1516+1_1517−1)del in *DOCK8*

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The eTable is available in the Appendix online at www.mdedge.com/dermatology.
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gene–affecting exons 5 to 13. The patient was transferred to our hospital for continued care and as a potential candidate for bone marrow transplant following resolution of the disseminated histoplasmosis infection.

During her hospitalization at the current presentation, she was noted to have a 2-cm linear erosion along the left posterior auricular sulcus. Initial wound care with bacitracin ointment was applied to the area while specimens were obtained and empiric oral acyclovir therapy was initiated (20 mg/kg 4 times daily [QID]), given a clinical impression consistent with cutaneous HSV infection despite acyclovir prophylaxis. Direct immunofluorescence and viral cultures were positive for HSV-1, while bacterial cultures grew methicillin-susceptible *S aureus*. Cephalexin and mupirocin ointment were started, and acyclovir was continued. After 2 weeks of therapy, there was no visible change in the wound; cultures were repeated, again showing the wound contained HSV. Bacterial cultures this time grew *Pseudomonas putida*, and the antibiotic regimen was transitioned to cefepime.

After no response to the continued course of therapeutic acyclovir, HSV cultures were sent to the Centers for Disease Control and Prevention for resistance testing, and biopsy of the lesion was performed by the otolaryngology service to rule out malignancy and potential alternative diagnoses. Histopathology showed only reactive inflammation without visible microorganisms on tissue HSV-1/HSV-2 immunostain; however, tissue viral culture was positive for HSV-1. The patient was transitioned back to acyclovir (intravenous [IV] 20 mg/kg QID) with the addition of empiric foscarnet (IV 40 mg/kg 3 times daily) given the worsening appearance of the lesion. The HSV acyclovir resistance test results from the Centers for Disease Control and Prevention returned soon after and were positive for resistance (median infectious dose, 3.29 μg/L [reference interval, sensitive <2.00 μg/L; resistant >1.90 μg/L]). The patient completed a 21-day course of combination foscarnet and acyclovir therapy, during which time the lesion showed notable improvement and healing. The patient was continued on prophylactic acyclovir (IV 20 mg/kg QID). Unfortunately, the patient eventually died due to complications related to pneumonia.

## Comment

*Infection in Patients With* DOCK8 *Deficiency*—The gene *DOCK8* has emerged as playing a central role in both innate and adaptive immunity, as it is expressed primarily in immune cells and serves as a mediator of numerous processes, including immune synapse formation, cell signaling and trafficking, antibody and cytokine production, and lymphocyte memory.[3] Cells that are critical for combating cutaneous viral infections, including skin-resident memory T cells and natural killer cells, are defective, which leads to a severely immunocompromised state in *DOCK8*-deficient patients with a particular susceptibility to infectious and inflammatory dermatologic disease.[4]

Herpes simplex virus infection commonly is seen in *DOCK8* deficiency, with retrospective analysis of a *DOCK8*-deficient cohort revealing HSV infection in approximately 38% of patients.[5] Prophylactic acyclovir is essential for *DOCK8*-deficient individuals with a history of HSV infection given the tendency of the virus to reactivate.[6] However, despite prophylaxis, our patient developed an HSV-positive posterior auricular erosion that continued to progress even after increase of the acyclovir dose. Acyclovir resistance testing of the HSV isolated from the wound was positive, confirming the clinical suspicion of the presence of acyclovir-resistant HSV infection.

*Acyclovir-Resistant HSV*—Acyclovir-resistant HSV in immunosuppressed individuals was first noted in 1982, and most cases since then have occurred in the setting of AIDS and in organ transplant recipients.[6] Few reports of acyclovir-resistant HSV in *DOCK8* deficiency exist, and to our knowledge, our patient is the youngest *DOCK8*-deficient individual to be documented with acyclovir-resistant HSV infection.[1,7-15] We identified relevant cases from the PubMed and EMBASE databases using the search terms DOCK8 *deficiency and acyclovir* and DOCK8 *deficiency and herpes*. The eTable lists other reported cases of acyclovir-resistant HSV in *DOCK8*-deficient patients. The majority of cases involved school-aged females. Lesion types varied and included herpes labialis, eczema herpeticum, and blepharoconjunctivitis. Escalation of therapy and resolution of the lesion was seen in some cases with administration of subcutaneous pegylated interferon alfa-2b.

*Treatment Alternatives*—Acyclovir competitively inhibits viral DNA polymerase by incorporating into elongating viral DNA strands and halting chain synthesis. Acyclovir requires triphosphorylation for activation, and viral thymidine kinase is responsible for the first phosphorylation event. Ninety-five percent of cases of acyclovir resistance are secondary to mutations in viral thymidine kinase. Foscarnet also inhibits viral DNA polymerase but does so directly without the need to be phosphorylated first.[6] For this reason, foscarnet often is the drug of choice in the treatment of acyclovir-resistant HSV, as evidenced in our patient. However, foscarnet-resistant HSV strains may develop from mutations in the DNA polymerase gene.

Cidofovir is a nucleotide analogue that requires phosphorylation by host, as opposed to viral, kinases for antiviral activity. Intravenous and topical formulations of cidofovir have proven effective in the treatment of acyclovir- and foscarnet-resistant HSV lesions.[6] Cidofovir also can be applied intralesionally, a method that provides targeted therapy and minimizes cidofovir-associated nephrotoxicity.[12] Reports of systemic interferon alfa therapy for acyclovir-resistant HSV also exist. A study found IFN-α production by peripheral blood mononuclear cells in *DOCK8*-deficient individuals to be significantly reduced relative to controls ($P<.05$).[7] There has been complete resolution of acyclovir-resistant HSV lesions

with subcutaneous pegylated interferon alfa-2b injections in several *DOCK8*-deficient patients.[7-9]

The need for escalating therapy in *DOCK8*-deficient individuals with acyclovir-resistant HSV infection underscores the essential role of *DOCK8* in dermatologic immunity. Our case demonstrates that a high degree of suspicion for cutaneous HSV infection should be adopted in *DOCK8*-deficient patients of any age, regardless of acyclovir prophylaxis. Viral culture in addition to bacterial cultures should be performed early in patients with cutaneous erosions, and the threshold for HSV resistance testing should be low to minimize morbidity associated with these infections. Early resistance testing in our case could have prevented prolongation of infection and likely eliminated the need for a biopsy.

## Conclusion

*DOCK8* deficiency presents a unique challenge to dermatologists and other health care providers given the susceptibility of affected individuals to developing a reservoir of severe and potentially resistant viral cutaneous infections. Prophylactic acyclovir may not be sufficient for HSV suppression, even in the youngest of patients, and suspicion for resistance should be high to avoid delays in adequate treatment.

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## APPENDIX

### Cases of Acyclovir-Resistant Cutaneous Lesions in *DOCK8* Deficiency

| Reference (year) | Age, y/ sex | *DOCK8* mutation | Lesion type | Clinical course of HSV | Effective therapeutic regimen | HSV test |
|---|---|---|---|---|---|---|
| Keles et al[7] (2014) | 6.5/F | Homozygous acceptor splice site mutation, intron 16, (c.1869-1 G>C) | Herpes labialis | Presented with recurrent herpes labialis despite acyclovir PPX, valacyclovir, and topical pegylated interferon alfa-2b; subcutaneous pegylated interferon alfa-2b was administered (40 μg/m$^2$, increased to maintenance dose of 80 μg/m$^2$/wk) and was efficacious | 60 μg/m$^2$/wk of subcutaneous pegylated interferon alfa-2b; complete resolution at 6 mo | Positive Tzanck smear |
| | 6/F | Homozygous deletion in exons 26–48. c.[3121 −?_7340 +?del] | Herpes labialis | Herpes labialis refractory to acyclovir, IV ABX, IVIG, and valacyclovir; regression with subcutaneous pegylated interferon alfa-2b was observed (40 μg/m$^2$ initial dose increased to 80 μg/m$^2$/wk) | Complete resolution after subcutaneous pegylated interferon alfa-2b therapy | Positive Tzanck smear |
| Papan et al[8] (2014) | 17/F | Homozygous c.3120+1G>T; skipped exon 25 | Left upper and lower eyelid blepharoconjunctivitis | HSV + upper and lower eyelid blepharoconjunctivitis despite IVIG, ABX, and antiviral PPX; nonresponsive to vancomycin, acyclovir, 2 courses of methylprednisolone, ofloxacin eye drops, or clobetasol propionate ointment; regression with subcutaneous pegylated interferon alfa-2b (0.6 μg/kg/wk followed by 1 μg/kg/wk). | Response of the lesion to subcutaneous pegylated interferon alfa-2b was observed within 24 h of initiation of treatment | Eyelid lesion biopsy, elevated HSV-1 DNA on quantitative PCR |
| Metin et al[9] (2016) | 7/F | Homozygous large deletion, exons 31 to at least 48 | Herpes labialis | Disseminated HSV and 7 mo of HSV + lip swelling on antifungal and ABX PPX; no response to 50 d of IV acyclovir or 14 d of foscarnet; regression observed with IVIG, an additional 14 d of foscarnet, and subcutaneous interferon alfa (3 d/wk) | Response to IVIG, 14 d of foscarnet, and interferon alfa that was administered 3 d/wk for an unspecified duration | Not specified |
| Zhang et al[10] (2009) | 18/F | Heterozygous c.538-15T>G intron 5 splice mutation | HSV keratitis, eczema herpeticum, and genital HSV | *DOCK8* deficiency posthumously identified in this patient with cutaneous T-cell lymphoma with superimposed eczema herpeticum in the setting of paranasal and vulvar squamous cell carcinoma and microcystic adnexal carcinoma; resistance was encountered with acyclovir or valacyclovir before death from pulmonary aspergillosis complications | Not achieved; resistance to acyclovir or valacyclovir was observed | HSV-1 positive on IHC of skin biopsy |

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eTable (continued)

| Reference (year) | Age, y/ sex | *DOCK8* mutation | Lesion type | Clinical course of HSV | Effective therapeutic regimen | HSV test |
|---|---|---|---|---|---|---|
| Shah et al[13] (2019) | 11/F | Compound heterozygous c.5815_5816insT, p. Y1939LfsX12 (exon 45), large deletion (exon 39-47) | Cutaneous HSV infection | Patient underwent a living donor liver and bone marrow transplant; posttransplant course was complicated by acyclovir-resistant cutaneous HSV in addition to veno-occlusive disease and graft failure | Patient did not survive hematopoietic stem cell transplant | Not provided |
| Freeman et al[14] (2019) | 11/F | Compound heterozygous mutations in *DOCK8* | Disseminated acyclovir-resistant HSV viremia (day +17 after transplant) | Patient with history of recurrent HSV infections who developed end-stage liver disease secondary to *Cryptosporidium* and required liver transplant then bone marrow transplant; posttransplant course was complicated by acyclovir-resistant HSV viremia in addition to primary graft failure, *Candida* sepsis, and sinusoidal obstruction syndrome complicated by multiorgan failure | Received foscarnet for acyclovir-resistant HSV; the patient did not survive the transplants due to multiorgan failure | Not provided |
| Casto et al[15] (2020) | 11–15 (study period)/M (both patient and younger sibling) | Not provided | Cutaneous HSV-1; multiple areas were involved including the scalp, ear, face, eye, lip, and scrotum | Adolescent male with *DOCK8* deficiency complicated by recurrent cutaneous HSV-1 infections; over a 4-y period, 12 HSV-1 samples were collected from the patient and 1 sample from his younger brother (also with *DOCK8* deficiency); the patient had HSV-1 infections involving multiple sites during the study period, most of which were acyclovir resistant; the patient's younger brother also with HSV gingivostomatitis and recurrent HSV keratitis; both patient's and sibling's viral samples were found to carry the same acyclovir-resistance gene mutation; the patient was later found to have a second mutation coding for cidofovir and possibly foscarnet resistance | Patient required additional therapies including high-dose IV acyclovir, IV foscarnet, IV and topical cidofovir and/or interferon alfa with variable clinical response | Viral culture |
| Current case (2021) | 2.7/F | Homozygous deletion c.(528+1_529-1) _ (1516+1_1517-1) del in *DOCK8* gene, exons 5 to 13 | Posterior auricular cutaneous lesion that was culture positive for HSV | Patient with a posterior auricular cutaneous lesion that was culture positive for HSV despite acyclovir prophylaxis and then treatment-dose acyclovir | Completed a 21-d course of combination foscarnet and acyclovir therapy with notable improvement and healing | Direct immunofluorescence and viral cultures |

Abbreviations: *DOCK8*, dedicator of cytokinesis 8; HSV, herpes simplex virus; F, female; PPX, prophylaxis; IV, intravenous; ABX, antibiotic; IVIG, intravenous immunoglobulin; PCR, polymerase chain reaction; IHC, immunohistochemistry; M, male.