CLINICAL VIGNETTE

Acyclovir-resistant Pseudotumoral Herpes Simplex Virus Infection

David X. Li, MD[1] and Whitney B. Nelson, MD[1]

[1]Department of Medicine, University of California Los Angeles

Introduction

Herpes simplex virus (HSV) infections are common in the United States, with reported seroprevalence of HSV-2 of about 16 percent in patients aged 14 to 49.[1] Although most commonly presenting as a genital infection, HSV-2 infections in immunosuppressed or immunocompromised patients may present with more variable, extensive and severe findings. These include disseminated cutaneous and visceral involvement with increased risk of disease recurrence.[2] Given the prevalence of HSV infections and the widespread use of acyclovir (ACV), concerns have been raised regarding increased ACV resistance.[3,4] Although infrequent in immunocompetent patients, ACV resistance has been increasingly reported in immunosuppressed patients. One publication reported greater than 14% of clinical HSV isolates from bone marrow transplant patients were ACV-resistant.[3] We present an immunosuppressed patient with acyclovir-resistant pseudotumoral HSV-2 infection.

A 56-year-old female with a history of deceased donor kidney transplantation on chronic immunosuppression presented to the hospital with a painful ulcerated, vegetative lesion in the gluteal cleft. The lesion progressed over the past three months (Figure 1) and trials of topical antifungals and doxycycline did not result in clinical improvement. Polymerase chain reaction assay was positive for HSV-2. Punch biopsy demonstrated positive HSV immunohistochemical stains (Figure 2) with negative bacterial, fungal and acid-fast stains. She was initially treated with oral valacyclovir with minimal clinical response. Due to concern for acyclovir resistance, she was started on intravenous foscarnet. Subsequent genotypic testing confirmed the presence of mutations in the thymidine kinase gene (UL23) conferring resistance to nucleoside analogues including acyclovir and valacyclovir. After several weeks of intravenous foscarnet and topical imiquimod therapies, her rash significant improved and she was discharged from the hospital. She was continued on indefinite acyclovir suppressive therapy after discharge and had not experienced relapse of her rash at 11-month follow-up.

Discussion

Vegetative, pseudotumoral cutaneous ulcers are an atypical presentation of HSV infection, but have been reported in immunosuppressed or immunocompromised patients.[5-7] In these patients, the diagnosis is usually confirmed via biopsy in order to exclude other malignant or infectious entities, including lymphoma and epidermoid carcinoma. Prior case reports suggested that such infections may be difficult to treat, and often responding poorly to routine systemic agents such as acyclovir and valacyclovir.[5-7] Parenteral and topical foscarnet, as well as topical imiquimod and thalidomide, have been utilized with varying degrees of success.[5-8]

In our patient, genotypic testing was performed to confirm the presence of mutations in the thymidine kinase gene (UL23). This confers resistance to nucleoside analogues such as acyclovir and valacyclovir. The prevalence of acyclovir-resistant HSV infections is elevated in immunocompromised patients with estimated prevalence up to 10%.[9] In particular, patients presenting with pseudotumoral ulcers have a poorer clinical response to acyclovir, raising suspicion of acyclovir-resistant HSV strains, although genotypic resistance testing is not widely utilized or available.[5] The mechanism of higher rates of acyclovir resistance in immunocompromised populations appears to be multifactorial, including frequent prior exposures to prolonged courses of acyclovir due to recurrent anogenital HSV infections and reduced drug delivery of acyclovir to pseudotumoral tissue.[7]

In this context, alternate therapies are available. Foscarnet is a pyrophosphate analogue frequently used for acyclovir-resistant HSV infections, although HSV strains that are cross-resistant to both acyclovir and foscarnet have been reported.[9] Imiquimod, a topical agent, is an immune response modulator that may induce the endogenous synthesis of various cytokines, interleukins and other factors, although the exact mechanism of its antiviral activity is unknown.[5] Topical thalidomide has also been used in previous case series with efficacy.[7] Relapse is common regardless of therapy and patients may require long-term antiviral suppressive therapy.

Our immunosuppressed patient with atypical HSV-2 anogenital infection manifested as vegetative, pseudotumoral lesions. In prior reports, patients with such lesions demonstrated a poor clinical response to acyclovir, suggestive of an intrinsic resistance. In our patient, genotypic testing confirmed a mutation in the thymidine kinase gene conferring resistance to nucleoside analogues including acyclovir. A subsequent favorable clinical response was achieved utilizing a combination of foscarnet and imiquimod. This patient with atypical presentation of HSV-2

anogenital infection highlights the importance of acyclovir resistance when treating complex HSV infections in immuno-compromised patients.

Figures

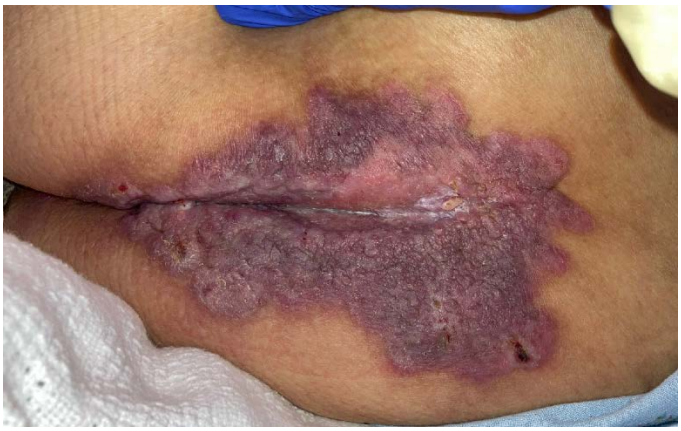

Figure 1.

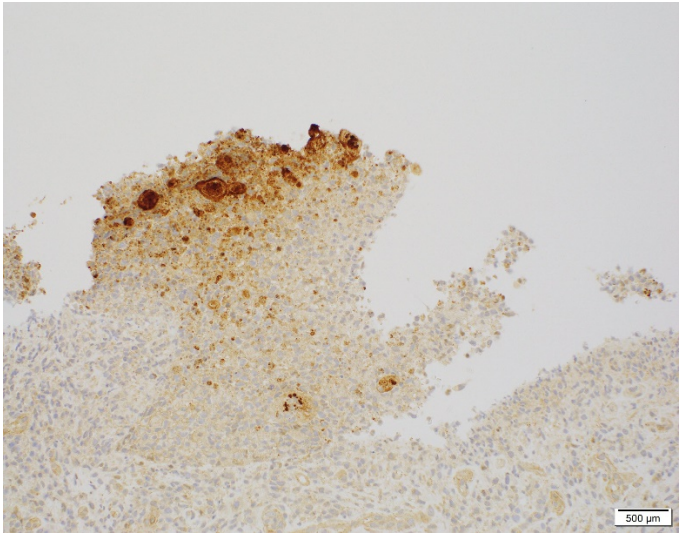

Figure 2.

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