Lip ulceration in an immunocompromised patient

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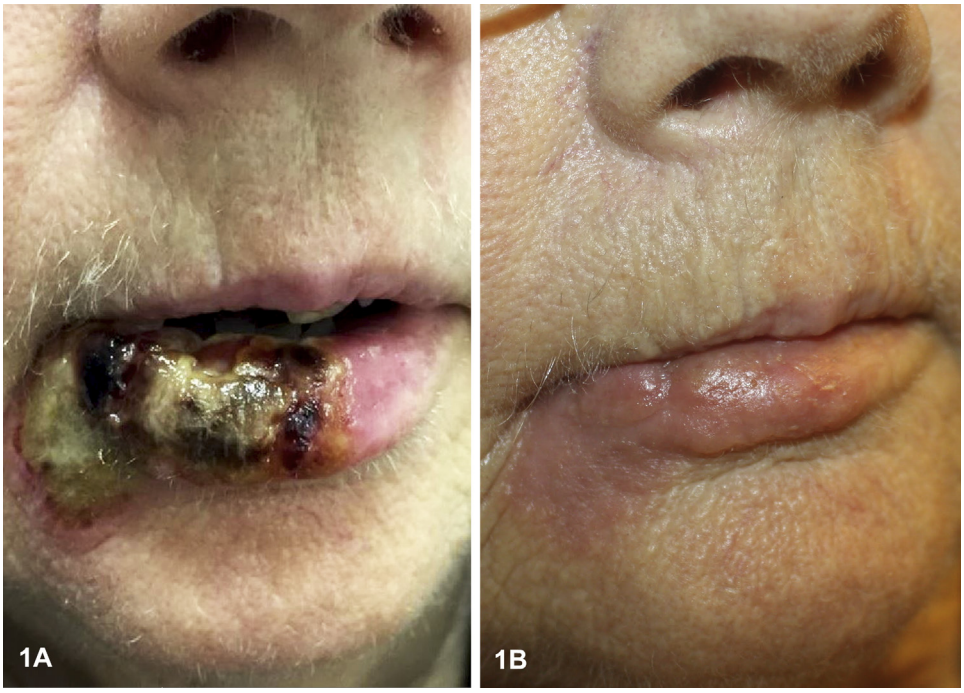

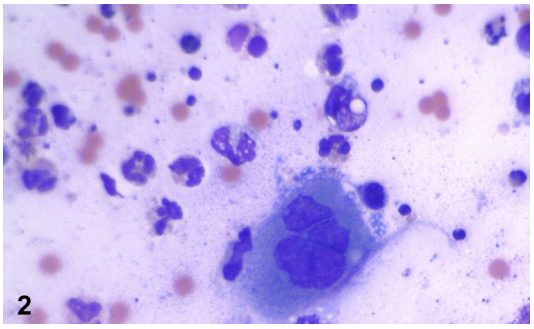

A 63-year-old woman presented with an enlarging, painful ulceration on the lip that developed over the previous 2 weeks. She had a history of myelodysplastic syndrome treated with azacitidine. History was remarkable for peripheral blood stem cell transplantation for myelodysplastic syndrome 1 year earlier. Physical examination found an ulceration of the right lower mucosal and vermilion lip extending onto the cutaneous lip, with overlying hemorrhagic crusts (Fig 1, *A*). She also had erosive papules on the hard palate. The remainder of her examination was unremarkable. Tzanck smear found multinucleated giant cells (Fig 2). The lesion continued to expand despite valacyclovir treatment for 7 days.

Question 1: What is the most likely diagnosis?

A. Labial necrotizing fasciitis

B. Herpes zoster

C. Paraneoplastic pemphigus

D. Treatment-resistant herpes labialis

E. Mucocutaneous histoplasmosis

Answers:

A. Labial necrotizing fasciitis — Incorrect. Labial necrotizing fasciitis is a rapidly progressive bacterial infection that results in fascial and subcutaneous necrosis of polymicrobial origin, with group A Streptococcus as a common cause. It is usually preceded by an invasive procedure, penetrating injury, or burns.[1]

B. Herpes zoster — Incorrect. Herpes zoster is caused by reactivation of varicella zoster virus and is common in individuals older than 60 years and immunosuppressed. The prodromal period of dysesthesia is followed by development of grouped vesicles on an erythematous base, classically in a dermatomal distribution.

C. Paraneoplastic pemphigus — Incorrect. Paraneoplastic pemphigus (PNP) is a mucocutaneous blistering disorder seen in association with lymphoproliferative disorders, presenting with severe stomatitis and polymorphous skin lesions.[2]

D. Treatment-resistant herpes labialis — Correct. Treatment-resistant herpes labialis was the most likely diagnosis given the patient's oral mucocutaneous presentation, positive Tzanck smear, immunocompromised state, and lack of clinical response to valacyclovir. The ulceration's extension onto the cutaneous lip with scalloped edges and hard palate involvement is typical for herpes simplex virus (HSV) infections. Approximately 4% to 7% of HSV isolates from immunosuppressed patients show acyclovir resistance compared with 0.3% in immunocompetent patients.[3] These lesions are larger, have deeper ulcerations, or have a verrucous appearance.

E. Mucocutaneous histoplasmosis — Incorrect. Mucocutaneous histoplasmosis usually occurs in the setting of disseminated histoplasmosis in immunocompromised individuals. Skin findings are nonspecific and may include mucocutaneous erosions, ulcers, or vegetative plaques. Other organs often involved include the lungs, bone marrow, liver, or spleen.

Question 2: What is the most appropriate test to determine further management?

A. Serology for HSV-1 IgM

B. Viral culture and sensitivity testing

C. Fungal culture

D. Aerobic and anaerobic bacterial cultures

E. Direct immunofluorescence (DIF) microscopy

Answers:

A. Serology for HSV-1 IgM — Incorrect. Serologic antibody titers to HSV-1 IgM may indicate a recent infection but are not as clinically useful as HSV-1 polymerase chain reaction or culture in establishing an active infection or treatment resistance.

B. Viral culture and sensitivity testing — Correct. The patient had multiple positive HSV-1 polymerase chain reaction results, which established the diagnosis of herpes labialis but failed to respond to therapeutic doses of valacyclovir for 1 week. To assess for antiviral resistance, HSV isolates must be obtained by tissue viral culture. Viral culture and sensitivity testing were done, which found acyclovir resistance and prompted reconsideration of treatment.

C. Fungal culture — Incorrect. Fungal cultures may be used to diagnose other infectious causes of oral mucosal lesions and should be considered in immunosuppressed patients before administration of antimicrobial agents. Our patient had a positive Tzanck smear and lesions clinically suggestive of herpes labialis; therefore, fungal cultures would not help guide further management.

D. Aerobic and anaerobic bacterial cultures — Incorrect. Given the patient's positive Tzanck smear and lesions clinically suggestive of herpes labialis, bacterial cultures would not help guide further management.

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E. DIF microscopy — Incorrect. DIF microscopy is useful in the evaluation of mucocutaneous immunobullous disorders, such as pemphigus vulgaris, bullous pemphigoid, cicatricial pemphigoid, and PNP. These conditions present with desquamative gingivitis, painful ulcerations of the gingiva, buccal and lingual mucosa, or severe stomatitis in the case of PNP.

Question 3: What is the most appropriate treatment?

A. Famciclovir

B. Intravenous (IV) acyclovir

C. IV foscarnet

D. IV cidofovir

E. IV vidarabine

Answers:

A. Famciclovir — Incorrect. Famciclovir is the inactive prodrug of valacyclovir. After oral absorption, famciclovir is deacetylated and oxidized to its active form of valacyclovir. Given that famciclovir, valacyclovir, and acyclovir are nucleoside analogues, none of these would be effective in treating acyclovir-resistant HSV.

B. IV acyclovir — Incorrect. Given the patient's immunosuppressed status and lack of response to 1 week of valacyclovir treatment, concern should be raised about acyclovir resistance. Therefore, IV acyclovir would not be an appropriate treatment.

C. IV foscarnet — Correct. Acyclovir resistance develops with mutations in the viral thymidine kinase gene. IV foscarnet is the most appropriate treatment for this patient because it does not require activation by viral protein kinases.[3,4] Foscarnet is a phosphonoformic acid, not a nucleoside analogue, and is a noncompetitive inhibitor of viral DNA polymerase. After administration of IV foscarnet, the patient showed rapid clinical improvement over the subsequent week (Fig 1, *B*).

D. IV cidofovir — Incorrect. Cidofovir is a nucleotide analogue, and in its active diphosphate form, it works by inhibiting DNA polymerase. It is approved for treatment of cytomegalovirus-induced retinitis in patients with HIV. Although it also has shown activity in resistant HSV infections, it has not been approved for this indication and has carcinogenic and teratogenic side effects.

E. IV vidarabine — Incorrect. Vidarabine is typically used for treatment of herpes zoster in patients with AIDS and has largely been replaced by more potent agents such as acyclovir and valacyclovir in the treatment of HSV.

Abbreviations used:

DIF: direct immunofluorescence
HSV: herpes simplex virus
PNP: paraneoplastic pemphigus

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