JAMA Dermatology Clinicopathological Challenge

Multiple, Tender Perianal Ulcers in a Young Woman

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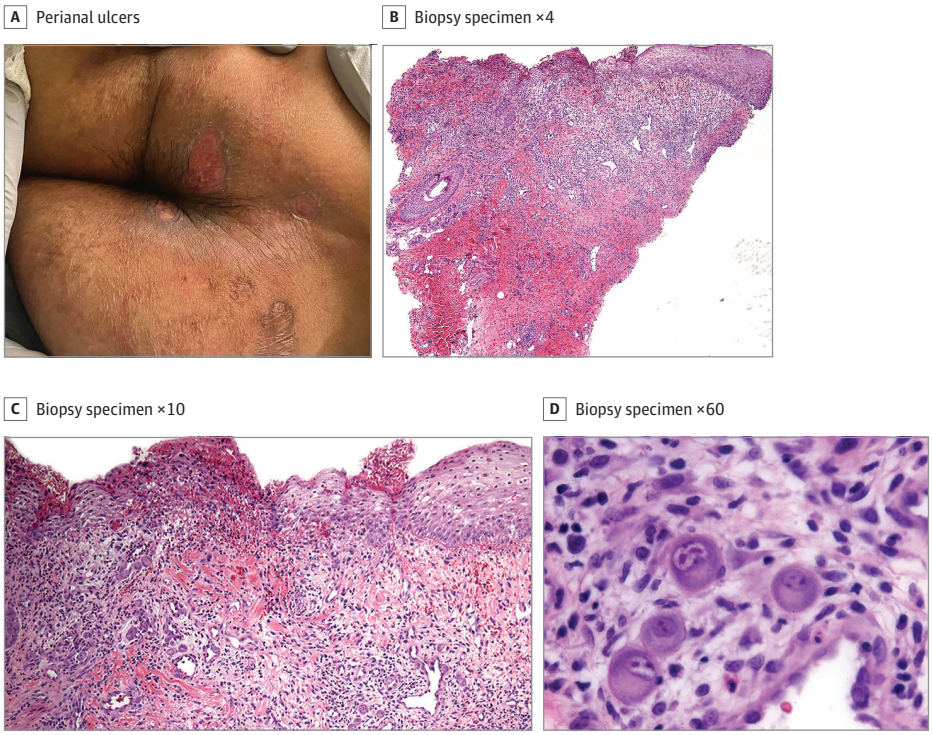

Figure. Clinical and histologic images of multiple perianal ulcers. A, Two round ulcers, each with well-demarcated borders, were present perianally. A smaller, third ulcer was also noted in the intergluteal cleft. B, Microscopic examination of the punch biopsy on low magnification reveals epidermal ulceration and mixed dermal inflammation (hemoxylin-eosin. C, On higher magnification, the epidermis lacks viral cytopathic changes but there are enlarged dermal fibroblasts and endothelial cells (hemoxylin-eosin). D, Higher magnification reveals large fibroblasts and endothelial cells with glassy cytoplasm and intranuclear inclusions (hemoxylin-eosin).

A woman in her late 30s was evaluated by the dermatology inpatient consult service for a 4-day history of perianal pain. Her medical history included systemic lupus erythematosus, antiphospholipid antibody syndrome, and external hemorrhoids. Six months before admission, she underwent a deceased donor kidney transplant. One month before presentation, she was hospitalized for acute cellular transplant rejection managed with systemic corticosteroids, belatacept, mycophenolate mofetil, and tacrolimus therapies. Her immunosuppressive regimen at the time of dermatologic evaluation consisted of prednisone, 5 mg daily, and mycophenolate mofetil, 500 mg twice daily.

On admission, she was afebrile and normotensive; laboratory results were notable for an elevated creatinine level of 1.43 mg/dL (reference range, 0.40-1.30 mg/dL) (to convert to micromoles per liter, multiply by 88.4) and thrombocytopenia (platelet count, 92 × 10^3/μL [reference range, 140-440 × 10^3/μL] [conversion to ×10^9 per liter is 1:1). She developed diarrhea 1 day after admission. Fecal leukocytes were absent. Stool antigen test results for cryptosporidium, giardia, and rotavirus were negative. Polymerase chain reaction (PCR) test results for campylobacter, norovirus, salmonella, shigella, Shiga toxin–producing *Escherichia coli* 1 and 2, *Vibrio cholerae*, and *Yersinia enterocolitica* in the stool were negative. Antigen and toxin test results for *Clostridium difficile* in the stool were positive.

Total body skin examination was notable for 1- and 3-cm tender, round perianal ulcers with a clean base. Another 4-mm round ulcer was present at the superior intergluteal cleft (**Figure**, A). There were no ocular or oral ulcers. A biopsy specimen of a perianal ulcer border was obtained for histopathologic analysis (Figure, B-D).

WHAT IS YOUR DIAGNOSIS?

A. Amebiasis cutis

B. Herpes simplex virus infection

C. Cytomegalovirus infection

D. Cutaneous Crohn disease

Quiz at jamacmelookup.com

Diagnosis

C. Cytomegalovirus infection

Microscopic Findings and Clinical Course

Examination of a punch biopsy specimen revealed epidermal ulceration with mixed dermal inflammation (Figure, B and C). There were large fibroblasts and endothelial cells with glassy cytoplasm and large intranuclear inclusions surrounded by a clear halo, giving the "owl's eye" appearance (Figure, D). Inclusions were positive for cytomegalovirus (CMV) immunohistochemical stain. Quantitative PCR results demonstrated a CMV load of 172 000 copies/mL (5.24 $\log_{10}$ IU/mL) in the blood. A PCR swab from the ulcer base was positive for CMV. Based on these findings, a diagnosis of cutaneous ulceration secondary to CMV infection was made.

A common infectious complication after renal transplant, CMV increases the risk for allograft rejection.[1] As with this patient, CMV-seronegative patients who receive renal transplants from seropositive donors are at highest risk of hospitalization from CMV disease.[1] In patients who receive a transplant, CMV infection may lead to significant morbidity and mortality, most notably owing to CMV colitis. This patient had diarrhea; however, the diagnosis of CMV colitis was obscured by concurrent *C difficile* colitis.

While CMV infection rarely presents in the skin, in immunosuppressed patients protean skin manifestations, including cutaneous vasculitis, morbilliform eruption, ulcers, petechiae, purpura, vesicles, and plaques, may be the presenting sign of disseminated disease.[2] The anogenital region is the most common site of cutaneous ulceration, likely because of fecal shedding of viral particles.[2] On histopathology, CMV initially shows an enlarged nucleus, then an enlarged cytoplasm, followed by intranuclear and intracytoplasmic inclusions. In resolving lesions, cells diminish in size and inclusions fade away.[3]

The diagnostic criterion standard for CMV is identification of inclusions or viral antigens on histopathologic examination. When examination of a biopsy specimen is inconclusive, tissue culture and viral load may aid in diagnosis.[4] In a recent series, CMV was detected via PCR swab in 4 of 4 patients who developed cutaneous lesions.[5] Herpes simplex virus (HSV) can cause perianal ulcers, and coinfection may be seen with CMV.[2] However, the biopsy specimen from this patient did not reveal ballooning degeneration or multinucleation of keratinocytes with the typical cytopathic intranuclear Cowdry type A (eosinophilic) or Cowdry type B ("steel gray") inclusions of HSV. Moreover, immunohistochemical stain and PCR test results were negative for HSV. Amebiasis cutis, an extension of colonic *Entamoeba histolytica* infection, may present with painful, serpiginous perianal ulcers with raised borders.[6] Histopathologic examination reveals amebic trophozoites with a small nucleus and erythrophagocytosis, findings that were absent in this case. Finally, cutaneous Crohn disease could be considered; however, the ulcers were not "knifelike" and noncaseating granulomas were not observed on histopathologic examination.

A graft transplant from a seronegative donor to a seronegative recipient is ideal to prevent CMV disease. When not feasible, a preventive approach involving prophylactic doses of oral ganciclovir, valganciclovir, letermovir, valacyclovir, or CMV immune globulin therapies can be used.[7] Alternatively, preemptive treatment with intravenous ganciclovir or oral valganciclovir therapy is administered after detection of CMV infection on weekly testing. Intravenous ganciclovir therapy is first-line treatment for CMV disease; however, CMV cutaneous ulcers have been successfully treated with oral valganciclovir therapy.[8] Cidofovir or foscarnet therapy can be useful in patients with ganciclovir-resistant CMV infection. The CMV vaccine candidates in development have recently shown promise in transplanted patients, decreasing the durations of viremia and ganciclovir treatment.[9]

This patient had a history of ganciclovir-resistant CMV after renal transplant; therefore, foscarnet, 40 mg/kg, IV therapy was initiated along with oral vancomycin for *C difficile* colitis. The patient's diarrhea resolved within 24 hours. Subsequent quantitative PCR after 4 days of foscarnet therapy demonstrated a CMV viral load of 13 300 copies/mL (4.13 $\log_{10}$ IU/mL) in the blood. She reported improvement in perianal pain and the ulcers decreased in size. She continued with foscarnet therapy until discharge 3 weeks later, and her medication was transitioned to oral letermovir therapy, 480 mg daily. She remained asymptomatic 3 months after discharge.

ARTICLE INFORMATION

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