Cytomegalovirus Ulcer

Successful Treatment With Valganciclovir

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 47-year-old man with multiple-drug–resistant AIDS was admitted to Yale–New Haven Hospital for evaluation of mental status and neuromotor changes and a 6-week history of a painful, nonhealing, enlarging ulcer on the lower extremity that the patient attributed to minor trauma. The patient had received outpatient wound care and several courses of oral antibiotics, but he was taking neither antiretroviral medications nor prophylaxis for opportunistic infections.

The patient’s most recent CD4 cell count was less than 20/µL with a viral load of 715000 copies/mL. He had a history of successfully treated cytomegalovirus (CMV) retinitis and Pneumocystis carinii pneumonia. On admission, he displayed clinical and radiologic features consistent with cerebral toxoplasmosis. He had no history of diabetes mellitus, peripheral vascular disease, or neuropathic disease.

During his hospital stay, the patient received intravenous and oral antibiotics (ampicillin sodium–sulbactam sodium, aztreonam, and clindamycin) for presumed bacterial infection of the ulcer, and a skin care nurse treated the wound daily with bacitracin zinc and dry dressings. After 4 days in the hospital with no improvement, dermatology consultation was requested.

On physical examination, there was a tender 3.0 × 2.0-cm ulcer on the right lateral part of the heel with surrounding erythema and induration (Figure 1). The border was well demarcated and not elevated, undermined, or scalloped. The base contained granulation tissue and necrotic debris. The patient had no oral, ocular, or anogenital ulcers. The remainder of the lower extremity examination was significant for 1+ pitting ankle edema, adequate capillary refill time, palpable dorsalis pedis pulses, and no evidence of compromised circulation or peripheral neuropathy. The patient also had molluscum contagiosum on his chest.

A punch biopsy specimen from the edge of the ulcer showed hyperplastic epidermis and numerous thick-walled blood vessels in the dermis, as well as a perivascular lymphocytic infiltrate. Among normal endothelial cells were many large, irregularly shaped endothelial cells with large basophilic intranuclear inclusions, in some cells surrounded by clear halos. Intracytoplasmic basophilic inclusions were also present (Figure 2).

Immunohistochemical studies showed CMV antigen reactivity within the endothelial cells. Direct immu-
no fluorescense examination of ulcer scrapings was negative for herpes simplex virus and varicella-zoster virus antigens. Polymerase chain reaction examination of the ulcer tissue for herpes simplex virus DNA also was negative. Special stains for fungal and bacterial organisms were negative. A biopsy culture from the wound edge failed to demonstrate bacterial, fungal, or mycobacterial growth. A superficial culture of the ulcer yielded mixed flora (Pseudomonas aeruginosa and Enterococcus).

These findings supported the diagnosis of cutaneous CMV infection. An ophthalmologic examination showed no evidence of concomitant retinal disease.

A bone scan demonstrated enhancement in the area of the right calcaneus. Complete blood cell count and electrolyte levels were within reference ranges. Three blood cultures were negative at 5 days. Cytomegalovirus antigenemia was present at greater than 2000 U. Cerebrospinal fluid cultures were negative for acid-fast bacilli, bacteria, and fungi.

Treatment for central nervous system toxoplasmosis with oral pyrimethamine and intravenous clindamycin resulted in improved neurologic status, but the ulcer worsened. Antiretroviral therapy was not initiated because the patient was infected with a multiple-drug-resistant strain of human immunodeficiency virus (HIV). The patient's discharge to home hospice care was planned with a regimen of intravenous clindamycin and oral leucovorin calcium treatment for the cerebral toxoplasmosis and intravenous aztreonam to treat the possible osteomyelitis. Oral dapsone and valganciclovir hydrochloride plus nystatin oral rinse were indicated for treatment of cutaneous CMV infections. Plasma levels of CMV antigenemia decreased to below the limits of detection and the dosage of valganciclovir was decreased to once daily for maintenance. Because of the concern of possible concomitant osteomyelitis, the patient also received a 6-week course of aztreonam. There was marked improvement of the swelling of the extremity and subsequent healing of the ulcer. Six weeks after the initiation of valganciclovir therapy, the ulcer was mostly resolved, and the patient was able to walk again (Figure 3).

Treatment of the cerebral toxoplasmosis resulted in improved cognitive function. Because the patient had a highly resistant HIV genotype and had not tolerated antiretroviral therapy well in the past, he opted to forgo HIV treatment. The patient died in hospice 10 weeks after our initial consultation.

Cytomegalovirus is a common opportunistic agent in immunocompromised hosts with AIDS and solid organ and hematologic transplantation and in the setting of iatrogenic suppression in the treatment of cutaneous lupus erythematosus.

Cytomegalovirus is a member of the herpes family of DNA viruses. Herpesviruses are capable of latency after infection with an acute disease followed by an asymptomatic, quiescent state. Eighty percent of adults have antibodies against CMV. Infection with CMV in most immunocompetent hosts is asymptomatic but can present as a mononucleosislike syndrome. A compromise of the host's immune system can lead to reactivation of latent viruses and viral proliferation.

Cytomegalovirus is the virus most frequently isolated from people with AIDS. Ninety percent of patients with AIDS are infected with CMV, and disseminated CMV is found during autopsy in 93% of patients with AIDS. Reactivation of latent CMV infection causes significant morbidity and mortality in immunocompromised patients. In an AIDS-infected host, CMV causes a variety of conditions, including pneumonia, encephalitis, gastrointestinal ulcers, hepatitis, retinitis, and disseminated disease. Cytomegalovirus retinitis is the most common manifestation of CMV in an HIV-positive host.

There are infrequent reports in the literature of cutaneous CMV infections. This may be because cutaneous CMV infections are uncommon or because making a diagnosis of CMV is difficult as a result of its multiple clinical presentations and subtle histopathological findings. Skin lesions of CMV characteristically affect immunocompromised hosts, presenting as maculopapular rashes, urticarial eruptions, scarlatiniform eruptions, cutaneous ulcerations, oral ulcerations, crusted papules, nodules, morbilliform eruptions, verrucous lesions, perifollicular papulopustules, urticaria, or vesiculobullous lesions.
Cutaneous CMV lesions often herald disseminated infection and are associated with a mortality of 85% within 6 months.10

There is some controversy surrounding the pathogenic role of CMV in cutaneous lesions. It has been argued that CMV found in ulcerative lesions could be the result of a hematogenously disseminated infection, reactivation within the endothelial cells, or autoinoculation through urine, feces, or saliva shedding because the majority of CMV ulcers are found in the genital and perianal regions.17 Other infectious agents are frequently cultured from lesions attributed to CMV. Cytomegalovirus has been found unexpectedly in healthy skin. Spontaneous healing of CMV–positive lesions may occur. We believe that CMV did play a pathogenic role in this patient's ulcer: no other microorganisms were detected; there was minimal risk of autoinoculation at this site, and treatment with a specific antiviral agent yielded rapid and dramatic clinical improvement, while there was no improvement in his HIV infection.

Ganciclovir and foscarnet have been efficacious in the treatment of cutaneous CMV.3,18 Valganciclovir was approved by the Food and Drug Administration in 2001 for the treatment of CMV retinitis in immunocompromised hosts. Sixty percent of oral valganciclovir is absorbed vs 6% to 9% of oral ganciclovir. Plasma levels of valganciclovir are comparable with those of intravenous ganciclovir,19 as are efficacy and adverse effects.20

This is, to our knowledge, the first report of successful treatment of cutaneous CMV infection with an oral medication. Moreover, this therapy was effective despite profound immunocompromise. This therapeutic option is extremely valuable because valganciclovir does not require an indwelling catheter and removes all of the complications associated with these devices, a risk reduction especially important in an immunocompromised patient population.

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REFERENCES


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