Recurrent Disseminated Herpes Zoster and Cytomegalic Perianal Ulcer: A Case Report and Review of the Literature

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GOAL

To discuss the concomitant presentation of disseminated herpes zoster (HZ) and cytomegalovirus (CMV)-related perianal ulcer

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe HZ infection and its risk factors.
2. Identify the relationship of HZ and CMV, including their histopathologic findings.
3. Summarize methods to diagnose CMV.

CME Test on page 66.

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We describe a patient with lymphocytic leukemia who developed multiple, disseminated, vesiculopustular eruptions in combination with perianal ulcer. Four years earlier, she had a herpes zoster (HZ) infection involving the ophthalmic division of her left trigeminal nerve with subsequent postherpetic neuralgia that was treated with steroids. After the studies, we concluded that the patient had a recurrent disseminated HZ infection and perianal ulcer caused by cytomegalovirus (CMV).

Herpes zoster (HZ) infection is common, with an incidence of 10% to 20% in the general population. It usually affects older adults and is limited to 1 or 2 dermatomes.[1] We describe a case of recurrent disseminated varicella-zoster virus (VZV) infection in a patient with lymphocytic leukemia. In this patient, there were many differential diagnoses to consider, and the condition was complicated by the development of a perianal ulcer. Histologic analysis of the perianal ulcer showed changes resulting from cytomegalovirus (CMV) infection, which was confirmed with polymerase chain reaction (PCR) analysis. Treatment with ganciclovir resulted in clinical resolution of both infections. A review of the literature will examine the relationship between HZ infection and immunosuppressive conditions, the incidence of infectious ulcers in immunocompromised patients, and the probability of both diseases coexisting.

Case Report

An 87-year-old woman with chronic lymphocytic leukemia, which had not required treatment, was referred to our department after experiencing severe perianal pain for 2 weeks. Examination revealed an ulcer in the anterior perianal zone that was painful, tender, and progressed rapidly over the previous 7 days. It had a marked regular border and a purulent exudate above it (Figure 1). The patient also presented with lesions on the face in a VI–VII dermatomal distribution. These vesiculopustular eruptions disseminated over the face, trunk (Figure 2), and arms.

The patient's medical history was significant for chronic lymphocytic leukemia since 1986, which had required no treatment; HZ infection involving the ophthalmic division of her left trigeminal nerve in 1992 with subsequent postherpetic neuralgia, which was treated with a long course of steroids; marked visual field defects attributed to either glaucoma or ischemic optic neuropathy; and recurrent upper respiratory bacterial infection.

Because of the patient's history of leukemia and the clinical presentation, we considered the possibility of herpes simplex virus (HSV), thereby connecting the 2 clinical presentations of perianal ulcer and multiple vesiculopustular eruptions. Other considerations for the generalized eruption included HZ infection, acute febrile neutrophilic dermatosis, CMV infection, leukemia cutis by itself, or leukemia cutis at the site of herpes infection. General examination was normal. The patient experienced chills, but had no documented fever. A complete blood count showed a white cell count of 60,000/mm^3, with 92% lymphocytes, 7% neutrophils, and an erythrocyte sedimentation rate of 100 mm (0–30 mm/h). Other parameters were normal. Biopsies were taken from the vesiculopustular eruption and perianal ulcer, and a Tzanck test and cultures were performed. Tissue from the perianal ulcer was examined for routine microscopy, herpes, CMV, fungus, and acid-fast bacilli. Routine sections from the vesiculopustular eruption on the left arm revealed an intraepidermal vesicle containing fibrin, neutrophils, and necrotic keratinocytes (Figure 3). Keratinocytes at the vesicle edge were occasionally multinucleated and contained eosinophilic intranuclear virus inclusion with a condensed chromatin rim.

Epidermal spongiosis was present adjacent to the vesicle. Viral inclusions were absent in the blood vessels and dermis. In situ hybridization for CMV and HSV types 1 and 2 were negative. PCR was positive for VZV. The histopathologic findings of the perianal biopsy showed complete epidermal necrosis extending into the reticular dermis and involving dermal appendages. A diffuse neutrophilic infiltrate extended into subcutaneous adipose tissue, and several thrombosed superficial blood vessels were present. Leukocytoclastic vasculitis was evident in the deep reticular dermis and subcutaneous tissue, with infiltration of vascular walls by neutrophils and fibrin deposits (Figure 4). Numerous endothelial cells and dermal fibroblasts in this region were cytomegalic and

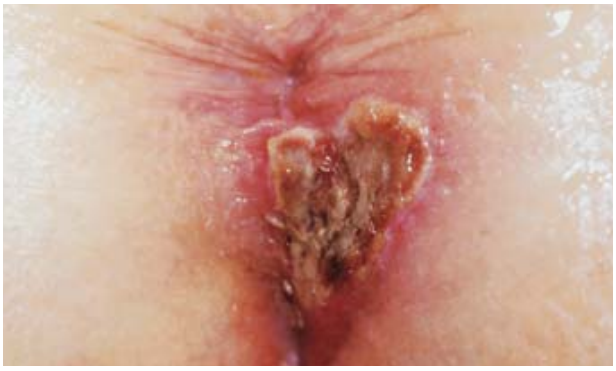

FIGURE 1. Perianal ulceration with regular border and purulent exudate.

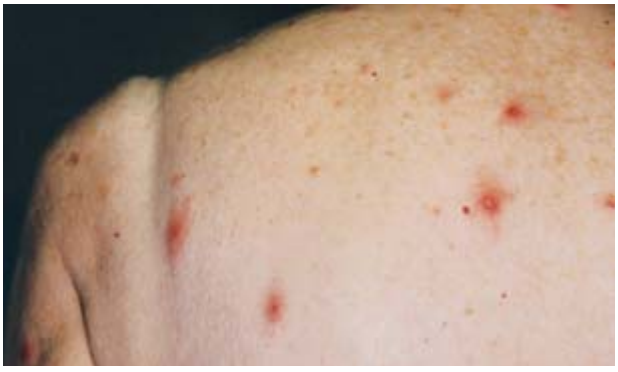

FIGURE 2. Vesiculopustular eruption on the back.

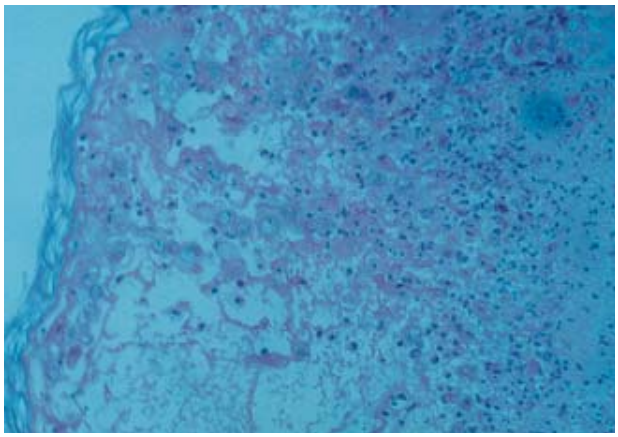

FIGURE 3. Routine sections from the vesiculopustular eruption on the left arm revealed an intraepidermal vesicle with necrotic keratinocytes and acute inflammation.

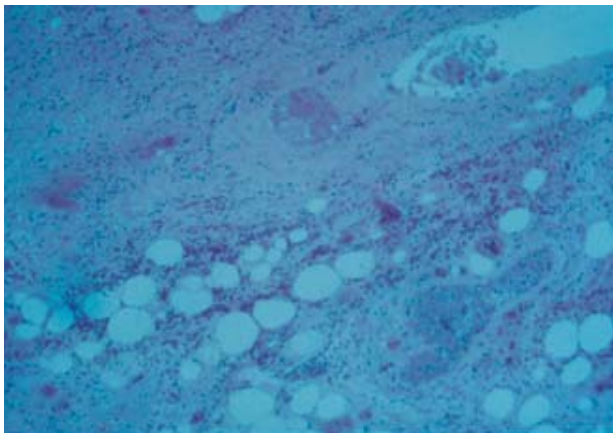

FIGURE 4. Histology of the perianal ulcer showing leukocytoclastic vasculitis with fibrin deposits.

contained eosinophilic intranuclear viral inclusions (Figure 5). The CMV infection was confirmed by PCR. A Tzanck test and cultures were negative. Bacteria cultures from the perianal region showed *Staphylococcus aureus*. The patient's urine was negative for CMV, and serology showed positive CMV IgG and negative CMV IgM.

The patient was started on a 4-week course of therapy with intravenous ganciclovir, 250 mg every 12 hours for 2 weeks, followed by 300 mg every 24 hours for 2 weeks. At the end of the first week, she showed clinical improvement and had granulation tissue at the site of the perianal ulcer. Complete resolution occurred after 4 weeks, with no evidence of recurrence after a year.

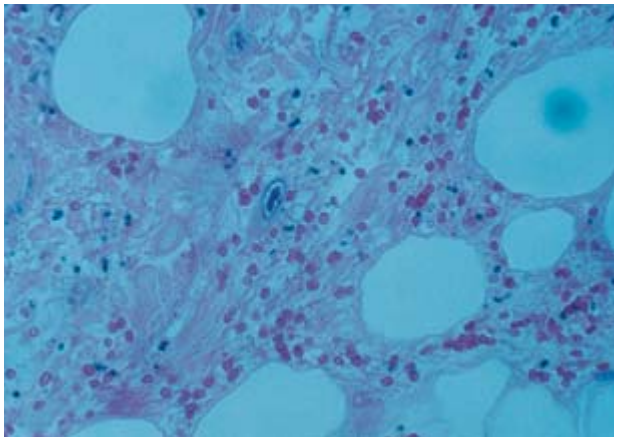

FIGURE 5. Histology of perianal ulcer showing enlarged fibroblasts with intranuclear inclusion bodies.

Comment

HZ often occurs concomitantly with internal malignancies, most commonly the hematologic ones such as Hodgkin's disease, chronic lymphocytic leukemia, and other lymphomas.[2,3] HZ rarely precedes the malignancy.[4] Furthermore, it may present in an atypical clinical aspect in immunocompromised patients[5] and may appear as a disseminated infection or a recurrent one, as in our patient. Recurrence is reported in immunosuppressive conditions, such as hematologic diseases, HIV, and systemic lupus erythematosus.[6] Other risk factors for developing HZ infection are intravenous drug use, radiation therapy, trauma, and organ transplantation.[1]

In our review of the literature, we found cutaneous localization of leukemia at the site of varicella and herpes eruptions; the mechanism involved is not clearly understood.[7,8] Our patient had a concomitant perianal ulcer caused by CMV, a member of the herpes virus family. A large percentage of the general population is infected with CMV at some point, but this infection is usually subclinical. Nonspecific eruptions similar to those seen in Epstein Barr infection have been reported in young, immunocompetent people receiving antibiotics.[9] Reactivation of latent CMV can occur as a result of host-immune suppression and is described in organ transplant recipients, patients with AIDS, and those receiving immunosuppressive therapy.[10,11]

CMV is the predominant cause of visceral diseases such as pneumonia, retinitis, gastrointestinal ulcers, and other widely disseminated diseases. In these cases, skin involvement is rare. CMV may present as purpura, nodules, ulcerations, morbiliform or vesicobullous eruption.[12]

Ulcerations appear to have a predilection for the perineal region. Anorectal diseases are common in HIV-infected individuals, with many studies showing the anal condyloma to be the first infection in these

patients; HSV and CMV are second. Fifty to 83% of perianal ulcers are associated with HSV and CMV. The remainder of cases are idiopathic. It is possible for both HSV and CMV to be present in the same ulcer.[13,14] Light microscopy cannot establish a difference between VZV and HSV, although HSV and VZV can be easily differentiated from CMV.

On routine histopathologic examination, HSV and VZV produce identical intranuclear inclusion bodies.[15,16] However, CMV produces intracytoplasmic and intranuclear inclusions, which are more basophilic. The infected cells are enlarged and show a characteristically preserved nucleolus. CMV inclusions are classically seen in vascular endothelial cells, and vasculitis is also common.[17] Distinguishing between HSV and VZV requires further study utilizing immunohistochemistry, in situ hybridization, and PCR techniques.

The methods used to confirm the presence of CMV are viral cultures and a more sensitive tissue culture method called *shell vial assay,* which uses viral cultures and monoclonal antibodies against CMV antigens. Immunohistochemistry, a rapid and sensitive method; in situ hybridization; and PCR amplification of DNA, a highly sensitive and specific technique, are also available.[18]

Conclusion

Immunosuppressive conditions teach us that skin diseases can show atypical features. A multidisciplinary medical team is necessary to follow these patients and to prevent infectious diseases that cause a high incidence of morbidity and mortality. Early recognition and prompt treatment can save lives.

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