A Vesiculobullous Eruption Following Solid Organ Transplantation

Nadine George, DO,* Ann Reed, DO,** Frank Don, DO, FAOCD,*** Stanley Skopit, DO, MSE, FAOCD****

*3rd-year resident, Larkin Community Hospital/NSU-COM Dermatology Residency Program, South Miami, FL
**2nd-year resident, Larkin Community Hospital/NSU-COM Dermatology Residency Program, South Miami, FL
***Dermatologist, Florida Academic Dermatology Center, Coral Gables, FL
****Program Director, Larkin Community Hospital/NSU-COM Dermatology Residency Program, South Miami, FL

Abstract

Viruses are the most frequent cause of cutaneous infections in organ transplant recipients, and herpes simplex virus (HSV) is one of the most commonly implicated, especially in the first few months post-transplant. Given a nonspecific presentation in these patients, it is essential to confirm the diagnosis with further laboratory testing. Notably, cutaneous cytomegalovirus (CMV) infection may mimic HSV or may co-infect affected skin lesions. Cutaneous CMV is present in approximately 20% of systemic CMV infections, and if left untreated it has a high mortality rate due to increased risk of graft rejection and other secondary infections. We describe a case of a chronic vesiculobullous eruption in a 75-year-old liver transplant recipient whose diagnosis of HSV was determined during her initial office visit using the reliable Tzanck smear, therefore allowing for rapid initiation of antiviral treatment. Confirmatory viral cultures were also performed to verify the causative agent and to rule out the possibility of co-infections.

Introduction

Herpes simplex virus infection is usually a relatively straightforward diagnosis to make. However, organ transplant recipients or immunosuppressed patients may present with clinically atypical lesions, necessitating the need for accurate diagnosis and prompt treatment to prevent dissemination to visceral organs. Moreover, other viral infections, such as cytomegalovirus, must be excluded from the diagnosis as they often significantly increase morbidity and mortality in organ transplant recipients.

Case Report

A 75-year-old Hispanic female presented to our outpatient dermatology clinic complaining of a three-week history of a burning, painful eruption on her buttocks. She admitted that this had been occurring intermittently for years. Her past medical history was significant for hypertension and a liver transplant in 1998 secondary to autoimmune hepatitis. At the time of her presentation, the patient was on several immunosuppressive agents including mycophenolate mofetil, cyclosporine, and prednisone. Other medications included valsartan, bisoprolol, and folic acid. A review of systems was negative for any fever, malaise, vision change, shortness of breath, chest pain, and gastrointestinal disturbances.

On physical examination, there were multiple shallow ulcers and grouped vesicles on the buttock region (Figures 1 and 2). The patient had no mucous membrane or other cutaneous involvement. There was no inguinal lymphadenopathy. Our initial differential diagnosis included a viral skin infection such as HSV types 1 and 2, varicella-zoster virus (VZV), and cytomegalovirus (CMV). Other diagnostic considerations were dermatitis herpetiformis and bullous allergic contact dermatitis.

A Tzanck smear was performed and showed characteristic multinucleated giant cells (Figure 3). Therefore, a presumed diagnosis of herpes simplex infection was made, later confirmed by viral culture. A skin biopsy was not performed. The patient was treated with valacyclovir 1 gram twice a day for one week and silver sulfadiazine cream twice daily to eroded areas. At one-month follow-up, the patient had dramatic improvement in the lesions, and a prophylactic twice daily dose of valacyclovir 500 mg was initiated.

Discussion

Organ transplant recipients are prone to developing a variety of skin diseases secondary to the potent immunosuppressive agents used to guarantee long-term graft survival and prevent organ rejection.1 Cutaneous infections occur in up to 80% of organ transplant recipients, and viral infections are the most common of these.2 The herpes simplex virus (HSV) types 1 and 2 are members of the Herpesvirus family and are distinguished by their ability to remain latent within a host and spontaneously reactivate with trauma, UV exposure, fever, or immunosuppression. The latent virus travels from the nerve root to innervated skin regions. Transplant patients can be infected with HSV-1, HSV-2, or both types, with prevalence similar to the distribution by age in the general population.1 Typically, reactivated, localized HSV infections occur within the first few weeks of transplantation, and mucocutaneous lesions of the oropharynx or genital regions are the most common presentation in organ transplant recipients.1,4 Compared to the general population, manifestation of HSV reactivation in immunosuppressed patients results in chronic, larger, slower-healing ulcers with greater potential for dissemination to visceral organs.1,2 Systemic involvement may manifest as fever, leukopenia, esophagitis, hepatitis,
pneumonitis or myocarditis.\textsuperscript{2,3} Widespread cutaneous dissemination is rare, but when it occurs it is associated with high mortality rates.\textsuperscript{1}

Diagnosis of HSV can be approached in several ways. A positive culture of the vesicles or ulcers indicates active infection. Furthermore, HSV-1 and HSV-2 can be distinguished by monoclonal antibody staining. Skin biopsy for histopathology may be performed, and common findings include keratinocytes with uniform steel-gray nuclei and margination of chromatin, ballooning degeneration with secondary acantholysis, multinucleated giant cells and an underlying mixed inflammatory cell infiltrate. The Tzanck smear, although underutilized in the clinical setting, is a rapid, simple, noninvasive method for the diagnosis of infections, autoimmune disorders, and less commonly for the diagnosis of various neoplasms and granulomatous diseases.\textsuperscript{1} A study by Eryilmaz et al. found that the Tzanck smear was a reliable diagnostic test for erosive vesiculobulose disease.\textsuperscript{A} A positive Tzanck smear shows multinucleated keratinocytes and acantholysis. However, the Tzanck smear and tissue histopathology without immunohistochemistry stains do not distinguish between HSV-1, HSV-2 or VZV.

According to Wilck et al., in the absence of antiviral prophylaxis, HSV-seropositive organ transplant recipients are at risk for clinical reactivation, even if they had not had prior clinical HSV disease. The incidence of clinically apparent HSV disease in seropositive patients not receiving prophylaxis, Wilck et al. state, ranges from 35% to 68%.\textsuperscript{3} HSV prophylaxis using acyclovir, valacyclovir, or foscarnet is recommended for all HSV-1 and HSV-2 seropositive organ recipients for the first month after transplantation.\textsuperscript{1} Following the first post-transplant period, treatment should be initiated promptly based on clinical diagnosis for improved clinical outcome. Of interest, a recent study by Mues et al. investigated dynasore, a small-molecule inhibitor of dynamin. Dynasore was found to have multiple deleterious effects on HSV-1 and HSV-2 infection by impeding crucial steps in the viral life cycle. This is a new and promising approach to HSV treatment and prevention that is on the horizon.\textsuperscript{9}

Acyclovir-resistant HSV should be suspected if there are very frequent recurrences while on suppressant therapy, which will require treatment with either ganciclovir or valganciclovir.\textsuperscript{1} Furthermore, if an ulcer fails to respond to therapy, HSV infection with concomitant CMV infection must also be considered. Schoenfeld et al. describe two cases of HIV patients who presented with genital ulcers in which both HSV and CMV were proven to be the causative agents. They stress that it is crucial to at least consider CMV as a causative agent when an immunocompromised patient presents with genital lesions, especially in those not responding to the usual treatment, as CMV may be a marker of impending systemic infection.\textsuperscript{10} Cutaneous infection by CMV is diagnosed by immunohistochemical staining or viral culture, while systemic disease or acute viremia is diagnosed by a CMV antigenemia assay or polymerase chain reaction.\textsuperscript{11}

In organ transplant patients, CMV is a major cause of disease and mortality, with a symptomatic infection occurring in 20% to 60% of all transplant recipients.\textsuperscript{4} Infection can occur as a result of reactivation of an existing latent infection in the recipient, from a donor strain of CMV, or as a primary infection in a previously CMV-naive individual. Cutaneous CMV is present in 10% to 20% of patients with systemic infection, and its presentation is often nonspecific and varied. Clinical manifestations includes ulcers, morbilliform rashes, petechiae, purpuric eruptions, necrotic papules, and vesiculobulose eruptions.\textsuperscript{7} Systemic manifestations include fever, leukopenia, malaise and arthralgias.\textsuperscript{11} Chronic CMV infections are associated with risk of acute and chronic graft rejection and an increased risk of subsequent bacterial and fungal infections. Wilck et al. state that when ganciclovir, acyclovir, valacyclovir and ganciclovir are given in standard doses for CMV prevention, they will also prevent most HSV reactivation. Ganciclovir, valganciclovir, foscarnet, and cidofovir have all been approved for the treatment of CMV, with foscarnet and cidofovir reserved for strains exhibiting ganciclovir resistance.\textsuperscript{10,11}

**Conclusion**

We describe a severe but typical presentation of HSV-1 occurring on the bilateral buttocks in an immuno suppressed organ transplant patient. The diagnosis was quickly confirmed at the patient’s initial presentation using the underutilized but reliable Tzanck smear, enabling prompt treatment with acyclovir 1 gm twice daily. Practitioners should be mindful to send viral cultures in immunosuppressed patients presenting with vesiculobulose lesions to rule out primary or concomitant CMV infection.

**References**


**Correspondence:** Nadine George, DO; nadine.george07@gmail.com