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Atypical Presentation of Exophytic Herpes Simplex Virus Type 2 With Concurrent Cytomegalovirus Infection: A Significant Pitfall in Diagnosis

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Abstract

We report 3 unusual cases of atypical exophytic cutaneous herpes simplex virus (HSV) type 2 with concurrent cytomegalovirus (CMV) infection in immunosuppressed patients and raise awareness to the significant clinical and pathologic challenges in establishing the correct diagnosis. In all the 3 cases, the lesions presented as fungating plaques and nodules with areas of superficial erosion. Initial clinical differential included genital warts, syphilis, versus cutaneous malignancy. All the 3 patients were referred to the dermatology clinic where a combination of cutaneous biopsies, viral cultures of the lesions, polymerase chain reaction, CMV antigenemia, and immunoperoxidase stains for CMV and HSV confirmed the diagnosis of HSV type 2 with concurrent CMV infection. All the 3 patients were treated with oral valganciclovir with significant improvement noted at the follow-up visit. In addition, we review the previously reported HSV/CMV cutaneous coinfection cases.

INTRODUCTION

The herpes simplex virus (HSV) has a wide range of clinical presentations. The most common symptomatic presentation in immunocompetent individuals includes painful vesicles on an erythematous base, which can progress to pustules and/or ulcerations.¹ In the case of immunosuppressed patients such as transplant recipients, patients with lymphoma and acquired immunodeficiency syndrome (AIDS), the HSV infection often presents in an atypical fashion.¹ These may include verrucous, exophytic, pustular, or ulcerative lesions. In addition to ulceration, chronic HSV infections can also present as eroded tumors.² There are reports in the literature of genital herpes with an atypical clinical presentation that mimics a neoplastic rather than infectious process.³ The lesions can disseminate and occur at multiple sites, including atypical locations such as buttocks, abdomen, and lower back. The severity of the clinical presentation and the duration usually correlates with the degree of immunosuppression.³

In immunosuppressed individuals, numerous infectious agents including cytomegalovirus (CMV) can cause severe clinical manifestations. The incidence of CMV infection is rising due to the higher number of human immunodeficiency virus (HIV) seropositive individuals and increased use of solid organ transplants and immunosuppressive agents.⁴ These individuals are at risk for persistent CMV replication and viremia with systemic dissemination to distant organs including the skin. Cutaneous manifestations are often atypical and range from vesicles to nodules to verrucous plaques, which can become superinfected with HSV or bacteria.⁴ Although rare, there are growing numbers of reports in the literature of concurrent CMV and HSV infections in skin biopsy specimens of immunocompromised individuals.^{5–7}

In this article, we report 3 cases of concurrent cutaneous HSV type 2 and CMV infection that presented as exophytic lesions and underline the challenges in the morphologic and clinical diagnosis of this entity. In addition, we review the existing literature on these rare entities and compare our cases with prior reports.

MATERIALS AND METHODS

The biopsy specimens were fixed in 10% buffered formalin and embedded in paraffin. For routine histology, 5-mm-thick sections were stained with hematoxylin and eosin.

Immunohistochemical (IHC) examination for HSV and CMV was performed according to the manufacturer's instructions. Briefly, 5-mm sections were obtained from formalin-fixed, paraffin-embedded block preparations. After antigen retrieval with 0.02 M citrate buffer (pH 6.0) CC1 at 120°C for 30 minutes for HSV and 97°C for 20 minutes for CMV, immunostaining was performed using prediluted HSV I and II antibodies (Cell Marque) and CMV DDG9 and CCH2 clone (DAKO) at 1:200 dilution. The immunostaining for the HSV was performed on a semiautomated immunostainer from Ventana Inc using a streptavidin–biotin–peroxidase approach and for CMV on a Labvision 720 semiautomated immunostainer from Thermo Scientific using UltraVision LP polymer system. The tissues were counterstained with hematoxylin. Appropriate positive and negative control slides were prepared.

RESULTS

Clinical Presentation

Clinical and laboratory findings for the 3 patients are summarized in Table 1 and illustrated in Figure 1. Patient #1 was a 50-year-old African American woman with a history of unrelated donor kidney transplant who presented to the nephrology clinic with a 1-year history of cutaneous lesions that gradually developed into fungating exophytic skin plaques on her upper thighs, inguinal folds, mons pubis, and lower abdomen (Fig. 1A). Clinical differential diagnosis included *Candida* infection and hematologic and cutaneous malignancies. The patient was referred to inpatient dermatology consultation service where a biopsy was performed. After HSV/CMV coinfection diagnosis, the patient was treated with intravenous ganciclovir and mupirocin, and the immunosuppressive therapy was reduced. The lesions showed clinical improvement with resolution of erythema and suppuration at 6 days after treatment. Repeat CMV testing by polymerase chain reaction (PCR) after 3 weeks of treatment showed <200 copies per milliliter (negative range) and negative CMV antigenemia.

Patient #2 was a 62-year-old white male with a history of living related kidney transplant who presented with a long standing history of an exophytic penile lesion diagnosed as “genital warts.” The patient underwent multiple excisions followed by recurrences. Eventually, the patient was referred to the dermatology clinic where an indurated oblong verrucous nodule was noted on the penile shaft (Fig. 1B). Viral cultures were found to be positive for HSV type 2 and negative for CMV, and the patient was started on famciclovir with only minimal improvement. A biopsy was performed for a clinical suspicion of HSV/CMV coinfection. After histologic confirmation of the diagnosis, the patient's therapy was changed to valganciclovir 450 mg twice a day, which resulted in almost complete resolution after 2 months of therapy.

Patient #3 was a 35-year-old HIV positive African American male with a low CD4 count who presented a 2-month history of a nonhealing superior gluteal cleft ulcer with raised border (Fig. 1C). Clinical differential diagnosis included verrucous HSV, CMV, squamous

cell carcinoma, and lichen simplex chronicus. A biopsy was performed, and after histologic confirmation of HSV/CMV coinfection, the patient was started on valganciclovir 900 mg twice a day with marked improvement at 1-month follow-up.

HISTOLOGICAL FINDINGS

The histologic features are summarized in Table 1 and illustrated in Figure 2. In patient #1, histologic examination revealed hyperplasia of the epidermis with irregular elongation of rete ridges and areas of epidermal ulceration with underlying dermal necrosis and inflammation. The epidermal acanthosis was very prominent in areas reaching pseudoepitheliomatous hyperplasia (Fig. 2A). Keratinocytes with multiple nuclei containing ground-glass intranuclear inclusions, consistent with HSV infection, were noted (Fig. 2B) and confirmed by an IHC stain for HSV. Although initial examination of the biopsy did not reveal CMV cytopathic effect, an IHC stain for CMV was performed, which showed positive labeling (Fig. 2D). A careful retrospective search demonstrated rare cells with large vesicular nuclei and prominent intranuclear inclusions suspicious for CMV infection within the granulation tissue present in the ulcerated areas, most likely representing endothelial cells or fibroblasts (Fig. 2C).

In patient #2, an initial excision showed a polypoid fragment of skin with epidermal acanthosis, ulceration and granulation tissue with a mixed inflammatory infiltrate (Fig. 2E). This initial examination did not detect HSV or CMV viral inclusions. A repeat biopsy revealed few large endothelial cells and fibroblasts with nuclear inclusions (Fig. 2G), suggestive of CMV cytopathic and IHC staining for CMV revealed positive nuclear staining in scattered large cells (Fig. 2H). There were no nuclear inclusions consistent with HSV infection and IHC for HSV I/II was negative likely secondary to prior treatment with famciclovir. Due to the clinical suspicion of HSV infections, the initial biopsy performed before treatment initiation was reviewed and multiple levels were obtained. Upon reexamination, a small focus of keratinocytes with nuclear inclusions consistent with HSV cytopathic effect overlooked by the original review was noted (Fig. 2F). Despite careful search, no CMV viral inclusions were noted; however, a CMV IHC stain showed positive nuclear staining in scattered large cells, presumably fibroblasts.

In patient #3, histopathologic examination revealed hyperparakeratosis overlying a markedly and irregularly acanthotic epidermis with pseudoepitheliomatous hyperplasia and reactive atypia of the epidermis. An ulcer with underlying dense acute and chronic inflammation was also noted (Fig. 2I). Numerous multinucleated keratinocytes showing peripheral clearing of chromatin and ground-glass appearance, consistent with herpetic viral cytopathic effect were identified (Fig. 2J), confirmed by IHC stain for HSV. Although careful histologic examination did not reveal cytopathic changes suggestive for CMV infection, IHC stain for CMV showed a few positive cells (Fig. 2K).

DISCUSSION

We report three unusual cases of atypical exophytic cutaneous HSV type 2 with concurrent CMV infection. The infections presented as a fungating exophytic lesion of uncertain diagnosis until biopsies were performed.

The overall HSV type 2 seroprevalence estimated by the National Health and Nutrition Examination Survey 2005–2008 was 16.2%; however, the majority of patients (81%) are not aware of having genital herpes infection.⁸ In immunocompromised patients, atypical clinical presentations of HSV include chronic large ulcers and exophytic lesions, which can mimic a malignant process and delay the correct diagnosis and treatment. Patients with HIV usually

have a higher recurrence rate than do immunocompetent patients, and the infection may have a more severe and/or chronic course with increased viral shedding.

CMV is a member of the herpes virus family infecting approximately 70%–90% of the worldwide population. The natural history of the disease includes primary infection, latent infection, and reactivation.⁴ Although CMV infection is typically asymptomatic in immunocompetent hosts, in immunocompromised subjects, the infection may be clinically apparent and characterized by a poor prognosis.⁴ Reactivation of CMV is the most frequent cause of symptomatic disease in renal transplant patients usually occurring within the first 4–12 months after transplant.^{9,10} Cutaneous signs such as macular rashes, ulcers, purpuric eruptions, hyperpigmented, indurated areas of the thighs, verrucous papules, or bullous lesions are often the first sign of CMV viremia and internal organ involvement.⁴ The use of IHC stains for CMV on skin biopsy or culture of the virus from skin lesions are 2 methods of diagnosing cutaneous CMV infections. To diagnose active viremia, CMV antigenemia test or the more sensitive PCR may be performed. In 2004, Slifkin et al¹¹ emphasized that CMV is the major microbial pathogen having a negative effect on solid organ transplant recipients and has been implicated in the pathogenesis of rejection. For these reasons, chemoprophylactic regimens against CMV using acyclovir, ganciclovir, valganciclovir, and valganciclovir have been recommended in the first year after an organ transplant.

One of the earlier case reports of concurrent CMV and HSV infection occurred in 1989 when Lee et al⁶ reported concurrent infections in skin biopsies from 2 AIDS patients with fatal CMV infection. Although histologic diagnostic findings for both infections were present, only one of the cases had positive immunoperoxidase stains for both CMV and HSV infections. Most of the reported cases of cutaneous HSV with concurrent CMV infection occur in patients affected with HIV/AIDS; however, there are several previously reported cases in non-HIV/AIDS patients that are immunosuppressed for other reasons. In 2006, Choi et al⁵ described 9 immunocompromised non-HIV patients (5 had hematological diseases, and 4 were organ transplant recipients) that had been diagnosed with cutaneous CMV infection. Using IHC analysis and PCR, they evaluated the tissue for the presence of HSV and found a coexisting HSV infection in only one of the patients. Although the CMV lesions showed similar clinical and histopathological features to those of the patients with AIDS, they concluded that the association of CMV with concurrent HSV infection was less frequent than that seen in patients with AIDS.

In cutaneous CMV infections, the virus is typically present within the mesenchymal cells (eg, endothelial cells, fibrocytes, and sometimes within inflammatory cells, eg, macrophages) in contrast to infection in other organs in which inclusions are usually present within ductal epithelial cells. One study documented 2 cases of cutaneous CMV, 1 of which demonstrated viral inclusions within eccrine ductal epithelium.¹² In our series, the viral inclusions were found in endothelial cells and fibroblasts similar to the typical reported location.

A case series recently published by Kaiser et al⁷ in 2008 included a 39-year-old female patient with numerous similarities to patient #1 of our series. The reported patient was status post-renal transplant and presented with a perianal ulceration that was initially treated with antibiotics. Her immunosuppressants included cyclosporine 100 mg AM/50 mg PM, MMF 750 mg twice a day, and prednisolone 5 mg daily. She was hospitalized due to chronic allograft nephropathy and upon admission a 5.0-cm × 3.0-cm exophytic ulcer surrounded by verrucous borders was observed. A presumptive diagnosis of HSV was made, and valganciclovir treatment was started. Histopathologic examination revealed epithelial hyperplasia and a superficial perivascular infiltrate with endothelial inclusions consistent with CMV, along with follicular destruction associated with concomitant HSV type 2

infections. Treatment with oral valganciclovir and oral ganciclovir gradually resolved her ulcers. Our first patient was also a kidney transplant patient who was on similar doses of the same immunosuppressants and presented with an ulcerated lesion that was treated with antibiotics. The lesion evolved to exophytic plaques suspicious for HSV, which had concurrent CMV and showed improvement with oral valganciclovir.

We would like to emphasize that correct pathological diagnosis may be challenging in these cases unless a high index of suspicion is maintained. The histological findings of HSV infection including large multinucleated cells, with molding of nuclei, margination of chromatin, and a homogeneous ground-glass appearance are usually easy to identify in a biopsy.¹³ However, in our series, in patient #2, the cytopathic changes were very focal and obscured by the inflammatory infiltrate and epidermal hyperplasia and were overlooked on the original review of the biopsy. The histologic features of CMV infection consist of enlargement of the affected cells, usually endothelial cells and fibroblasts and the presence of intranuclear large eosinophilic inclusions surrounded by a clear halo.¹³ Positive identification of CMV cytopathic changes can be at times challenging, especially when the affected cells are sparse and associated with a dense inflammatory infiltrate. In addition, symptomatic cutaneous infections with CMV in the absence of recognizable cytopathic changes have been reported.¹⁴ In our series, in all the 3 patients, the histologic features pointing to a cutaneous CMV infection were very subtle and masked by the secondary changes present in the biopsy. Only in patient #2 the CMV viral changes were noted initially in the H & E-stained biopsy. However, even in this patient, the diagnosis of CMV infection was missed in the first 2 biopsies. In patient #1 the cytopathic changes of CMV were very focal and only recognized in retrospect after a positive CMV IHC stain was obtained and in patient #3 the CMV infection could be documented solely by IHC despite careful examination of the H & E slides. One of the reasons for the initial pathologic misdiagnosis in these cases and at the same time a significant pitfall is the atypical clinical presentation. All the 3 patients presented initially with a fungating, verrucous mass, and the initial diagnosis included condylomas or a cutaneous malignancy. Only in patient #3 the clinical diagnosis at presentation, besides squamous cell carcinoma and lichen simplex chronicus included a CMV or verrucous HSV infection. For patients #1 and #2, a diagnosis of CMV or HSV infection was added to the differential diagnosis only after patients have failed several medical and surgical therapies. Both patients had suffered from eroded fungating lesions for >1 year (4 years for patient #2) while seeing multiple physicians before correct diagnosis by the dermatologist and dermatopathologist. In view of this clinical scenario, histological evaluation may overinterpret the pseudoepitheliomatous hyperplasia seen in some of these cases as a well-differentiated squamous cell carcinoma and overlook focal viral changes. Awareness of the possibility of atypical presentations of HSV infection with verrucous forms and of possibility of concurrent CMV infection is essential for a correct clinical and pathologic diagnosis to be rendered in a timely fashion. It is worth mentioning also that both patients #1 and #2 were CMV positive recipients at the time of renal transplant and had been treated posttransplant with acyclovir prophylaxis. In both cases, the lesions developed only after this antiviral prophylaxis had been discontinued.

In conclusion, the 3 cases described highlight the atypical presentation of cutaneous HSV type 2 and CMV coinfection as fungating exophytic lesions. Because CMV and HSV are among the most common infections occurring in immunocompromised patients, they should always be in the differential diagnosis for infectious processes in these patients. Heightened awareness of atypical presentations of HSV and CMV infections in immunocompromised patients and a high index of suspicion will result in rapid diagnosis and prompt broadcoverage antiviral treatment leading to a better patient outcome. We encourage reporting of further cases of concurrent CMV and HSV cutaneous infections, particularly those that have an atypical presentation or occur in non-HIV immunocompromised patients.

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FIGURE 1.

Clinical presentation. A, Patient #1—exuberant granulation tissue and exophytic malodorous plaques with slight bleeding on upper thighs, labia majora, and mons pubis. B, Patient #2—nonhealing verrucous, indurated and eroded nodule on the penile shaft. C, Patient #3—nonhealing superior gluteal cleft ulcer with raised border and verrucous appearance.

FIGURE 2.

Histological features: A, Patient #1—epidermal ulceration with pseudoepitheliomatous hyperplasia and mixed inflammatory infiltrate (H & E stain, 4x). B, Patient #1—multinucleated cells with ground-glass appearance consistent with HSV infection (H & E stain, 40x). C, Patient #1—intranuclear and intracytoplasmic inclusion bodies (arrows) consistent with CMV infection (H & E stain, 100x). D, Patient #1—immunoperoxidase stain for CMV shows positive nuclear staining in scattered cells (40x). E, Patient #2—polypoid fragment of skin with epidermal acanthosis, ulceration and granulation tissue (H & E stain, 2x). F, Patient #2—retrospective examination shows focal multinucleated cells with ground-glass appearance consistent with HSV infection (H & E stain, 100x). G, Patient #2—large endothelial cells (arrows), with nuclear inclusions, suggestive of CMV cytopathic changes (H & E stain, 100x). H, Patient #2—immunoperoxidase stain for CMV shows positive nuclear staining in scattered cells (40x). I, Patient #3—acanthotic epidermis with pseudoepitheliomatous hyperplasia and reactive atypia of the epidermis with an ulcer with underlying dense acute and chronic inflammation (H & E stain, 10x). J, Patient #3—numerous multinucleated keratinocytes showing peripheral clearing of chromatin and ground-glass appearance, consistent with HSV cytopathic effect (H & E stain, 40x). K, Patient #3—immunoperoxidase stain for CMV shows positive nuclear staining in scattered cells (40x).

TABLE 1

Clinical and Pathologic Characteristics of the CMV/HSV-Infected Patients Reported

	Patient #1	Patient #2	Patient #3
Age (yrs)	50	62	35
Gender	Female	Male	Male
Location of lesion	Genital area	Dorsal penis	Gluteal cleft
Clinical appearance	Fungating, ulcerated, weeping plaques	Large verrucous nodule	Verrucous ulcerated plaque
Immune status	Immunosuppressed (renal transplant)	Immunosuppressed (renal transplant)	Immunosuppressed (HIV infection)
Initial clinical DDX	Fungal or bacterial infection, hematologic malignancy, SCC, Kaposi sarcoma	Condyloma acuminatum	Verrucous HSV, SCC, LSC
Documentation of HSV infection			
Histology	Viral inclusions	Viral inclusions [*]	Viral inclusions
IHC	Positive	Positive [†]	Positive
Culture	Positive for HSV2	Positive for HSV2	N/P
PCR from serum	N/P	Negative	N/P
Documentation of CMV infection			
Histology	Viral inclusions [‡]	Viral inclusions	Negative
IHC	Positive	Positive	Positive
Culture	N/P	Negative	N/P
PCR from serum	Positive	N/P	N/P
CMV antigenemia	Positive	Negative	N/P
Treatment	IV gancyclovir then oral valganciclovir	Oral valganciclovir	Oral valganciclovir
Response to treatment	Significant improvement at 3 wks	Resolution at 2 mos	Significant improvement at 1 mo

^{*}The HSV nuclear inclusions were detected only in retrospect after reexamination of the biopsy was performed in view of a positive culture for HSV2.

[†]The IHC for HSV was performed in retrospect in view of a positive culture for HSV2.

[‡]The inclusions were detected only in retrospect after reexamination of the biopsy was performed in view of a positive IHC for CMV.

CMV, cytomegalovirus; DDX, differential diagnosis; HSV, herpes virus; IHC, immunohistochemistry; IV, intravenous; N/P, not performed; PCR, polymerase chain reaction; SCC, squamous cell carcinoma.