Chronic Varicella-zoster Virus Epithelial Keratitis in Patients With Acquired Immunodeficiency Syndrome

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Objective: To characterize further a chronic epithelial keratitis caused by varicella-zoster virus infection in patients with acquired immunodeficiency syndrome (AIDS).

Methods: Patients with AIDS and chronic epithelial keratitis associated with varicella-zoster virus from 3 institutions were identified. Patient records were reviewed retrospectively for the following data: medical and demographic characteristics, techniques of diagnosis, physical findings, course, response to treatment, and outcome.

Results: Sixteen patients were studied. CD4+ T-lymphocyte cell counts were available in 11 patients, with a median of 0.034 x 10^9/L (range, 0-0.094 x 10^9/L). Two patients had no history of a zosteriform rash. In the remaining patients, the interval between rash and keratitis ranged from 0 days to 6 years. In all cases, the keratitis was chronic and characterized by gray, elevated, dendriform epithelial lesions that stained variably with fluorescein and rose bengal. The peripheral and midperipheral cornea was most commonly affected, and, in 13 of the 16 patients, the lesions crossed the limbus. Pain was a prominent feature, occurring in 12 of 16 patients. In 9 of 12 patients tested, varicella-zoster virus was identified by culture, direct fluorescent antibody testing, polymerase chain reaction testing, or a combination of these studies, with direct fluorescent antibody testing (6 of 8 positive results) and polymerase chain reaction testing (3 of 3 positive results) appearing to be the most sensitive. Response to antiviral medication was variable.

Conclusions: In patients with AIDS, varicella-zoster virus may cause a chronic infection of the corneal epithelium. The keratitis is characterized by dendriform lesions, prolonged course, and frequently by extreme pain. It can occur without an associated dermatitis.


RESULTS

The clinical and laboratory features of 16 patients with AIDS and chronic epithelial keratitis associated with VZV are summarized in Table 1.

All patients were men, ranging in age from 25 to 65 years (median, 36 years). CD4+ T-lymphocyte cell counts were available in 11 patients and ranged from 0 to 0.094 x 10^9/L (median, 0.034 x 10^9/L). There was a history of VZV infection in 15 of the 16 patients. Fourteen patients had cutaneous herpes zoster. Eight patients had herpes zoster ophthalmicus that began between 1 and 3 months before development of the keratitis. One patient had an episode of herpes zoster ophthalmicus 6 years before keratitis. In 1 additional patient, the onset of dendriform keratitis occurred concurrently with active herpes zoster ophthalmicus. Two patients had thoracic herpes zoster preceding the keratitis by 1 month and 18 months. One patient had primary VZV infection (chickenpox) 8 months before developing the keratitis. Two patients had no history of zosteriform rash. Two patients, 1 with and 1 without a his-
PATIENTS AND METHODS

We retrospectively reviewed the clinical records of 16 patients with AIDS and chronic VZV keratitis at 3 institutions. Patients were included if they had documented AIDS, chronic dendriform epithelial keratitis, and either dermatozoster within 6 months or laboratory evidence of VZV in corneal epithelial scrapings. Symptoms and signs at initial evaluation, treatment, diagnostic tests, course, and outcome were studied.

REPRESENTATIVE CASE REPORTS

Patient 2

A 35-year-old man with AIDS (CD4+ T-lymphocyte cell count, 0.094 × 10^9/L) developed progressive outer retinal necrosis syndrome of the right eye. He was treated with intravenous (IV) acyclovir and then received oral acyclovir. Two months later, he noted a foreign-body sensation in the left eye. Pseudodendrites present on the left cornea persisted for the next 5 months, despite therapy with topical trifluridine and IV acyclovir. He complained of chronic burning pain of the left eye that was unaffected by cyclopia or oral amitriptyline hydrochloride, but completely relieved by topical proparacaine hydrochloride. He had no history of dermatozoster.

Examination of the left eye revealed multiple elevated, gray corneal pseudodendrites that crossed the limbus and stained well with rose bengal, but poorly with fluorescein dye (Figure 1, A). There was no inflammation in the anterior chamber or vitreous. Combined antiviral therapy (IV acyclovir and either topical trifluridine, topical vidarabine, or topical acyclovir) was ineffective in resolving the signs or symptoms. All antiviral drug therapy was stopped for 2 days, and the corneal lesions were scraped and cultured. Cytological examination revealed multinucleated giant cells and direct fluorescent antibody staining was positive for VZV antigen. Viral cultures were positive for VZV. Herpes simplex virus (HSV) was not detected with either direct fluorescent antibody staining or culture.

Six months after the onset of the epithelial keratitis, therapy with oral sorivudine, 40 mg/d, was started. Within 10 days, the patient noted marked relief in symptoms and resolution of the epithelial lesions with a faint residual stromal haze contiguous with the limbus with no intervening clear zone. On day 17 of therapy with sorivudine, the epithelial pseudodendrites in the left eye recurred (Figure 1, B). By day 29 of sorivudine therapy, the pain had returned and multiple pseudodendrites were present on the left cornea. To control pain, Hess drops (0.5% cocaine and 3% epinephrine in a 2% boric acid solution) were administered every 4 to 6 hours with oral narcotics. Neither topical trifluridine, oral acyclovir, topical 10% acetylcysteine, nor an increase in the dose of oral sorivudine to 80 mg/d had any apparent therapeutic benefit. The patient died 6 weeks later.

Patient 4

A 35-year-old man with AIDS (CD4+ T-lymphocyte cell count, 0.024 × 10^9/L) developed decreased vision, irritation, and redness of his right eye. One month before, he had a thoracic rash of unknown cause, but no recent facial dermatitis.

On examination, the bulbar conjunctiva of the right eye was congested, most notably temporal to the limbus. Multiple, gray, raised dendriform lesions of the corneal epithelium stained poorly with fluorescein but well with rose bengal. There was a faint haze in the temporal corneal stroma, extending from the limbus with no intervening clear zone. Corneal sensation was normal except over the region of corneal stromal haze, where sensation was moderately decreased. The pseudodendrites were debrided, and tissue samples sent for laboratory analysis. Giemsa staining revealed multinucleated giant cells, direct immunofluorescence test result was negative for HSV antigen, but responding to the epithelial lesions. One patient had mild stromal haze and corneal edema. An additional patient developed subepithelial infiltrates.

In 12 of the 16 patients, pain was an important management issue. Corneal pain was variably described as a foreign-body sensation, reminiscent of a paper cut, or severe burning. For the 7 patients in whom the effect of topical anesthetics on the pain was documented, the anesthetic provided relief in all cases. The pain was difficult to control in 3 patients, who required systemic narcotics (2 patients), chronic topical anesthetic drops (3 patients), and retrobulbar alcohol (1 patient).

Varicella-zoster virus was identified in the corneal epithelium of 9 patients by 1 or more of the following techniques: direct fluorescent antibody staining for VZV antigen (6 patients); viral culture of VZV (2 patients); and polymerase chain reaction amplification of VZV DNA (3 patients). A Giemsa stain of the epithelial scraping also demonstrated multinucleated giant cells in 3 of these 9 patients. All 6 clinical samples that had positive results for VZV antigen by direct fluorescent antibody staining had negative results by direct fluorescent antibody stain-
positive for VZV antigen, and viral cultures were negative for both VZV and HSV.

The patient was treated with oral acyclovir, 800 mg 5 times daily, and topical trifluridine every 3 hours. After 9 days of therapy, his symptoms had improved markedly and the corneal pseudodendrites had resolved; however, the corneal stromal haze had worsened, and there was now a mild anterior chamber inflammatory reaction. With the addition of topical 1% prednisolone acetate, the corneal haze promptly cleared. The trifluridine was discontinued, and the patient remained asymptomatic while receiving the oral acyclovir and topical corticosteroid drops for the next 7 weeks. He discontinued the acyclovir for financial reasons, and the pseudodendrites recurred 7 days later. Acyclovir and trifluridine drops were restarted, and, within 2 weeks, the pseudodendrites had disappeared. The patient remained free of active corneal lesions for the next month and was then unavailable for follow-up.

**Patient 6**

A 38-year-old man with AIDS (CD4+ T-lymphocyte cell count, <0.020 × 10^9/L) came in with acute onset of right herpes zoster ophthalmicus and was admitted for IV acyclovir therapy. Ophthalmologic examination of the right eye revealed vesicular lesions around the eyelids, conjunctival injection and chemosis, punctate defects of the corneal epithelium, and small corneal pseudodendrites. Topical trifluridine was added to the therapy. Within 5 days, all the skin lesions had crusted over and the pseudodendrites had cleared. Antiviral therapy was discontinued shortly thereafter. During the next 2 months, the patient had 2 recurrences of corneal pseudodendrites. Each episode promptly resolved following therapy with oral acyclovir and topical trifluridine.

He returned 4 months later with severe right eye pain and pseudodendrites over the superior third of the cornea. The pseudodendrites crossed the limbus and extended onto the bulbar conjunctiva. The pseudodendrites were gray, elevated, and stained poorly with fluorescein but extremely well with rose bengal (Figure 2, A). There was no loss of corneal sensation. The pseudodendrites were debrided, and tissue samples were sent for viral culture and immunofluorescence, both of which were negative for VZV and HSV. Despite treatment with acyclovir and trifluridine, the pain and pseudodendrites slowly worsened. Cycloplegia, topical 0.1% diclofenac sodium, systemic amitriptyline, topical 1% prednisolone acetate, and topical 3% acyclovir ointment failed to relieve the pain or have any apparent effect on the pseudodendrites. The pain became excruciating, and the patient began having suicidal ideation.

The patient was admitted to the hospital for IV acyclovir therapy, 800 mg every 8 hours, with moderate, but incomplete resolution of his corneal disease after 2 weeks of therapy (Figure 2, B). Treatment was changed to IV foscarnet sodium, 3.7 g every 8 hours, with dramatic resolution of the pain and pseudodendrites (Figure 2, C). After 17 days of therapy, however, the foscarnet was discontinued because of unexplained fevers, elevated liver function test results, and granulocytopenia. Oral acyclovir, 800 mg 5 times daily, was resumed, but within 3 weeks the pseudodendrites had returned much more extensively than before (Figure 2, D). Recombinant human interferon alfa-2a was administered topically 4 times daily, but without improvement in signs or symptoms. All therapy was stopped for 24 hours, and the pseudodendrites were scraped for laboratory examination. Direct immunofluorescent antibody staining of the tissue was positive for VZV antigen and negative for HSV antigen. Giemsa staining of the tissue revealed multinucleated giant cells. The patient’s pain became worse after debridement, and within 1 week the pseudodendrites had returned. Topical 10% acetylcysteine and oral sorivudine, 40 mg/d, had no obvious effect on signs or symptoms of the persistent keratitis. Pain control was achieved with systemic morphine sulfate and topical Hess drops until the patient died 14 months after the initial onset of the pseudodendrites.

We present a retrospective review of 16 patients with AIDS and low CD4+ T-lymphocyte cell counts who developed an unusual form of chronic epithelial keratitis, characterized by dendriform corneal lesions, pain, and variable clinical response to antiviral medications.
Laboratory evidence implicates VZV as the cause of this disorder. Direct fluorescent antibody staining and polymerase chain reaction testing confirmed the presence of VZV in 8 patients. In 2 of 9 patients in whom viral cultures of corneal epithelial scrapings were taken, VZV was isolated. Our inability to detect VZV in the remaining 7 patients by culture is not unusual, since VZV is highly cell associated and is difficult to culture, especially with the extremely small samples procured from corneal scrapings. A recent report of keratitis caused by cytomegalovirus in a patient with AIDS showed that cytomegalovirus can also cause chronic dendriform keratitis. We did not consider cytomegalovirus to be a likely cause of the keratitis in our patients for several reasons. First, many of the patients had a recent history of VZV dermatitis. Second, in 9 of 12 patients, direct fluorescent antibody staining, polymerase chain reaction testing, or viral culture confirmed the presence of VZV in the corneal epithelium. Third, many of our patients responded to topical acyclovir, a drug with little activity against cytomegalovirus. Finally, although we did not specifically culture for cytomegalovirus in our epithelial
samples, we did not detect cytomegalovirus DNA by polymerase chain reaction in any of the 3 patients tested.

The corneal epithelial lesions described in this study have features that distinguish them from both acute and chronic forms of VZV keratitis that have been described previously (Table 2). The acute epithelial dendriform lesions of VZV in immune-competent patients have been described as small, fine, elevated intraepithelial lesions that occur several days following a rash and are accompanied by catarhal conjunctivitis. These early dendriform lesions are self-limited with resolution within 6 days, found most frequently in the corneal periphery, and associated with loss of corneal sensation. Varicella-zoster virus can be cultured from these lesions, but only within the first 48 to 72 hours after onset of cutaneous eruption. Superficial stromal infiltration can be seen with

### Table 1. Clinical and Laboratory Characteristics of Patients With Chronic Varicella-zoster Virus (VZV) Epithelial Keratitis

<table>
<thead>
<tr>
<th>Patient No./Age, y</th>
<th>CD4+ T- Lymphocyte Count, ×10^9/L</th>
<th>Affected Eye</th>
<th>Previous VZV Infection</th>
<th>Duration of Keratitis</th>
<th>Treatment: Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/53</td>
<td>0</td>
<td>OD</td>
<td>Right V2 zoster 7 wk before, PORN syndrome OS 3 wk before</td>
<td>ND</td>
<td>Oral acyclovir, trifluridine: resolved</td>
</tr>
<tr>
<td>2/35</td>
<td>0.094</td>
<td>OS</td>
<td>PORN syndrome OS 8 wk before</td>
<td>Multinucleated giant cells</td>
<td>6 mo</td>
</tr>
<tr>
<td>3/28</td>
<td>0.050</td>
<td>OD</td>
<td>Thoracic VZV 1 mo before</td>
<td>Negative</td>
<td>Oral acyclovir: resolved, recurrence when discontinued</td>
</tr>
<tr>
<td>4/35</td>
<td>0.024</td>
<td>OD</td>
<td>Primary zoster infection (chickenpox) 8 mo before</td>
<td>Negative</td>
<td>Oral acyclovir, trifluridine: resolved</td>
</tr>
<tr>
<td>5/35</td>
<td>0.050</td>
<td>OD</td>
<td>V1, V2 zoster 4 wk before</td>
<td>ND</td>
<td>Oral and topical acyclovir: unresolved</td>
</tr>
<tr>
<td>6/38</td>
<td>0.025</td>
<td>OD</td>
<td>V1 zoster 6 wk before</td>
<td>Multinucleated giant cells</td>
<td>14 mo</td>
</tr>
<tr>
<td>7/33</td>
<td>NA</td>
<td>OU</td>
<td>Thoracic zoster 18 mo before</td>
<td>Negative</td>
<td>Oral acyclovir, trifluridine: resolved</td>
</tr>
<tr>
<td>8/41</td>
<td>NA</td>
<td>OS</td>
<td>V1 zoster 12 wk before</td>
<td>Positive</td>
<td>Oral acyclovir, trifluridine: resolved</td>
</tr>
<tr>
<td>9/36</td>
<td>0.076</td>
<td>OD</td>
<td>V1 zoster 5 mo before</td>
<td>Negative</td>
<td>Vidarabine ointment: resolved</td>
</tr>
<tr>
<td>10/39</td>
<td>NA</td>
<td>OD</td>
<td>V1 zoster 4 mo before</td>
<td>Negative</td>
<td>Oral acyclovir, trifluridine: resolved</td>
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<tr>
<td>11/43</td>
<td>0</td>
<td>OS</td>
<td>V1 zoster 6 y before</td>
<td>Positive</td>
<td>Oral acyclovir: partial response</td>
</tr>
<tr>
<td>12/65</td>
<td>0.080</td>
<td>OS</td>
<td>None</td>
<td>Negative</td>
<td>Oral acyclovir, trifluridine: resolved, recurrence when discontinued</td>
</tr>
<tr>
<td>13/29</td>
<td>NA</td>
<td>OS</td>
<td>V1 zoster 12 wk before</td>
<td>Negative</td>
<td>IV acyclovir, foscarnet,</td>
</tr>
<tr>
<td>14/38</td>
<td>NA</td>
<td>OD</td>
<td>V1 zoster 12 wk before</td>
<td>Negative</td>
<td>Oral acyclovir, trifluridine: resolved, recurrence when discontinued</td>
</tr>
<tr>
<td>15/34</td>
<td>0.034</td>
<td>OD</td>
<td>V1 zoster 12 wk before</td>
<td>Negative</td>
<td>Oral acyclovir, trifluridine: resolved</td>
</tr>
<tr>
<td>16/25</td>
<td>0.012</td>
<td>OD</td>
<td>V1 zoster at initial examination</td>
<td>ND</td>
<td>Oral acyclovir: resolved</td>
</tr>
</tbody>
</table>

*DFA indicates direct fluorescent antibody; PCR, polymerase chain reaction; V1, distribution of the first division of the fifth cranial nerve; V2, distribution of the second division of the fifth cranial nerve; NA, data not available; ND, test not done; PORN, progressive outer retinal necrosis; and IV, intravenous.

†This patient required narcotics for pain control.
‡This patient developed acyclovir-resistant thoracic zoster.
§This patient required retrobulbar alcohol for pain.
resolution of the dendrites. Although our patients had replicating virus, their lesions differed from those of acute VZV in several ways. First, unlike the small, fine lesions that we have seen and have been described by Marsh et al3 and others4,5, most of the lesions described herein were thick and discontinuous with blunt ends, bearing little resemblance to the Medusa-like lesions described by Pavan-Langston and McCulley.4 Second, in 13 of the 16 affected eyes, the lesions crossed the corneal limbus. Third, the lesions in our patients were chronic, persisting for weeks to months, and, in many cases, first appeared months after a zosteriform rash.

Chronic epithelial pseudodendrites, or mucus plaques, as described by Marsh and Cooper6 and others5,7 can occur from 7 days to 2 years following herpes zoster ophthalmicus. These transitory plaques are gray, elevated, linear or branching, and stain well with rose bengal and poorly with fluorescein. Abnormal accumulation of mucus, possibly a consequence of poor tear film quality, has been postulated to be the mechanism for the formation of these plaques, which frequently respond to topical mucolytics. Varicella-zoster virus has not been cultured from these lesions, and VZV antigen has not been detected. These lesions tend not to respond to antiviral medications. The clinical appearance of the dendriform lesions in our patients resembled in some ways that of mucus plaques; however, in contrast to the late lesions described by Marsh and Cooper6 and others5,7, the epithelial lesions in our patients crossed the limbus, were associated with pain, and, in many cases, had either recoverable virus or VZV antigen. In addition, the epithelial lesions in many of our patients responded to antiviral medications, then worsened or recurred when the antiviral medications were discontinued. Mucolytics had no discernible effect on the epithelial lesions in our patients. The dendriform lesions described herein may therefore more closely resemble those described by Piebenga and Laibson7 and more recently by Pavan-Langston et al.8 In that study,8 these lesions had a positive result for VZV DNA by polymerase chain reaction testing and responded variably to topical antiviral medications. To date, however, in patients without AIDS, we have been unable to amplify by polymerase chain reaction techniques VZV DNA from chronic mucus plaques that resemble lesions described by Marsh and Cooper."
human immunodeficiency virus (HIV) have shown this propensity to chronicity. Chronic forms of herpes zoster dermatitis resulting in hyperkeratotic verrucous lesions have been recognized.\(^6,11\) These lesions are thought to be caused by ongoing viral replication, possibly modified by drug resistance,\(^12\) or be a limited form of lytic infection.\(^13\) It is likely that the same mechanisms contribute to the chronic nature of the disease in our patients.

Five of the 16 patients described herein developed keratitis without a preceding history of facial herpes zoster dermatitis, although 2 patients had prior thoracic herpes zoster and 1 patient had primary systemic herpes zoster. The development of VZV disease without skin eruption has been termed zoster sine herpete.\(^7,14,15\) Varicella-zoster virus ocular disease without skin manifestations has been described in both immunosuppressed and immunocompetent patients, including VZV iritis,\(^16,17\) keratitis,\(^18\) and VZV necrotizing retinitis.\(^19,20\) The cases that presented sine herpete in this series suggest that it is important to consider VZV in the differential diagnosis of chronic dendriform keratitis in patients with HIV disease even in the absence of skin lesions.

Pain was a prominent feature of the disease in 12 of the 16 patients. Since the pain was rapidly relieved by topical anesthesia, but not by tricyclic antidepressants, it was unlikely to be postherpetic neuralgia. The severity of the pain is exemplified by the 2 patients in whom systemic narcotics and chronic topical anesthetic drops were required for relief. An additional patient required a retrobulbar injection of alcohol to control the pain. All 4 patients without pain had preceding herpes zoster dermatitis in the distribution of the first division of the trigeminal nerve and loss of corneal sensation.

Treatment of the keratitis was difficult. Based on our experience, we would recommend initial treatment with oral or topical acyclovir or trifluridine. In the event of treatment failure, alternative antiviral drugs, such as oral foscarnet or cidofovir, which do not depend on thymidine kinase for activation, should be considered. Although others\(^21\) have reported that topical interferon alfa-2a may modify the severity of VZV in immunosuppressed patients, we found this treatment to have minimal effect in the 2 patients treated. As with other viral infections in patients with AIDS and low CD4\(^+\) T-lymphocyte cell counts, antiviral therapy is likely to be prolonged. In view of the recent success of Pavan-Langston et al\(^8\) in using vidarabine for the treatment of 2 cases of late pseudodendrites, this drug should be considered.

Varicella-zoster keratitis in HIV-infected patients should be differentiated from HSV keratitis, which has also been described in this population.\(^22,23\) Perhaps more importantly, this disease must be differentiated from dry eye and exposure keratopathy, both of which are seen with high frequency in patients with AIDS who have low CD4\(^+\) T-lymphocyte cell counts. We have found the use of rose bengal to be valuable in helping to differentiate these entities.

In summary, we believe that there may be forms of epithelial dendriform lesions associated with VZV that are distinct from the classic acute dendrites and late pseudodendrites described by Marsh and Cooper.\(^24\) In our patients, we have found the chronic, dendriform epithelial lesions to have recoverable virus. Host immunosuppression and viral pathogenicity may play a role in the development and persistence of these lesions.

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