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Late Varicella-Zoster Virus Dendriform Keratitis in Patients With Histories of Herpes Zoster Ophthalmicus

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Abstract

PURPOSE—To describe the characteristics and course of late varicella-zoster virus (VZV) dendriform keratitis in patients with histories of herpes zoster ophthalmicus (HZO); to describe responses of corneal lesions to antiviral treatment; and to investigate risk factors for recurrence.

DESIGN—Retrospective case series.

METHODS—Included were patients known to have 1 or more episodes of dendriform lesions beginning at least 2 weeks after HZO in 2 academic practices. Epithelial lesions were evaluated for the presence of VZV DNA by a polymerase chain reaction assay. Demographic, medical, and ophthalmic data were collected for each episode. Responses to treatment with antiviral medications were evaluated. Cumulative risk of recurrence was determined using Kaplan-Meier analysis; potential risk factors for recurrence (age, systemic disease, lesion characteristics, corticosteroids) were evaluated using univariate Cox proportional hazard models.

RESULTS—We identified 20 patients (14 women; median age, 65 years) who met inclusion criteria. Dendriform lesions were pleomorphic with thickened, opaque epithelium. Seven patients had systemic diseases characterized by altered immune function. VZV DNA was identified in 15 of 16 cases tested, and all lesions responded to antiviral therapy. The 1-year incidence of first recurrence was 95.8 lesions per 100 person-years of follow-up. Patients had multiple recurrences, but risk of recurrence appeared to decrease over time. No statistically significant risk factors for recurrence were identified.

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This study was approved by the Institutional Review Boards at UCLA and U.C. San Francisco.

CONCLUSIONS—Late dendriform lesions associated with HZO are foci of productive VZV infection. Lesions can be treated effectively with topical or systemic antiviral agents. Patients can have multiple recurrences of dendriform lesions despite treatment.

A variety of corneal disorders can occur in patients with herpes zoster ophthalmicus (HZO). Recoverable virus has been demonstrated in dendriform lesions that develop soon after the onset of cutaneous lesions.¹ In contrast, late epithelial lesions, including mucous plaques, have traditionally been considered noninfectious in nature.² In 1988, Engstrom and Holland described chronic varicella-zoster virus (VZV) infection of the corneal epithelium in a patient with acquired immunodeficiency syndrome (AIDS).³ Chern and associates subsequently confirmed the occurrence of such infections and described the characteristics and course of lesions in a series of 16 patients with human immunodeficiency virus (HIV) infection.⁴ Pavan-Langston and associates have shown that similar lesions can occur in people without HIV infection; they described 4 patients with “delayed pseudodendrites” that were found to contain VZV DNA and that responded to antiviral therapy.⁵ Al-Muammar and Jackson subsequently described 3 patients with histories of HZO and dendriform corneal lesions that responded to treatment with a combination of topical and oral antiviral agents.⁶ There is little additional information in the medical literature about such lesions. The purpose of the current study is to describe in greater detail the spectrum of clinical characteristics, the clinical course, and the response to antiviral treatment of late VZV dendriform keratitis in patients with histories of HZO who do not have HIV disease.

METHODS

Included were all patients in 2 academic practices (those of G.N.H. and T.P.M.) who had histories of HZO or had histories of HZO *sine herpete* (ocular disease without skin lesions), and who developed dendriform keratitis at least 2 weeks after the onset of HZO. Also included were all patients who had other epithelial lesions following the onset of HZO, and whose lesions were evaluated with polymerase chain reaction (PCR) techniques for VZV DNA. For purposes of this report, these cases provided a control to investigate whether VZV was associated specifically with dendriform lesions. Excluded were patients who were known to be HIV-infected or who had histories suggestive of HIV disease. HIV testing was not performed routinely on other patients who met inclusion criteria.

As an additional control for the specificity of the PCR assay, we reviewed results for the 23 patients with HSV keratitis reported by Leigh and associates, whose corneal specimens had been tested in our laboratories.⁷ All had positive tests for HSV but had been tested for evidence of VZV as well.

DATA COLLECTION

Retrospective chart reviews were performed for all patients. For each, the following demographic and medical data were collected: age, gender, and systemic diseases that might be associated with altered immune function. For each examination at which dendriform lesions were identified, the following factors were collected: eye affected and interval from onset of HZO to development of lesions (for first-identified dendriform lesions) or from previous dendriform lesions (for recurrent lesions). The following medical data were

collected for each subject throughout the course of follow-up: medications used (corticosteroids, topical and systemic antiviral agents, immunosuppressive drugs) and temporal relationship of medication use to development of first-observed or recurrent lesions. If medical records that identified the date on which first-identified dendriform lesions developed were available from referring physicians, that information was used to calculate the intervals from onset of HZO to development of dendriform lesions and from onset of dendriform lesions to treatment. All other analyses use data only from examinations at our institutions.

The following ophthalmic data were collected for each episode of dendriform lesions: associated symptoms; characteristics of lesions (appearance, presence of fluorescein staining, location [central, midperipheral, limbal]); presence of stromal involvement (infiltrates, scar); and anterior chamber cells. All slit-lamp biomicroscopic examinations had been performed by 1 of 2 authors (G.N.H., T.P.M.).

The following information about treatment for each episode was collected: use of oral or topical antiviral agents; use of topical corticosteroids; and changes in lesions following start of antiviral agents.

All evaluations of corneal scrapings for VZV DNA by PCR-based assays were performed in the Clinical Microbiology Laboratory at the Francis I. Proctor Foundation, University of California, San Francisco, using methods described previously.³ All specimens were also tested for the presence of herpes simplex virus (HSV) DNA as previously described.⁷

STUDY DEFINITIONS

An epithelial lesion was considered dendriform if it had a linear pattern with multiple branches or components that were identified by epithelial opacity or by fluorescein staining. A lesion was considered central if it involved the apex of the cornea; a lesion was considered limbal if any aspect of the lesion extended to, or involved, the limbal conjunctiva; all other lesions were considered to be midperipheral. Recurrence was defined as a new dendriform lesion after resolution of previous lesions, whether the new lesion was in the same or a different location than the previous dendriform lesions. Active uveitis was defined as the presence of anterior chamber cells. Cells had been assigned semi-quantitative scores, as defined by Hogan and associates.⁸

DATA ANALYSIS AND STATISTICAL TECHNIQUES

We compared the proportion of dendriform lesions found to contain VZV DNA to the proportion of other, nondendriform epithelial lesions found to contain VZV DNA using the Fisher exact test. Cumulative risk of first recurrence was determined by Kaplan-Meier analysis.

Three factors associated with first-observed lesions (age, presence of systemic disease, lesion location) and 3 factors identified at first-observed episode or during follow-up examinations before first recurrence (presence of stromal involvement, use of topical corticosteroids, presence of anterior uveitis) were investigated as potential risk factors for first recurrence using univariate Cox proportional hazard models.

REPRESENTATIVE CASE HISTORIES

Case histories of 3 representative patients are presented in the Supplemental material (available at ajo.com). They illustrate the spectrum of clinical characteristics and courses of dendriform keratitis. Corneal lesions for each case are illustrated in Figure 1.

RESULTS

We identified 20 patients with histories of HZO who developed late dendriform keratitis. Two patients had HZO *sine herpete*; diagnosis was suspected on the basis of chronic keratouveitis consistent with herpetic disease (interstitial keratitis, decreased corneal sensation, segmental iris atrophy) and associated facial pain suggestive of post-herpetic neuralgia. We identified an additional 5 patients with histories of HZO who had other corneal epithelial lesions that were evaluated with the PCR assay to rule out the presence of VZV DNA; 2 had nondendriform punctate epithelial keratitis and 3 had persistent epithelial defects associated with underlying stromal keratitis.

Table 1 lists demographic, medical, and ophthalmic characteristics of first-observed lesions for the 20 patients with late dendriform keratitis. The majority of patients were women. Seven of 20 (35%) had a systemic disease that could be associated with altered immune function or were receiving immunosuppressive medications; the specific conditions are listed in Table 1. Five of 12 patients (42%) who were 65 years of age or younger, including the 2 youngest patients (aged 45 and 51 years), had 1 of these medical conditions associated with altered immune function. In contrast, only 2 of 8 patients (25%) older than 65 years had such medical conditions. We identified no unique disease characteristics in the subgroup of patients with possible alterations in immune function. The median interval from onset of HZO to development of first-observed dendriform lesions was 5 months, but was as long as 15 months in 1 patient. The majority of patients described 1 or more symptoms (18 patients, 90%) and had decreased corneal sensitivity (14 patients, 70%).

VZV DNA was identified by PCR assay in 15 of 16 first-observed lesions tested (94%), including both patients with HZO *sine herpete*; in contrast, no VZV DNA was identified in the other epithelial lesions of 5 patients with histories of HZO ($P < .0003$, Fisher exact test). All tests for HSV DNA were negative. None of the 23 patients with HSV keratitis reported by Leigh and associates had positive PCR assay results for VZV.⁷

There was a spectrum of clinical features associated with the first-observed dendriform lesions (Figure 1). The epithelial lesions often had multiple components, including a variable mixture of dots, lines, and branching forms with blunt ends. The components could be discontinuous. The epithelium was often thickened and opaque, but linear portions of the lesions were generally delicate in appearance. All lesions were gray/white in color and stained variably with fluorescein, rose bengal, or lissamine green stains. There was a tendency for lesions to be more irregular and their appearance to be either more coarse or more delicate than the discrete dendrites caused by HSV. None of the branches had terminal bulbs, as seen with HSV-associated dendrites. Lesions were either central or midperipheral in 19 cases (95%). Only 1 first-observed lesion involved the limbus; the patient had

undergone stem cell transplantation for non-Hodgkin lymphoma and was being treated with prednisolone acetate 1%.

Among 17 patients for whom information about the anterior chamber was available, 14 had active anterior uveitis; cells were scored as 1 or more in 7 patients (41%) at the time of first-observed dendriform lesions. Stromal involvement, characterized by diffuse stromal haze or by sectoral stromal haze subjacent to epithelial lesions, was present in the majority (71%) of patients (n = 17 eyes); there were no dense focal inflammatory infiltrates.

Among the 19 patients with dendriform lesions who were followed by us (1 patient was seen only once by us for a consultative visit), the mean $\pm$ SD duration of follow-up was 2.7 ± 2.6 years (median, 1.6 years; range, 0.06 years [22 days] to 8.7 years). Eight of 19 patients were followed by us for less than 1 year. None of the 5 HZO patients with other lesions developed dendriform lesions during follow-up. Information about disease course is provided in Table 2.

Treatment with topical trifluridine or an oral antiviral agent (acyclovir, famciclovir, valacyclovir) or both, with or without topical corticosteroid, was administered to all 20 patients. The purpose of topical corticosteroid was to manage concomitant stromal keratitis or anterior uveitis. In all patients having a follow-up examination within 1 month of the first-observed dendriform lesion (n = 18), epithelial changes resolved completely. After resolution of epithelial lesions, the corneas of 3 patients had underlying stromal changes including persistent stromal haze (2 patients) and Descemet membrane folds (1 patient). The mean $\pm$ SD duration of dendriform lesions from diagnosis to initiation of treatment (24 ± 16 days; n = 9 eyes) was longer and more variable than the mean $\pm$ SD time to resolution of these lesions after initiation of treatment (13 days $\pm$ 10 days; n = 18 eyes).

At least 1 recurrence was seen in 10 eyes (53%); some eyes had multiple recurrences. There was a total of 23 recurrences: 3 eyes (16%) had 1 recurrence, 3 eyes (16%) had 2 recurrences, 3 eyes (16%) had 3 recurrences, and 1 eye (5%) had 5 recurrences. Within 1 year of follow-up, there were 14 recurrences (7 eyes). The overall, cumulative incidence of recurrence was 45.6 per 100 person-years (PY) of follow-up. Risk of first recurrences is illustrated in Figure 2. The risk of recurrence decreased over time. The 1-year, 2-year, and 5-year incidences of recurrence were 95.8, 73.4, and 53.2 per 100 PY, respectively. For the 23 recurrences, the median (range) interval between documented episodes was 0.40 years (0.1–2.6 years).

Maximum anterior chamber cell score during follow-up at any time after first observed dendriform lesions but before recurrences was 1 or more in 6 of 10 first recurrences (60%). Active uveitis was present at the time of recurrence in 7 of 22 recurrences (32%) (cells unknown in 1 eye). As determined by univariate risk factor analysis, none of the potential risk factors studied was statistically associated with time to first recurrence (Supplemental Table, available at ajph.com).

Of 10 first recurrences, 3 occurred while patients were taking oral antiviral drugs. Patients were taking acyclovir 800 mg, 3 to 5 times daily (2 patients), or valacyclovir, 1 g, twice daily (1 patient); all were being treated with prednisolone acetate 1%, 2 to 3 times daily. Of

the 7 patients who developed first recurrences while not receiving antiviral agents, 6 had been treated with antiviral agents at some point between resolution of the first observed dendriform lesion and the first recurrence; the time from discontinuation of antiviral treatment to first recurrence for these 6 patients ranged from 2 weeks to 7 months (median 1.5 months). Because of the small sample size and because of intermittent use and variable doses of antiviral agents, we were unable to assess the effect of prophylactic antiviral therapy on time to recurrence.

DISCUSSION

Epidemiologic studies suggest that 4% to 13% of patients with HZO will develop late mucous plaque keratopathy.^{2,9–11} As reported previously,^{3–5} and expanded upon in our study, corneal epithelial lesions that fit this general description occur in both immunocompetent and immunocompromised patients; they may contain VZV DNA and respond to antiviral therapy; and they can occur without a history of prior VZV skin disease. Furthermore, these infectious lesions can recur, even in patients who are not HIV-infected or receiving systemic immunosuppressive drug therapy. In an earlier study, Pavan-Langston and associates described recurrent episodes in 2 of 6 patients.⁵ In our study, we noted recurrences in 10 of 20 patients, with 1 patient having 5 recurrences over 8.7 years. The recurrent nature of this disease gave us the opportunity to observe 43 distinct episodes of this infectious disease of the corneal epithelium. Pavan-Langston and associates referred to this entity as “delayed herpes zoster pseudodendrites,”⁵ but we prefer the term late VZV dendriform keratitis.

The dendriform lesions seen in our patients were pleomorphic. Lesion components could have various shapes, but key features were the delicate nature of linear portions and the lack of terminal bulbs. The appearances of these lesions were similar to those described previously in patients with or without HIV disease;^{3–5} however, in contrast to the descriptions of lesions in patients with AIDS, only 1 of the lesions in the current study crossed the limbus. The lesions that we observed were also similar to those that have been labeled mucous plaque keratitis or mucous plaque keratopathy for many years in the medical literature.^{1,2,6,9–11} Based on our experience, we suspect that many of the previously described cases of presumed noninfectious mucous plaques were, in fact, late VZV dendriform keratitis, as described herein. Our results do not, however, rule out the possibility that some patients with HZO may develop noninfectious lesions, such as filaments or adherent mucoid material. It would be appropriate to refer to the latter type of lesion as a mucous plaque, an entity distinct from late VZV dendriform keratitis.

Although the recurrent pattern of infectious VZV dendriform keratitis that we describe is at odds with the traditional teaching about VZV corneal disease, other evidence also suggests that VZV can cause recurrent or persistent infection. Several large epidemiologic studies clearly demonstrate that dermatomal zoster recurs in about 5% of affected individuals, almost always in the same dermatome of the initial disease.^{12,13} Also, a recent PCR-based study by Cohrs and associates¹⁴ suggests that peripheral shedding of VZV in the absence of clinical signs of disease may occur more often than is generally believed. Because pathology studies indicate that VZV can persist in the eye for many years after an episode of HZO,^{15,16}

late VZV dendriform keratitis might represent a persistent viral infection of the cornea, which remains subclinical except under circumstances that allow the virus to overcome local defenses and cause recurrent clinical disease. Alternatively, it may represent viral reactivation from a distant site of latent infection, such as the trigeminal ganglion. In either case, it is likely that local or systemic immunosuppression makes this condition more likely to occur, accounting for the fact that we first recognized this entity in HIV-infected individuals, and the fact that 7 patients in this series had a systemic disease that could be associated with altered immune function or were receiving immunosuppressive drugs.

Based on the prior success of others,³⁻⁶ our approach to the management of late VZV dendriform keratitis consisted of initiating antiviral medication (a number of different medications, doses, and routes were used) and reducing iatrogenic immunosuppression. Because we treated all of the patients in our series, the natural history of this disease, as well as the effectiveness of our management, is difficult to assess. Response to treatment was suggested, however, by the consistently shorter time course to disease resolution after initiating therapy than the duration of lesions prior to therapy. Given that most of our patients with late VZV dendriform keratitis both were symptomatic and had an associated stromal keratitis or iritis or both, we believe strongly that this disease should be treated with an antiviral drug.

This study suffers from the usual limitations of retrospective series, including referral and recall bias. Conclusions about the effect of treatment were based in part on the difference between intervals from development of dendriform lesions to the start of treatment and the intervals from start of treatment to resolution of lesions; however, those intervals were available for only a minority of patients, and the 2 intervals corresponded to a different subgroup of patients. Also, they were based on historical data not collected by us for all patients. In addition, because some of the patients were returned to the referring physicians, follow-up information about them was limited. Although we have no reason to believe that patients were preferentially followed by us on the basis of disease severity (including time to recurrence), we cannot rule out the possibility of differential follow-up based on disease characteristics. Because this study was retrospective, it is also possible that we underestimated the length of time that late VZV dendriform keratitis was present before we began treatment and overestimated the time to resolution of these corneal lesions after treatment was initiated.

Despite published reports regarding this entity, it has been our experience that most ophthalmologists, even corneal specialists, are unaware of the infectious nature of late VZV dendriform keratitis. In summary, we have provided data from 20 patients that further support the infectious nature of this condition. Also, we have described the temporal association of these lesions with HZO, and highlighted their recurrent nature. We hope that this case series will serve not only to inform clinicians but to encourage further study regarding this important condition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Biography

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FIGURE 1.

Slit-lamp biomicroscopic photographs of late varicella-zoster virus dendriform keratitis. (Top left) A peripheral lesion with multiple, lacy branches. (Top right) A more coarse dendriform lesion in the paracentral cornea that stains with fluorescein (representative case 1). (Bottom left) Recurrent multifocal epithelial lesions that responded to antiviral therapy in a patient who previously had dendriform lesion containing VZV DNA. This case illustrates the pleomorphic nature of the condition (representative case 2). (Bottom right) Dendriform lesions with thickened opaque epithelium. There is mild stromal haze subjacent to the

epithelial lesions (representative case 3). Representative case histories can be found in the Supplemental materials at ajo.com.

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FIGURE 2.

Kaplan-Meier analysis of time to first recurrence of dendriform keratitis after first-observed episodes in 19 patients with histories of herpes zoster ophthalmicus (thick line); the 95% confidence interval is indicated by the thin lines.

TABLE 1

Demographic, Medical, and Ophthalmic Characteristics of 20 Patients (20 Eyes) With Histories of Herpes Zoster Ophthalmicus at Development of First-Observed Late Varicella-Zoster Virus Dendriform Keratitis

Variable	Value
Median age (range)	65 (45–82) years
Female	14 patients (70%)
Systemic diseases ^a	7 patients (35%)
Median interval from HZO to first-observed dendriform lesions ^b (range, n = 18 ^c)	5 (0.5–15) months
Symptomatic ^d	18 patients (90%)
Location of lesions ^e	
Central	5 corneas (25%)
Midperipheral	14 corneas (70%)
Limbal	1 cornea (5%)
Anterior chamber cells (n = 17 ^c)	14 eyes (82%)
Stromal keratitis (n = 17 ^c)	12 eyes (71%)
VZV DNA present ^f (n = 16 ^c)	15 lesions (94%)

HZO = herpes zoster ophthalmicus; VZV = varicella zoster virus.

^aIncluding rheumatoid arthritis being treated with methotrexate (2 patients); non-Hodgkin lymphoma/Waldenstrom macroglobulinemia, history of bladder cancer/breast cancer, history of inflammatory bowel syndrome, non-Hodgkin lymphoma status post stem cell transplantation, and mixed connective tissue disease/history of breast cancer (1 patient each).

^bNot included were 2 patients with HZO sine herpete.

^cNumber of patients/eyes/lesions for whom the factor was known, if less than 20.

^dSymptoms included foreign body sensation, photophobia, and tearing.

^eCentral was defined as involving the apex of the cornea; limbal was defined as crossing the limbus; all other lesions were identified as midperipheral.

^fAs determined by polymerase chain reaction technique.

TABLE 2

Clinical Course of Late Varicella-Zoster Virus Dendriiform Lesions in 20 Patients (20 Eyes) Treated With Antiviral Agents

Variable	Value
Median interval from onset of first-observed lesion to start of treatment (range, n = 9 ^a)	21 (2–52) days
Response to treatment (n = 18 ^{ab})	
Resolution of epithelial lesion	18 eyes (100%)
Resolution with residual stromal changes	3 eyes (17%)
Median time to resolution of lesions (range)	13 (7–35) days
Number of eyes with recurrences (n = 19 ^{ac})	10
Number of documented episodes per eye, range	1–5
Median interval between documented episodes (range)	0.4 (0.1–2.6) years

^aNumber of patients/eyes for whom the factor was known, if less than 20.

^bTwo patients were excluded (1 patient did not have any follow-up examinations, and 1 patient had follow-up only 2 months after the first-observed dendriiform lesion, and was therefore censored from this analysis).

^cOne patient was excluded due to lack of any follow-up data.