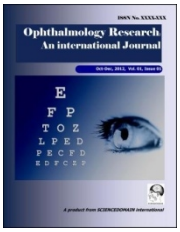

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Remission of Multiple Recurrent Dendriform Keratitis in Herpes Zoster Ophthalmicus after Long-term Oral Acyclovir Therapy

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Authors' contributions

Author EWC did literature review and extensively drafted the manuscript. Author SS wrote the first draft of the manuscript and designed the study. Author BCC critically reviewed the manuscript and co-managed the patient. All authors read and approved the final manuscript.

Case Study

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ABSTRACT

Dendriform keratitis is a recurrent sequelae of herpes zoster ophthalmicus (HZO). A 76-year-old immunocompetent Indian male with HZO developed left eye keratouveitis, uveitic glaucoma and superior orbital fissure syndrome. After treatment with intravenous acyclovir for two weeks, there was resolution of cranial nerve palsies. However, he developed 5 recurrences of dendriform keratitis and uveitis over 4.5 years. The spectrum of corneal epithelial lesions included: lacy branching pseudodendrites without true terminal bulbs, thickened grayish epithelium resembling mucous plaque keratitis, and dot-like epithelial erosions or superficial punctate keratopathy in a linear configuration. Each recurrence resolved with treatment with topical acyclovir and steroids. After the 5th recurrence, oral acyclovir 400 mg twice daily was started and continued for 21 months. Thereafter, he remained recurrence-free for 2 years and 9 months to date. Conclusions: Long-term oral acyclovir may have a prophylactic role against recurrent zoster dendriform keratitis and uveitis, suggesting a need for further studies Epithelial recurrences are characterized by a spectrum of pleomorphic patterns.

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Keywords: Herpes zoster ophthalmicus; complete ophthalmoplegia; dendriform keratitis; acyclovir.

1. INTRODUCTION

Late dendriform keratitis is a recognized sequelae of herpes zoster ophthalmicus (HZO). Epithelial recurrences are known to occur between 33% to 50% of patients with late dendriform keratitis [1,2]. However, morphologic characterization of recurrent epithelial lesions, factors associated with recurrences, and optimal treatment strategies are unclear [3].In this case report, we describe a patient with HZO who developed recurrent anterior uveitis and late dendriform keratitis characterized by pleomorphic epithelial lesions. Each recurrence resolved with topical acyclovir and steroids. However, initiation of oral acyclovir therapy for 21 months resulted in a recurrence-free period of 2 years and 9 months to date.

2. PRESENTATION OF CASE

A 76-year-old Indian male presented with a history of left-sided facial and periocular pain and erythema of 1 week duration. He had a medical history of hypertension, obstructive sleep apnea, previous lower limb cellulitis, and had previous bilateral cataract surgery with intraocular lens implantation.

On examination, he had a papulovesicular rash over the left side of his face and forehead. There were no vesicles at the tip of the nose. Visual acuity was 20/30 in the right eye and 20/40 in the left eye. There was no relative afferent pupillary defect, and color vision and confrontation visual fields were normal. Extra-ocular motility was full in all directions of gaze, and the rest of the cranial nerves examination were within normal limits. The intraocular pressure was 37 mm Hg in the left eye and 20 mm Hg in the right eye. Slit-lamp examination of the left eye revealed punctate epithelial erosions of the cornea, with a quiet anterior chamber. The posterior segment was normal. Examination of the right eye was unremarkable. He was diagnosed with HZO and started on oral acyclovir 800 mg five-times a day and topical timolol 0.5% twice daily.

Fifteen days after the onset of HZO, the rashes had resolved with crusting. The patient still had persistent left-sided periorbital pain. Healso developed uveitic glaucoma with conjunctival injection, corneal epithelial edema and anterior uveitis with 1+ cells, and intraocular pressure of 32 mm Hg. The posterior segment was normal. There was also a superior orbital fissure syndrome with V1, 3rd, 4th, and 6th cranial nerve palsies with motility examination revealing complete ophthalmoplegia in the left eye, associated with complete ptosis and a dilated pupil. There were no signs of optic neuropathy. The other cranial nerves were not involved and there were no signs of meningitis or encephalopathy. Magnetic resonance imaging revealed changes consistent with old infarcts in the corona radiata, but no abnormalities were seen in the cavernous sinuses, orbits, meninges cranial nerves or orbit. He was started on intravenous acyclovir 500 mg 3 times daily, topical steroids to the left eye, and gabapentin for neuralgia. There was improvement in ophthalmoplegia and ptosis within two weeks of initiation of treatment, and complete resolution by 2 months.

The patient's subsequent clinical course recurrent dendriform keratitis of pleomorphic patterns (Table 1). There were corneal epithelial irregularities, including punctate epithelial erosions, pseudodendriform patterns, heaped-up grayish epithelium, coarse superficial punctate opacities, and geographic patterns of radiating lines, dots and branches (Fig. 1).

Other corneal changes included stromal edema, descemet membrane folds, and pigmented keratic precipitates, due to uveitis. Epithelial recurrences involved paracentral and central lesions. Recurrence in our case was defined as a new dendriform corneal lesion after resolution of previous lesions, with or without anterior chamber inflammation, consistent with the definition used in a previous retrospective case series [3]. He had five recurrences of epithelial keratitis with or without anterior uveitis (Table 1). Each recurrence was treated with topical steroids with or without topical acyclovir. Each recurrence responded completely to treatment. Unfortunately he developed glaucomatous optic neuropathy due to sustained ocular hypertension 4 months after presentation. There was neuroretinal rim loss with a corresponding nasal step defect on Humphrey perimetry. Subsequently, his intraocular pressure remained consistently ≤21 mm Hg on 3 IOP medications, and optic nerve head and visual fields were stable on follow-up.

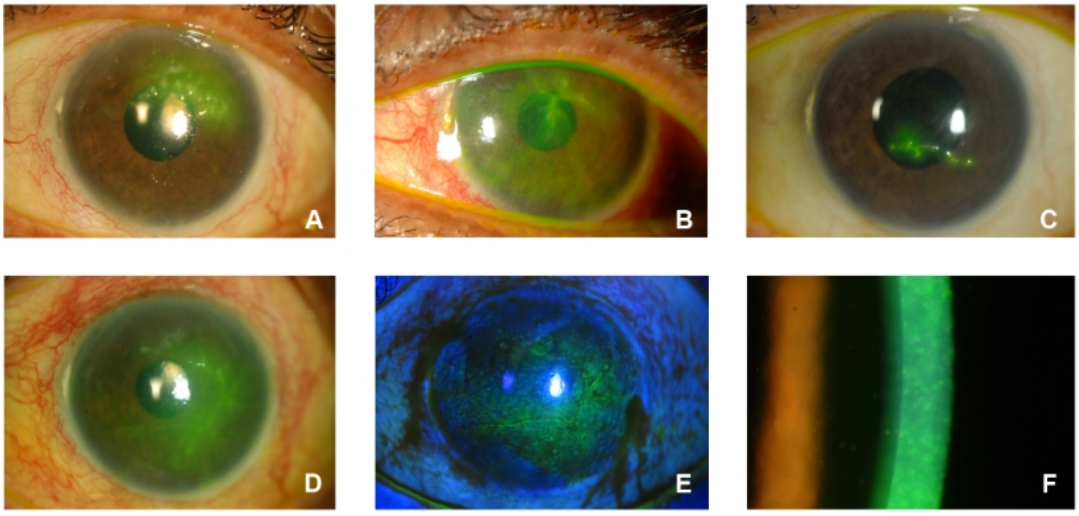

Fig. 1. Anterior segment photographs of recurrent herpes zoster dendriform keratopathy lesions

A- Paracentral nodular epithelial lesions with thickened epithelium (4 months)
B- Central stellate lesion with multiple, lacy branches (5.5 months)
C- Paracentral pseudodendriform lesions with peripheral bulbs (9 months)
D- Combined superior and inferior dendriform lesion with punctate epithelial erosions (15 months)
E- View with cobalt blue filter of fluorescein-stained dendriform lesions illustrated in D
F- Slit view showing coarse punctate epithelial keratitis (19 months)

Table 1. Timeline, Profile and Treatment of Recurrent Dendriform Keratopathy in Herpes Zoster Ophthalmicus

Timeline	Morphology of Dendriform Keratopathy	Stromal Keratitis	Anterior Uveitis	Topical Acyclovir 3%	Topical Steroids	Systemic Acylovir	Time to resolution of corneal epithelial lesions
Index presentation	PEE	No	Yes	No	G. prednisolone acetate 1%	IV acyclovir 500 mg TDS	1 month
4 months	Paracentral thickened epithelium in dendriform pattern	No	Yes	No	G. prednisolone acetate 1%	No	1 month
5.5 months	Central stellate dendriform lesion with lacy branches	No	Yes	No	G. dexamethasone 0.1% (Preservative-free)	No	2 months
9 months	Paracentral dendriform lesion with pseudo peripheral bulbs, thickened epithelium	No	Yes	Yes	G. dexamethasone 0.1% (Preservative-free)	No	2 months
15 months	Circinate paracentral dendriform lesion involving superior and inferior cornea, PEE	No	Yes	Yes	G. dexamethasone 0.1% (Preservative-free)	No	6 weeks
19 months	Coarse SPK in linear configuration	No	No	No	G. dexamethasone 0.1% (Preservative-free)	Continued on oral acyclovir	1 month
28 months	PEE	No	No	No	No	400 mg BD prophylaxis from Month 19 to Month 40	3 weeks
53 months	Clear cornea	No	No	No	No	No	-

Abbreviations: PEE, Punctate epithelial erosions; BD, Twice a day; TDS, Three times a day; IV, Intravenous

3. DISCUSSION

To the best of our knowledge, this is the first case of multiple recurrent late dendriform keratitis and uveitis in a patient with HZO complicated by superior orbital fissure syndrome. This case demonstrates a spectrum of epithelial lesions over five recurrence episodes. The treatment of recurrences with only topical steroids for uveitis, with or without topical acylovir, but without systemic acyclovir, could explain these multiple recurrences. This report may suggest a potential prophylactic role for long-term oral acyclovir against such recurrences.

Anterior segment involvement has been documented in cases of HZO. Punctate epithelial keratitis and pseudodendrites are early and transient features. Development of recurrent epithelial lesions in herpes simplex virus keratitis is a well-recognized complication of virus reactivation. Similarly, late complications in our case, i.e. recurrent varicella zoster (VZV) dendriform keratopathy, anterior uveitis, and superior orbital fissure syndrome could all be attributable to viral reactivation. There is evidence for an direct viral infection as a cause for keratopathy, particularly in immunosuppressed hosts, i.e. VZV DNA has been recovered in first-observed and recurrent corneal lesions [2,4,5]. Our patient was immunocompetent, and although no microbiologic or serologic investigations for VZV were conducted, there was distinct complete resolution of recurrent episode in the 9th and 15th month to topical aciclovir, supporting an infective basis. Development of multiple cranial nerve palsies has been postulated to be due to retrograde viral spread from the trigeminal ganglion to other ocular motor nerve nuclei in the brainstem [6].

Hu et al. [3] described a spectrum of clinical features associated with the first-observed epithelial lesions in HZO: there were branching forms with blunt ends without true terminal bulbs, and comprising thickened and opaque epithelium. This patient had lacy branching pseudodendrites, some of which assumed a stellate configuration, grayish heaped-up epithelium, and dot-like epithelial erosions (Fig. 1). However, the recurrent lesions in our case appeared coarser and larger. Our case provides further evidence that the well-described mucous plaque keratitis sequelae of HZO is infective in origin, based on the complete resolution of these lesions to topical acyclovir therapy.

This case may suggest that contributory factors towards multiple recurrences include the use of topical steroids concurrently with topical acyclovir. To date, no study has identified any factor predisposing to recurrence of late dendriform keratopathy. There was a treatment dilemma as our patient also had recurrent anterior uveitis and uveitic glaucoma, necessitating topical steroid therapy. In herpes simplex virus (HSV) concurrent epithelial and stromal keratitis, steroids are typically not started before the epithelial defect has healed, for fear of viral reactivation. One study has concluded that combined steroid and acyclovir is superior to steroid alone in reducing the incidence of rebound inflammations [7].

This case suggests a potential role of oral acyclovir prophylaxis in preventing epithelial and uveitic recurrences of HZO. There was no stromal keratitis in this patient. Of note, oral acyclovir 400 mg twice a day for 12 months led to an almost 50% reduction in the incidence of ocular HSV recurrences only in patients with stromal keratitis, but not for individuals with epithelial keratitis [8]. Thus, there may be differences between HSV and VZV in their response to long-term acyclovir treatment. Oral acylovir prophylaxis was discussed with the patient at the 4th month of his clinical course with uveitis, however he did not wish to take long term systemic medication despite being counselled on the potential high risk of recurrences. He eventually agreed after his 5th recurrence. After he was treated with oral acyclovir for 21 months, he remained recurrence-free for 2 years and 9 months. Oral

steroids were not considered at any point in the patient's management as the keratouveitis was unilateral and most of the recurrences resolved with topical medication alone. Furthermore, oral steroids are also indicated more so during the acute illness for pain reduction, and for disabling post-herpetic neuralgia.

4. CONCLUSIONS

In conclusion, recurrent HZO late dendriform keratitis is characterized by varied dendriform patterns. Topical acyclovir and topical steroids is effective in acute management of recurrent episodes of keratouveitis. However, there is a potential prophylactic role for long-term systemic acyclovir in HZO, and further longitudinal cohort data would be important.

CONSENT

A written consent was obtained for the patient's photographs to allow for publication purposes. However there are no patient identifiers in this particular case report.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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