

3 **Remission of Multiply Recurrent Dendriform Keratitis in Herpes Zoster**

4 **Ophthalmicus after Long-term Oral Acyclovir Therapy**

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ABSTRACT (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

SAMPLE 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 2.5 years to date.

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

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1. INTRODUCTION (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

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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 (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

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 previously **underwent** 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 was 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%.

Fifteen days after the onset of HZO, the rashes had resolved with crusting. The patient still had persistent left-sided periorbital pain. He had also developed uveitic glaucoma with conjunctival injection, corneal epithelial edema and anterior uveitis

71 with 1+ cells, and intraocular pressure of 32 mm Hg. There was also a superior
72 orbital fissure syndrome with V1, 3rd and 6th cranial nerve palsies with motility
73 examination revealing complete ophthalmoplegia in the left eye, associated with
74 complete ptosis and a dilated pupil, consistent with a superior orbital fissure
75 syndrome. No optic neuropathy was present. The posterior segment was normal.
76 The other cranial nerves were not involved and there were no signs of meningitis or
77 encephalopathy. Magnetic resonance imaging revealed changes consistent with old
78 infarcts in the corona radiata, but no abnormalities were seen in the cavernous
79 sinuses, orbits, meninges cranial nerves or orbit. He was started on intravenous
80 acyclovir 500 mg 3 times daily, topical steroids to the left eye, and gabapentin for
81 neuralgia. There was improvement in ophthalmoplegia and ptosis within two weeks
82 of initiation of treatment, and complete resolution by 2 months.

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84 The patient's subsequent clinical course was characterized by pleomorphic patterns
85 of dendriform keratitis (**Table 1**). There were corneal epithelial irregularities,
86 including punctate epithelial erosions, pseudodendriform patterns, heaped-up
87 grayish epithelium, coarse superficial punctate opacities, and geographic patterns of
88 radiating lines, dots and branches (**Figure 1**). Other corneal changes included
89 stromal edema, descemet membrane folds, and pigmented keratic precipitates, due
90 to uveitis. Epithelial recurrences involved paracentral and central lesions.
91 Recurrence in our case was defined as a new dendriform corneal lesion after
92 resolution of previous lesions, with or without anterior chamber inflammation,
93 consistent with the definition used in a previous retrospective case series.³ He had
94 five recurrences of epithelial keratitis with or without anterior uveitis (**Table 1**). Each

95 recurrence was treated with topical steroid with or without topical acyclovir. Each
96 recurrence responded completely to treatment. Unfortunately he developed uveitic
97 glaucoma 4 months after initiation of treatment. There was glaucomatous
98 neuroretinal rim loss with a corresponding nasal step defect on Humphrey
99 perimetry. Subsequently, his intraocular pressure remained consistently ≤ 21 mm Hg
100 on 3 IOP medications, and optic nerve head and visual fields were stable on follow-
101 up.

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104 **3. DISCUSSION**

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

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114 Anterior segment involvement has been documented in cases of HZO. Punctate
115 epithelial keratitis and pseudodendrites are early and transient features.

116 Development of recurrent epithelial lesions in herpes simplex virus keratitis is a well-
117 recognized complication of virus reactivation. Similarly, late complications in our
118 case, i.e. recurrent varicella zoster (VZV) dendriform keratopathy, anterior uveitis,
119 and superior orbital fissure syndrome could all be attributable to viral reactivation.
120 There is evidence for an direct viral infection as a cause for keratopathy, particularly

121 in immunosuppressed hosts, i.e. VZV DNA has been recovered in first-observed
122 and recurrent corneal lesions.^{2,5} Our patient was immunocompetent, and although
123 no microbiologic or serologic investigations for VZV were conducted, there was a
124 distinct complete resolution of each recurrent episode to topical acyclovir, supporting
125 an infective basis. Development of multiple cranial nerve palsies has been
126 postulated to be due to retrograde viral spread from the trigeminal ganglion to other
127 ocular motor nerve nuclei in the brainstem.⁶

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129 Hu et al³ described a spectrum of clinical features associated with the first-observed
130 epithelial lesions in HZO: there were branching forms with blunt ends without true
131 terminal bulbs, and comprising thickened and opaque epithelium. This patient had
132 lacy branching pseudodendrites, some of which assumed a stellate configuration,
133 grayish heaped-up epithelium, and dot-like epithelial erosions (**Figure 1**). However,
134 the recurrent lesions in our case appeared coarser and larger. Our case provides
135 further evidence that the well-described mucous plaque keratitis sequelae of HZO is
136 infective in origin, based on the complete resolution of these lesions to topical
137 acyclovir therapy.

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139 This case may suggest that contributory factors towards multiple recurrences
140 include the use of topical steroids concurrently with topical acyclovir. To date, no
141 study has identified any factor predisposing to recurrence of late dendriform
142 keratopathy. There was a treatment dilemma as our patient also had recurrent
143 anterior uveitis and uveitic glaucoma, necessitating topical steroid therapy. In
144 herpes simplex virus (HSV) concurrent epithelial and stromal keratitis, steroids are

145 typically not started before closure of the epithelial defect, for fear of viral
146 reactivation. One study has concluded that combined steroid and acyclovir is
147 superior to steroid alone in reducing the incidence of rebound inflammations.⁷
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149 This case suggests a potential role of oral acyclovir prophylaxis in preventing
150 epithelial and uveitic recurrences of HZO. There was no stromal keratitis in this
151 patient. Of note, oral acyclovir 400 mg twice a day for 12 months led to an almost
152 50% reduction in the incidence of ocular HSV recurrences only in patients with
153 stromal keratitis, but not for individuals with epithelial keratitis.⁸ Thus, there may be
154 differences between HSV and VZV in their response to long-term acyclovir
155 treatment. Oral acyclovir prophylaxis was discussed with the patient at the 4th month
156 of his clinical course with uveitis, however he did not wish to take long term systemic
157 medication despite being counselled on the potential high risk of recurrences. He
158 eventually agreed after his 5th recurrence, and he was put on oral acyclovir for 21
159 months. He was recurrence-free for 2 years and 9 months. Oral steroids were not
160 considered at any point in the patient's management as the keratouveitis was
161 unilateral and most of the recurrences resolved with topical medication alone.
162 Furthermore, oral steroids are also indicated more so during the acute illness for
163 pain reduction, and for disabling post-herpetic neuralgia.
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165 In conclusion, recurrent HZO late dendriform keratitis is characterized by varied
166 dendriform patterns. Topical acyclovir and topical steroids is effective in acute
167 management of recurrent episodes of keratouveitis. However, there is a potential

168 prophylactic role for long-term systemic acyclovir in HZO, and further longitudinal
 169 cohort data would be important.

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

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Timeline	Morphology of Dendriform Keratopathy	Stromal Keratitis	Anterior Uveitis	Topical Acyclovir 3%	Topical Steroids	Systemic Acyclovir	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	Inferior 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	No	Yes	Yes	G. Dexamethasone 0.1% (Preservative-free)	No	6 weeks

	m lesion involving superior and inferior cornea, PEE				e-free)		
19 months	Coarse SPK in linear configuration	No	No	No	G. Dexamethasone 0.1% (Preservative-free)	Continued on oral acyclovir 400 mg BD prophylaxis from Month 19 to Month 40	1 month
28 months	PEE	No	No	No	No		3 weeks
53 months	Clear cornea	No	No	No	No	No	-

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174 Abbreviations: PEE, Punctate epithelial erosions; BD, Twice a day; TDS, Three

175 times a day; IV, Intravenous

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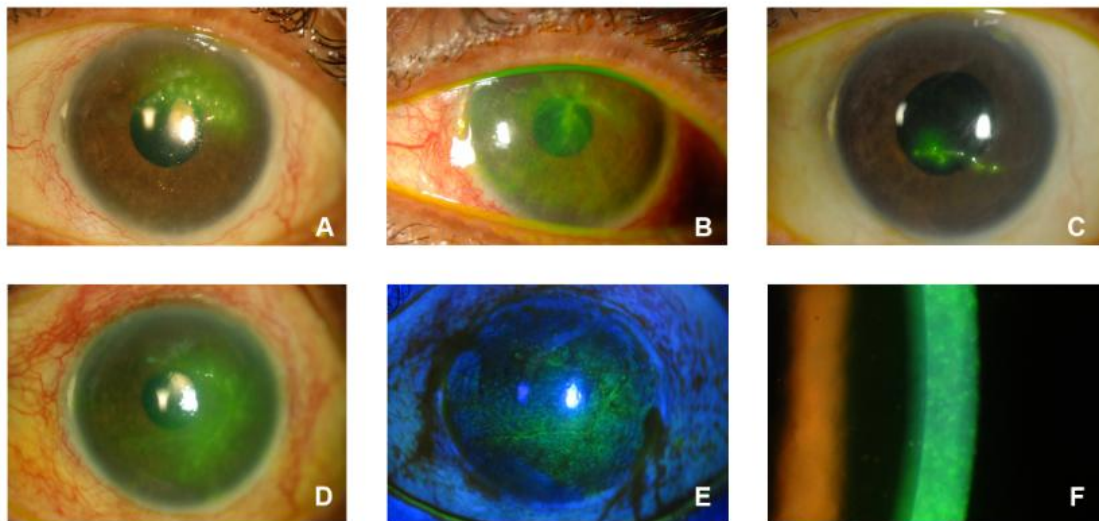
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191 **Figure 1: Anterior Segment Photographs of Recurrent Herpes Zoster Dendriform**
192 **Keratopathy Lesions**

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197 A- Paracentral nodular epithelial lesions with thickened epithelium (4 months)

198 B- Central stellate lesion with multiple, lacy branches (5.5 months)

199 C- Inferior pseudodendriform lesions with peripheral bulbs (9 months)

200 D- Extensive superior and inferior dendriform lesions with punctate epithelial
201 erosions (15 months)

202 E- View with cobalt blue filter of fluorescein-stained dendriform lesions illustrated
203 in D

204 F- Slit view showing coarse punctate epithelial keratitis (19 months)

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206 **ACKNOWLEDGEMENTS**

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208 NIL

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213 **COMPETING INTERESTS**

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215 NIL

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217 **AUTHORS' CONTRIBUTIONS**

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219 “‘Author 1’ wrote, did literature search and extensively drafted the manuscript. ‘Author 2’
220 wrote the first draft of the manuscript, designed the study. ‘Author 3’ critically reviewed the
221 manuscript and co-managed the patient. All authors read and approved the final
222 manuscript.”

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224 **CONSENT (WHERE EVER APPLICABLE)**

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

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229 **ETHICAL APPROVAL (WHERE EVER APPLICABLE)**

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