

Recurrent Kerato-uveitis associated with Herpes Zoster Ophthalmicus Ophthalmoplegia

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

SAMPLE ABSTRACT:

Aims: To describe a protracted course of a patient with keratouveitis with dendriform patterns in a patient.

Study design: Retrospective case report

Place and Duration of Study: Alexandra Hospital, Khooteck Puat Hospital, Singapore. 52 months.

Methodology: A 76-year-old Indian male with HZO developed unilateral complete ophthalmoplegia following HZO.

Results: **Complete resolution of ophthalmoplegia and ptosis was achieved with intravenous acyclovir for a period of two weeks. His clinical course was complicated by nine recurrences of keratouveitis which was treated with topical aciclovir and steroids. The spectrum of corneal epithelial lesions included: (1) lacy branching pseudodendrites without true terminal bulbs (2) thickened grayish epithelium resembling mucous plaque keratitis, and (3) dot-like epithelial erosions in a linear configuration.**

HZO-associated complete ophthalmoplegia and keratouveitis are rare sequelae of HZO. Different corneal dendriform patterns can occur in the same patient with each recurrence of keratitis. Initiation of oral aciclovir 400 mg twice daily for over nine month prevented recurrence of symptoms.

Conclusion: **This case report documents pleomorphic epithelial lesions in a patient with multiple recurrent dendriform keratitis. Oral aciclovir may have a prophylactic role.**

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Keywords: Herpes zoster ophthalmicus; Complete ophthalmoplegia; Dendriform keratitis;

Aciclovir

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

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48 Late dendriform keratitis is a recognized sequelae of herpes zoster ophthalmicus (HZO).
49 Epithelial recurrences are known to occur between 33% to 50% of patients with late
50 dendriform keratitis.^[1,2] However, morphologic characterization of recurrent epithelial lesions,
51 factors associated with recurrences, and optimal treatment strategies are unclear.^[3] In this
52 case report, we describe a patient with HZO who developed recurrent anterior uveitis and
53 late dendriform keratitis characterized by pleomorphic epithelial lesions. Recurrences were
54 successfully managed with topical acyclovir and steroids, and initiation of oral acyclovir
55 therapy resulted in no further recurrences to date.

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57 **2. PRESENTATION OF CASE (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)**

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59 A 76-year-old Indian male presented with a history of left-sided facial and
60 periocular pain and erythema of 1 week duration. He had a history of
61 hypertension, obstructive sleep apnea, a previous episode of lower limb
62 cellulitis. and previously undergone cataract surgery in both the eyes with
63 intraocular lens implantation.

64
65 On his first clinical evaluation he had a papulovesicular rash over the left side
66 of his face and forehead. There were no vesicles at the tip of the nose or at
67 the external auditory meatus. There was also no regional lymphadenopathy.
68 Visual acuity was 20/30 in the right eye and 20/40 in the left eye. There was no
69 relative afferent pupillary defect, and color vision and confrontation visual
70 fields were normal. Extra-ocular motility was full, and the rest of the cranial
71 nerves examination was within normal limits. The applanation intraocular
72 pressure was 37 mm Hg in the left eye and 20 mm Hg in the right eye. Slit-
73 lamp examination of the left eye revealed punctate epithelial erosions of the

74 cornea, with a quiet anterior chamber. Fundus examination was normal. A
75 diagnosis of HZO was made and he was started on oral aciclovir 800 mg five-
76 times a day and topical timolol eye drops.

77

78 Fifteen days after the onset of HZO, the rashes had resolved with crusting.

79 The patient still had persistent left-sided periorbital pain. Evaluation of the left
80 eye showed visual acuity of counting fingers at 2 metres, conjunctival
81 injection, corneal epithelial edema and anterior uveitis with an intraocular
82 pressure of 32 mm Hg. Fundoscopic examination was normal. There was
83 also a superior orbital fissure syndrome with V1, 3rd and 6th cranial nerve
84 palsies with motility examination revealing complete ophthalmoplegia in the
85 left eye, associated with complete ptosis and a dilated pupil. The other cranial
86 nerves were not involved and there were no clinical signs of meningitis or
87 encephalopathy. MRI revealed changes consistent with old infarcts in the
88 corona radiata, but no abnormalities were seen in the cavernous sinuses,
89 orbits, meninges or central nervous system. He was started on intravenous
90 aciclovir at 500 mg thrice-daily, oral gabapentin 300 mg once a day and a 3
91 hourly topical steroids to the left eye. There was improvement in
92 ophthalmoplegia and ptosis within two weeks of initiation of treatment. At 2
93 months follow up, there was a residual abduction deficit and partial ptosis,
94 and the left pupil remained dilated. There was complete resolution of
95 ophthalmoplegia and ptosis.

96 The patient's subsequent clinical course with varying keratitis patterns,
97 treatment and outcome has been outlined in Table –1. He had corneal

98 epithelial irregularities presenting as punctate epithelial erosions,
99 pseudodendriform patterns, dendrites, heaped up epithelium, coarse nodular
100 opacities, nummular keratitis, geographic patterns of radiating lines/dots and
101 branches (Figure 1). He also had corneal stromal edema, descemet membrane
102 folds and endothelial deposits, including pigmented keratic precipitates.
103 Epithelial recurrences involved paracentral and central lesions.
104 Recurrence in our case was defined as a new dendriform corneal lesion after
105 resolution of previous lesions, with or without anterior chamber inflammation
106 consistent with previous reports.^[3] He had nine recurrences and remissions of
107 epithelial/stromal keratitis with or without anterior uveitis. Treatment involved
108 topical steroid eye drops, concurrently with aciclovir eye ointment and
109 lubricant eye drops. He subsequently had persistent raised intraocular
110 pressure with features of glaucomatous optic disc cupping 4 months after
111 initiation of treatment. Fortunately, from 9 months, IOP was consistently ≤ 21
112 mm Hg with IOP medications and stable optic nerve head rim loss and visual
113 fields on follow-up.

114 3. DISCUSSION 115

116
117 To the best of our knowledge, this is the first case of multiple recurrent late
118 dendriform keratitis and uveitis in a patient with HZO complicated by superior
119 orbital fissure syndrome This case demonstrates a spectrum of epithelial
120 lesions over five recurrence episodes. Both the duration of topical acyclovir
121 therapy, and steroid usage for concurrent uveitic recurrences could explain
122 these multiple recurrences. Lastly, this report suggests a possible
123 prophylactic role for oral acyclovir against such recurrences .Anterior

124 segment involvement has been documented in cases of HZO
125 ophthalmoplegia. These clinical features include conjunctivitis, corneal
126 epithelial defects, edema or keratitis and anterior uveitis. Corneal
127 complications of HZO tend to occur in a temporal course related to virus
128 infection and immune reactions, vasculopathy and neuropathy.^[4] Punctate
129 epithelial keratitis and pseudodendrites are early and transient features.
130 Keratouveitis/endotheliitis presents with localized stromal edema, keratic
131 precipitates, anterior chamber cells and flare, and may represent direct viral
132 infection or an immune reaction of the endothelium.^[1] The release of viral
133 antigens in the iris and ciliary body initiates a mild uveitis often accompanied
134 by temporary elevation of the intraocular pressure that may become chronic.
135 ^[1] Similarly, late complications in our case, i.e. recurrent VZV dendriform
136 keratopathy, anterior uveitis, and superior orbital fissure syndrome could all
137 be attributable to viral reactivation. There is evidence for an direct viral
138 infection as a cause for keratopathy, particularly in immunosuppressed hosts,
139 i.e. VZV DNA has been recovered in first-observed and recurrent corneal
140 lesions.^[2,5] Our patient was immunocompetent, and although no
141 microbiologic or serologic investigations for VZV were conducted, there was a
142 distinct complete resolution of each recurrent episode to topical aciclovir,
143 supporting an infective basis. Development of multiple cranial nerve palsies
144 has been postulated to be due to retrograde viral spread from the trigeminal
145 ganglion to other ocular motor nerve nuclei in the brainstem.^[6]

146

147 Hu et al ³ described a spectrum of clinical features associated with the first-
148 observed epithelial lesions in HZO: there were branching forms with blunt
149 ends without true terminal bulbs, and comprising thickened and opaque
150 epithelium. This patient had lacy branching pseudodendrites, some of which
151 assumed a stellate configuration, grayish heaped-up epithelium, and dot-like
152 epithelial erosions (Figure 1). However, the recurrent lesions in our case
153 appeared coarser and larger. Our case provides further evidence that the well-
154 described mucous plaque keratitis sequelae of HZO is infective in origin,
155 based on the complete resolution of these lesions to topical acyclovir therapy.
156
157 The pathogenic mechanism for recurrent keratouveitis could be due to
158 persistence of viral genomes, most likely accompanied by gene expression or
159 slow viral replication.
160 This case may suggest that contributory factors towards multiple recurrences
161 include the use of topical steroids concurrently with topical acyclovir for
162 epithelial recurrences. To date, no study has identified any factor
163 predisposing to recurrence of late dendriform keratopathy. There was a
164 treatment dilemma as our patient also had recurrent anterior uveitis and
165 uveitic glaucoma, necessitating topical steroid therapy. In HSV concurrent
166 epithelial and stromal keratitis, steroids are typically not started before
167 closure of the epithelial defect, for fear of viral reactivation. medications
168 individually or in combination at different stages in the clinical course.
169 Combined steroid and acyclovir is questionably better than steroid alone and
170 causes marginally fewer rebound inflammations.^[7]

171

172 **Oral anti-viral prophylaxis was discussed with the patient in an earlier setting**
 173 **around the 4th month of his presentation with uveitis, however he did not**
 174 **wish to take long term systemic medication despite the risk of recurrence.**
 175 **Finally the oral acyclovir was started at the 19th month and continued beyond**
 176 **28th month. The patient defaulted appointment and had stopped medications**
 177 **when he presented about 24 months later. He was apparently symptom free**
 178 **for about 2 years. Oral steroids were not considered in the patient's**
 179 **management as the keratouveitis was unilateral and most of the episodes of**
 180 **recurrence resolved with topical medication alone.**

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183 **HZO ophthalmoplegia associated hypertensive keratouveitis with varied**
 184 **dendriform patterns can occur. Long term antiviral, anti-inflammatory and**
 185 **antiglaucoma medications are necessary to prevent recurrences. There is a**
 186 **role for both topical aciclovir and steroid drops in managing this condition.**

187 **Table-1 showing the clinical course, management and outcome in our patient**

188

Time line	Symptoms	Presentin g VA	IOP (mmHg)	Signs	Intervention	Outcome	Remarks
0 days	Vesiculopapular rashes on left side of face and forehead	20/40	37	• PEE • Dilated pupil	• Oral aciclovir 800mg 5 times/day • G. timolol 0.5% bd • Artificial lubricants	Resolution of rashes	
15 days	• Drooping of left eyelid • Inability to move the LE	CF-2m	32	• Crusting of rashes • Corneal epithelial edema • Anterior uveitis	• IV aciclovir 500mg tds for 2 weeks • PO Gabapentin 300 mg OM • G. prednisolone	Improvement in Ophthalmoplegia	MRI Brain and anterior visual pathway - Normal

				Complete ophthalmoplegia of the left eye	- acetate 1% qds G. homatropine 2% bd - Artificial lubricants		
2 months	Partially able to open the LE	20/40	24	- Residual abduction deficit - Partial ptosis - Dilated pupil	G. prednisolone acetate 1% qds tapered and stopped over a month		
4 months Fig 1A	- Decreased vision LE of two weeks duration - Pain in LE	CF-1m	31	- PEE - Corneal epithelial edema - Paracentral nodular epithelial lesions with thickened epithelium - Epithelial irregularities - Endothelial pigmentary deposits - Anterior uveitis	G. prednisolone acetate 1% G. timolol 0.5% bd G. brimonidine 0.15% bd G. homatropine 2% bd - Artificial lubricants	Improvement in corneal surface	
5 months	Pain in LE	20/50	24	Pigmented KP	G. timolol 0.5% bd G. brimonidine 0.15% bd G. prednisolone acetate 1% qds tapered and stopped over a month	- Resolution of corneal epithelial irregularities - Anterior uveitis resolution	
5 ½ months Fig 1B	Pain in LE	20/40	30	- A central dendriform lesion with multiple lacy branches - Epithelial irregularities - Endothelial pigmentary deposits - Anterior uveitis	G. dexamethasone (preservative free) qds G. timolol 0.5% bd G. brimonidine 0.15% bd G. dorzolamide 2% tds - Artificial lubricants	Optic disc changes consistent with glaucoma	All eye medications were continued for three months
9 months Fig 1C	Pain in LE	20/40	16	Inferior paracentral dendriform lesions with pseudo peripheral bulbs, associated with some grayish thickened epithelium	G. dexamethasone (preservative free) once at night G. timolol 0.5% bd G. brimonidine 0.15% bd	- Optic disc changes consistent with glaucoma - ERM	- o/c aciclovir 3% 5 times/daily for 1 month were added - Anti

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				• Epithelial irregularities • Anterior uveitis (mild)	• G. dorzolamide 2% tds • Artificial lubricants		glaucoma medications were continued
15 months Fig 1D	• Decreased vision LE of 4 days duration • Pain in LE	20/150	12	• Circinate paracentral dendriform lesion involving superior and inferior cornea with punctate epithelial dot-like erosions • Anterior uveitis	• G. dexamethasone (preservative free) qds • G. timolol 0.5% bd • G. brimonidine 0.15% bd • G. dorzolamide 2% tds • o/c aciclovir 3% 5 times/daily • Artificial lubricants	Reactivation of keratouveitis	VA improved to 20/40 3 months later. o/c aciclovir 3% stopped after 6 weeks
19 months Fig1F	• Decreased vision LE of 6 days duration • Pain in LE	20/150	15	• Coarse nodular SPK	G. dexamethasone (preservative free) ON • G. timolol 0.5% bd • G. brimonidine 0.15% bd • G. dorzolamide 2% tds • o/c aciclovir 3% 5 times/daily • Artificial lubricants	Reactivation of epithelial keratitis	Tab Aciclovir 400mg bd started
28 months	• Pain LE • Tearing LE	20/30	17	• PEE	G. dexamethasone (preservative free) once at night • G. timolol 0.5% bd • G. brimonidine 0.15% bd • G. dorzolamide 2% tds • Artificial lubricants		Tab Aciclovir 400 mg continued
52 month	Blurring of vision LE	20/60	16	-Cornea clear - AC quiet -Posterior capsular opacification -	. dexamethasone (preservative free) once at night • G. timolol 0.5% bd		Patient had stopped T aciclovir., after the last visit about 14 months and had defaulted follow up. As he was

							symptom free.
53 month		20/25		Cornea clear - AC quiet	Artificial lubricants		

Legend:

HZO- Herpes Zoster Ophthalmicus

VA- Snellen Visual acuity

IOP- Intra ocular pressure in mm Hg

LE- Left eye

CF- Counting Fingers

PEE-Punctate epithelial erosions

bd- Twice a day

IV- Intravenous

Tds- thrice daily

PO- Per oral

ON- Once in the night time

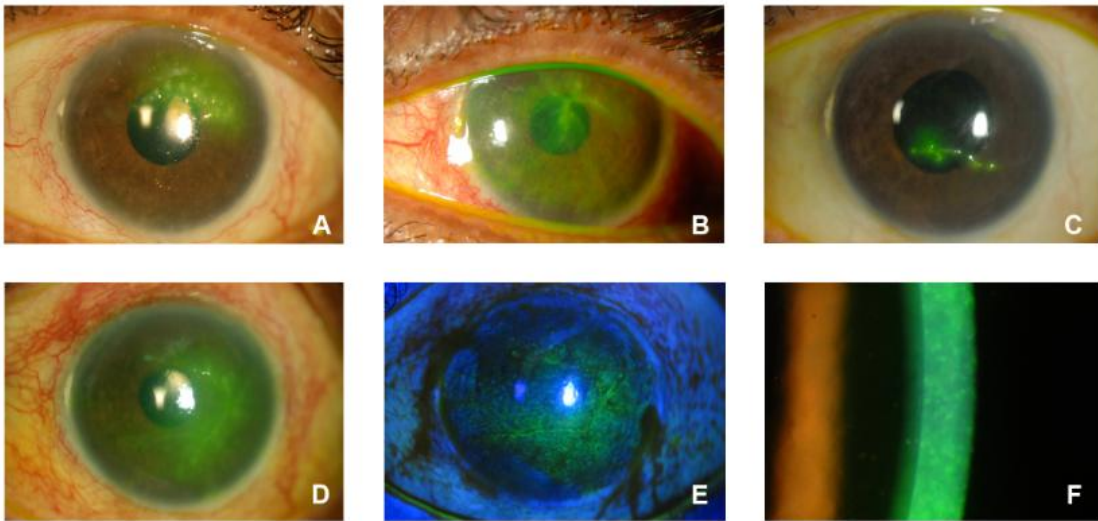
OM- Once in the morning

Qds- four times daily

MRI- Magnetic resonance Imaging

KP- Keratic precipitates

ERM- Epiretinal membrane



Legends for Figure 1

Figure 1: Slit-lamp biomicroscopic photographs of our patient with HZO keratitis patterns with fluorescein staining

A- Paracentral nodular epithelial lesions with thickened epithelium (4th month)

- 212 B- Central multiple, lacy branches (5^{1/2} month)
- 213 C- Inferior pseudodendriform lesions with peripheral bulbs(9th month)
- 214 D- Extensive superior and inferior dendriform lesions with punctate epithelial erosions (15th
- 215 month)
- 216 E- View with cobalt blue filter of fluorescein stained dendriform lesions illustrated in D
- 217 F- Slit view showing coarse punctate epithelial keratitis.(19th month)

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219 **ACKNOWLEDGEMENTS**

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221 NIL.

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226 **COMPETING INTERESTS**

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228 NIL

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230 **AUTHORS' CONTRIBUTIONS**

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232 “ ‘Author 1’ wrote, did literature search and extensively edited the study, and. ‘Author 2’
233 wrote the first draft of the manuscript, designed the study and ‘Author 3’ did critical review of
234 the manuscript and co-managed the patient. All authors read and approved the final
235 manuscript.”

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237 **CONSENT (WHERE EVER APPLICABLE)**

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

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

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244 NA

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246 **REFERENCES**

247

- 248 1. Liesegang TJ. Herpes zoster ophthalmicus natural history, risk factors,
249 clinical presentation, and morbidity. *Ophthalmology*.2008;115:S3-12.
- 250 2. Pavan-Langston D, Yamamoto S, Dunkel EC. Delayed herpes zoster
251 pseudodendrites. Polymerase chain reaction detection of viral DNA
252 and a role for antiviral therapy. *Arch Ophthalmol* 1995;113:1381-1385
- 253 3 Hu AY, Strauss EC, Holland GN, Chan MF, Yu F, Margolis TP. Late
254 Varicella-Zoster Virus Dendritiform Keratitis in Patients With Histories of
255 Herpes Zoster Ophthalmicus. *Am J Ophthalmol*. 2010;149:214-
256 220.e3. Epub 2009
- 257 4 Liesegang TJ. Varicella-zoster virus eye disease. *Cornea*.1999;18:511-
258 31.
- 259 5 Chern KC, Conrad D, Holland GN, et al. Chronic varicella-zoster virus
260 epithelial keratitis in patients with acquired immunodeficiency
261 syndrome. *Arch Ophthalmol* 1998;116:1011-7.

262 6 Sanjay S, Chan EW, Gopal L, Hegde SR, Chang BC. Complete unilateral
263 ophthalmoplegia in herpes zoster ophthalmicus. *J Neuroophthalmol.*
264 2009 ;29:325-37.

265 7 Marsh RJ, Cooper M. Double-masked trial of topical aciclovir and
266 steroids in the treatment of herpes zoster ocular inflammation. *Br J*
267 *Ophthalmol.* 1991;75:542-6.

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