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Case Series

Herpetic keratitis with new characterisations - A unique case series highlighting punched-out ulcer margin with lamellar cleavage

Parthasarathi Roy^{1*}, Sarbaraj Nag¹

¹Dept. of Ophthalmology, Calcutta National Medical College, Kolkata, West Bengal, India



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ABSTRACT

Although HSV keratitis is one of the leading infectious causes of blindness world-wide, its misdiagnosis is not infrequent in clinical practise. We present here six eyes of five cases, all of which were initially misdiagnosed as bacterial / fungal ulcers. All these ulcers had some characteristics in common like, overt/ impending sloughing ulcer with punched out margin and clear-cut lamella planar separation. To the best of our knowledge these characterisations of HSV keratitis were not discussed earlier in literature. Diagnosis rested on clinical findings and response to antiviral therapy. A possible pathophysiology based on anatomical distribution of corneal nerves was discussed. Placement of this distinct group of ulcers in the classification of infective HSK, between dendritic, geographical, punctate ulcers at one end of the spectrum and neurotrophic ulcers at the other, and named as 'neuropathic ulcers' is hereby suggested.

Key Message: Apart from dendritic, geographical, punctate ulcers at one end of the spectrum and neurotrophic ulcers at the other, there seemed to be another distinct group of herpetic ulcers in between. This new group was characterised by sloughing of that area of the cornea, which was innervated by the HSV infected corneal nerve. The process of sloughing might be aggressive or slow and seemed to progress in an orderly fashion. The area of cornea supplied by the affected nerve was separated from normal cornea by a punched-out border of demarcation followed by lamellar cleavage (separation) following the architecture of lamella- planar distribution of the affected corneal nerve. The lamellar separation could be demonstrated by the pooling of fluorescein dye in the cleaved inter lamellar space. Treatment with oral and local Acyclovir established healing.

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1. Introduction

HSV keratitis has an estimated global incidence of roughly 1.5 million, including 40,000 new cases of severe monocular visual impairment or blindness each year.¹ Although HSV keratitis remains the leading infectious cause of corneal ulcer and blindness worldwide,² its misdiagnoses range from 9% to 30% across different studies.^{3,4}

In the foregoing six eyes of five cases, we will demonstrate certain unique characteristics of Herpes simplex keratitis (HSK) which were never been discussed in

literature. We believe these tell-tale signs will help to reduce misdiagnoses of HSK and thus save precious time before initiation of appropriate therapy.

2. Case Reports

2.1. Case 1

A male patient aged 17 years presented in OPD with history of pain, redness, watering, photophobia and dimness of vision in his right eye for 15 days. He also noticed whitening of cornea. He was initially treated by some local eye specialist with antifungal and antibacterial eye-drops

* Corresponding author.

E-mail address: ps_roy2002@yahoo.com (P. Roy).

with no results. There was no history of any systemic illness. On examination right eye- best corrected visual acuity was 6/18 with projection of rays accurate in all quadrants. Severe blepharospasm was present. Slit- lamp examination: Conjunctiva- severe congestion, cornea- an oval shaped 5 mm (vertical) x 4 mm (transverse) vascularised deep infiltrate, with central punched out ulcer of about 3 mm x 3 mm was noted in the inferotemporal quadrant between 6-7 o'clock position in proximity to limbus (Figure 1 a, c). Corneal sensation was grossly diminished (Figure 1 b). The ulcer was fluorescein stain test positive. Anterior chamber - a very aggressive looking cork-screw type infiltrate emanating from endothelium was approaching in the anterior chamber towards lens iris diaphragm (Figure 1 d); no hypopyon. Flare ++, cells++, Left eye was normal. A diagnosis of HSV keratitis right eye was made and patient was put on Acyclovir 3% eye ointment eight times a day, with other adjuvant drugs of corneal ulcer. Adjuvant drugs comprised Homatropine 2% eye drop tid, Timolol maleate 0.5% eye drop bid, Carboxymethyl cellulose eye drop qid, Vitamin C tablet od, and a pain killer for reducing pain. The ulcer healed in 15 days (Figure 1 e), however treatment continued for another 15 days. The final BCVA right eye was 6/9.

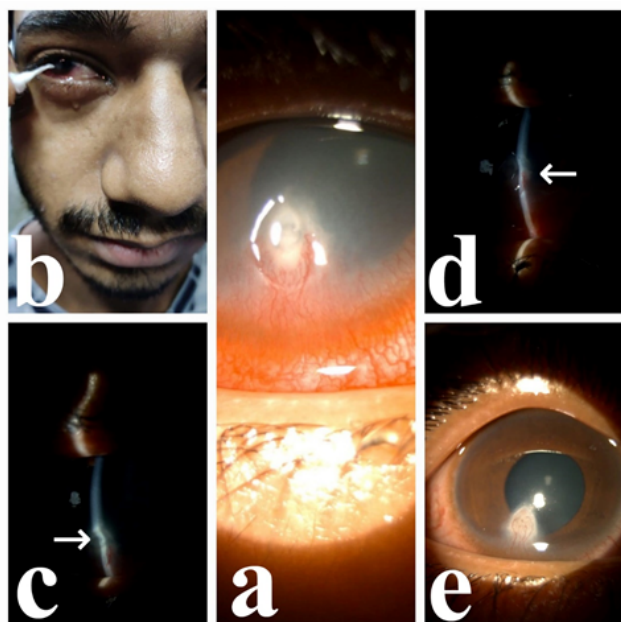


Figure 1: Herpetic keratitis: (Case 1) **a):** Punched-out ulcer, vascularised deep stromal infiltrate and endothelial plaque; **b):** Profound diminution of corneal sensation; **c):** Punched out margin of the ulcer (arrow); **d):** 'Cork screw' endothelial plaque (arrow); **e):** Healed ulcer.

2.2. Case 2

A male patient aged 39 years attended OPD with history of pain, redness, watering, photophobia and dimness of vision in his left eye for 10 days. He also noticed whitening of the cornea during this period. On examination Left Eye: - visual acuity – perception of light +VE, with projection of rays accurate in all quadrants, Lid- severe blepharospasm, Conjunctiva- severe congestion, cornea- a well – circumscribed central stromal infiltrate of about 7 mm x 7 mm. Anterior chamber - no hypopyon. Corneal sensation was grossly diminished. A wisp of cotton could be negotiated from the inferotemporal margin of the ulcer, deep into a lamellar plane as far as the centre of the cornea, part of punched out border clearly stood out over the cotton wisp, and advancing end of cotton wisp was hidden under anterior lamellar flap of the sloughing ulcer. (Figure 2 a, arrow) Right Eye- visual acuity 6/6 unaided, with anterior and posterior segment within normal limits. No h/o diabetes and hypertension. A diagnosis of 'sloughing HSV ulcer' left eye was made and patient was put on Acyclovir 3% eye ointment eight times, with other adjuvant drugs of corneal ulcer. The ulcer healed in two weeks leaving a nebulo-macular corneal opacity, and the medication continued for another two weeks. At the end of four weeks the best corrected visual acuity was 6/24.

2.3. Case 3

A female of 36 years of age attended OPD with complain of pain, redness, watering, photophobia and dimness of vision in her right eye for 28 days. At first, she was diagnosed as 'nebular opacity with fresh fungal infiltrate' 3 weeks back elsewhere and treated with eye drop Natamycin, Moxifloxacin, homatropine, timolol, carboxymethyl cellulose eye drops and Vitamin C tablets. However, her condition deteriorated and she attended our OPD. She had a history of recurrent episodes of redness, pain of her right eye since childhood. On examination: Right Eye BCVA - Counting finger 0.5 metre with PR accurate in all quadrants, conjunctiva congested, an intensely fluorescein positive corneal ulcer in the upper half of the cornea of about 3 mm x 3 mm size with punched out margin and vascularised nebulo-macular opacities in the inferior half were found (Figure 2 b, c). Corneal sensation was diminished. No flare and no cell was found in the anterior chamber. Left Eye BCVA 6/6. A diagnosis of "recurrent viral keratitis with nebulomacular opacities" of right eye was made. Along with existing treatment Acyclovir 3% eye ointment was started eight times a day, and natamycin discontinued. The ulcer healed in five weeks time with this treatment (Figure 2 d) Final visual acuity of the right eye was 6/60 with refraction.

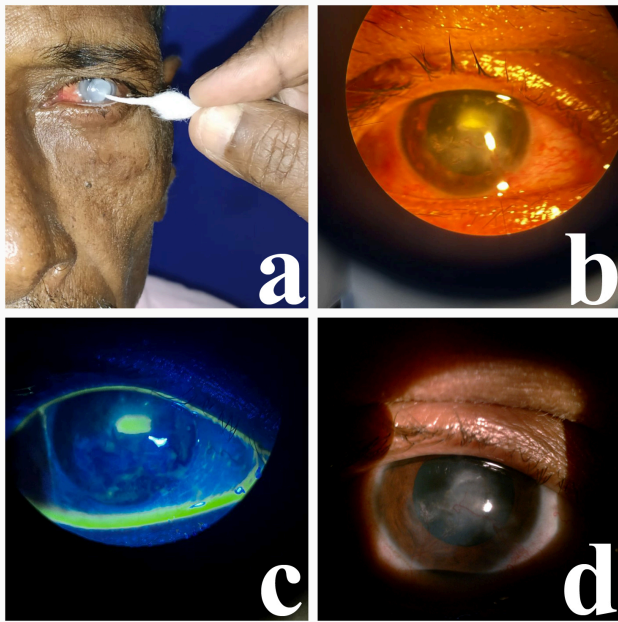


Figure 2: Herpetic Keratitis. (Case 2): **a**): Grossly diminished corneal sensation. A wisp of cotton could be negotiated deep into a lamellar plane (arrow) (see text). (Case 3): **b**): Punched-out lower margin of sloughing in progress; **c**): Pooling of fluorescein dye in cleaved lamellar plane; **d**): Healed ulcer

2.4. Case 4

A 30 years old male attended eye OPD with history of sudden onset dimness of vision both eyes followed by pain, redness and burning sensation since seven days. He was non-diabetic, non- hypertensive. He had a seizure disorder in the past for which he was on antiepileptic medication. There was no history of trauma or surgery. On examination: visual acuity both eyes PL+, PR accurate in all quadrants, central corneal infiltrate both eyes (Right eye: 8 mm X 8 mm & Left Eye - 7 mm X 7mm) with severe blepharospasm, conjunctival and ciliary congestion, and heavy anterior chamber reaction were noted. Ultrasonogram A scan showed chain of low amplitude spikes in both eyes suggestive of endophthalmitis. Therefore a diagnosis of 'bilateral endogenous endophthalmitis progressing to panophthalmitis' was made (Figure 3 a, d). Intravitreal ceftazidime and vancomycin was given in both eyes and vitreous aspirates was sent for culture sensitivity. Blood was also sent for culture and sensitivity. Vitreous showed no growth after 48 hours of incubation. Blood culture showed growth of enterococcus sp. sensitive to Linezolid. As vitreous culture showed no growth of organism and I.V. Linezolid for 7 days only produce some equivocal improvement, we reviewed our diagnosis. Careful examination revealed that corneal sensation was grossly diminished in both eyes and there was progressive peripheral sloughing with clear-cut punched out border in

both eyes (Figure 3 a,b,c,d,e) with inferior descemetocoele in right eye (Figure 3 c). Detailed tests for detection of autoimmune diseases were negative. Herpes Simplex Virus-1 IGG showed high titre (2.95, Reference value: <0.8 Negative, 0.8-1.2 intermediate, >1.2 Positive). Our final diagnosis was bilateral sloughing PUK due to herpes simplex infection. Therefore patient was put on Tablet Acyclovir 400mg thrice a day and topical Acyclovir 3% eye ointment eight times daily. However right eye, which was already in an advanced stage due to descemetocoele, needed therapeutic keratoplasty. The left eye healed leaving a nebulo-macular corneal opacity. Patient didn't follow up after discharge following thirty-two days of hospital stay and final visual acuity of the patient could not be ascertained.

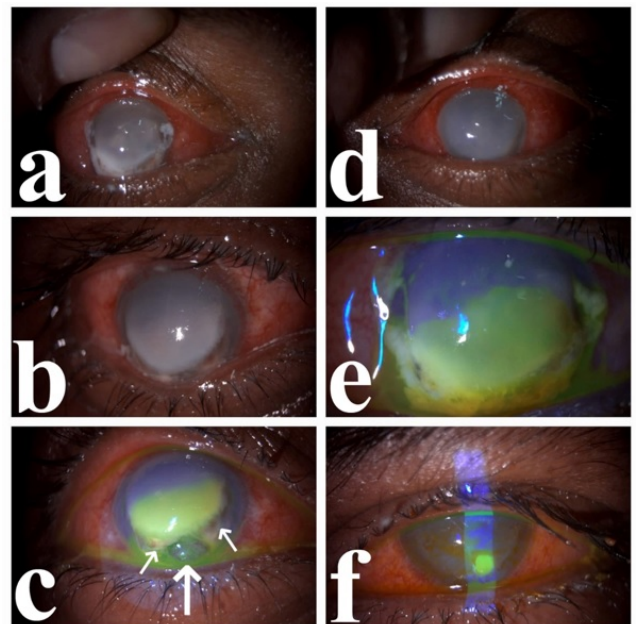


Figure 3: Bilateral HSV-related peripheral ulcerative keratitis (Case 4): Right eye: **a**): Border of separation; **b**): Same as 'a' after two weeks; **c**): Same as b with upper lid retracted: inter-lamellar fluorescein pooling, exposed plane of separation (short arrows), descemetocoele (long arrow) Left eye: **d**): at presentation; **e**): Inter-lamellar fluorescein pooling; **f**): Fluorescein pooling reduced signifying healing

2.5. Case 5

A male patient aged 32 years attended our opd with complain of pain, redness, irritation, watering and diminution of vision in the left eye for eight days. His vision in the left eye was finger counting at one metre with PR accurate in all quadrants. He was wearing an artificial eye in the right side. On examination under slit lamp microscope, conjunctival and circumcorneal ciliary congestion, a fluorescein positive corneal ulcer of about

6mm x 5mm in dimension in the lower half and hypopyon of about 2 mm were found. Corneal sensation was intact. A diagnosis of fungal corneal ulcer of left eye was made and the patient was put on natamycin 5% eye drop, 1 drop one hourly in daytime and two hourly in the night. Adjunct medications like homatropine 2% tid and timolol maleate 0.5% bid were also added to the regimen. On follow-up visit after one week, a conspicuous punched-out margin of the ulcer was noticed (Figure 4 a,b). Corneal sensation was now found to be diminished. We reviewed our clinical diagnosis and stamped it as a viral corneal ulcer. Natamycin eye drop was stopped and Ganciclovir ophthalmic gel 0.15% was started 8 times a day. On next follow up visit, an exudative membrane in the pupillary area was noted. We therefore further reviewed our diagnosis as viral keratouveitis of the left eye and added tablet acyclovir 400 mg tid in the therapeutic regimen. With this regimen, and with sub-conjunctival injection of Atropine to relieve posterior synechia, the keratouveitis healed in two months of therapy (Figure 4 c). Final visual acuity was 6/9 unaided.

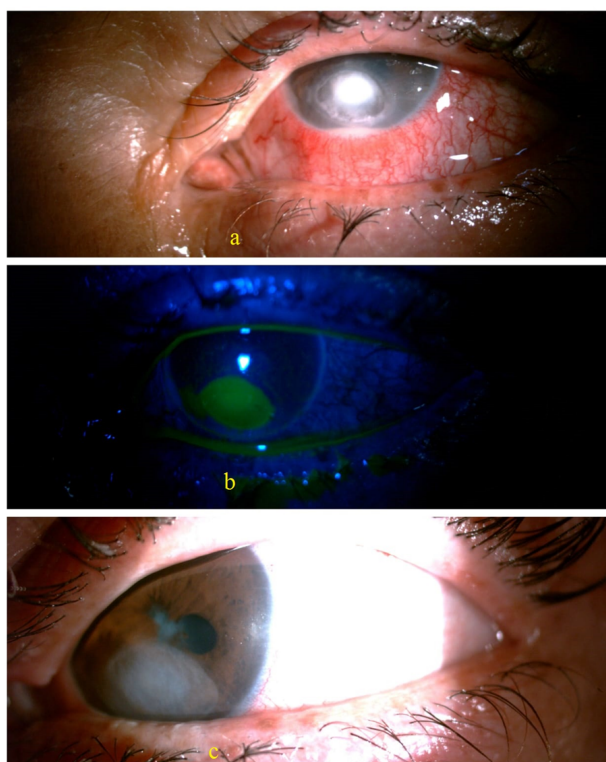


Figure 4: Herpetic Keratitis. (Case 5): **a**): deep gutter-like punched out margin all around; **b**): Fluorescent pooling in cleaved lamellar plane; **c**): healed ulcer

3. Discussion

Herpes simplex virus is the commonest etiological agent of infectious corneal ulcer.² Maximum chance of virus

confirmation in suspected viral etiology is through PCR testing of corneal scrapings and is only 36.66%.⁵ Therefore the diagnosis of viral keratitis essentially depend upon characteristic clinical findings and response to antiviral medication.

The common denominators of these ulcers of six eyes of five cases were progressive sloughing in different stages of development and characterised by 1. diminished corneal sensation 2. Punched-out margin of the ulcer, 3. Lamellar separation 4. Rapid healing with antiviral medication.

The bottomline of diagnosis of all six eyes were finding of diminished corneal sensation. However while the diagnoses of the cases 1, 2 and 3 were clinched at the time of presentation, in case 4 it was delayed because the overwhelmingly masquerading feature distracted our attention so that testing of corneal sensation was not thought of initially. Hamra P et al⁶ found reduction of corneal sensation in 81% of diagnosed HSK. They demonstrated by in vivo confocal microscopy that the loss of corneal sensation in HSK correlated strongly with profound diminishment of the sub-basal nerve plexus after herpes simplex virus (HSV) infection. Therefore we suggest inclusion of corneal sensation test for work up of all cases presenting with corneal sign.

In all the six eyes the ulcers were characterized conspicuously by punched out margins. The cornea is the most densely innervated tissue in the body, 40 times more than the tooth pulp and 400 times more than skin.⁷ An ulcer caused by affection of nerve supply (neuropathic ulcers) is characterized by punched out margin.⁸ Therefore a corneal ulcer having a punched out margin is likely to be a herpetic ulcer.

The progress of sloughing of cornea in case 2,3, 4 and 5 seemed to take place in an orderly fashion. First the area of cornea supplied by affected nerve was separated from normal cornea by a punched out border of demarcation (Figure 1 a, Figure 2 a, b, Figure 3 a, d, Figure 4 a) followed by cleavage (separation) at one of the lamellar planes (Figure 1 c, Figure 2 a, c, Figure 3 c, e, Figure 4 b). Al-Aqaba MA et al⁹ showed that corneal nerves were distributed in lamellar planes. Therefore the probable explanation of lamellar cleavage in the cases of 1,2,3,4 and 5 was planar (lamellar) distribution of one of the affected anterior stromal / posterior stromal nerves respectively, depending upon the depth of cleavage plane. Sharma A et al. showed that non-healing lamellar cleavage in laser in situ keratomileusis could be diagnosed by pooling of fluorescein dye in the inter lamellar plane in the absence of epithelial defect.¹⁰ In case 3 (Figure 2 c) in case 4 (Figure 3 c, e) and case 5 (Figure 4 b) fluorescein dye was seen to be pooled in the cleaved lamellar plane, in the absence of any obvious epithelial defect to explain for such staining. In case 2 lamellar separation was physically demonstrable by a cotton wisp (Figure 2 a.) and in case 1 the lamellar

flap sloughed out completely exposing the floor of the ulcer (Figure 1 a.).

In case 1, under slit lamp biomicroscopy, an endothelial plaque was found to be progressing very aggressively towards lens-iris diaphragm in a cork-screw fashion (Figure 1 d. arrow). To the best of our knowledge, this type of cork-screw plaque was never been described in literature. Endothelial plaque can be found in bacterial, fungal and viral keratitis.¹¹ Therefore a cork-screw endothelial plaque in slit lamp examination may be a differentiating feature of HSV keratitis from bacterial and fungal keratitis.

The case 4 initially masqueraded as bilateral endogenous panophthalmitis because of its presentation and revelation of 'chain of low reflective spikes' in vitreous on A-Scan ultrasonography (USG). Spillage of inflammatory cells from anterior chamber to vitreous cavity causing sterile vitritis might be a probable explanation for such USG finding.¹² Like other four cases the diagnosis of this case was also clinched by diminishment of corneal sensitivity, aided by characteristic punched out lamellar sloughing (Figure 3 c, e), high level of detected HSV IgG antibody (although not specific) and healing (left eye) accomplished by antiviral therapy and characterized by diminished area of interlamellar fluorescein pooling¹⁰ (Figure 3 f). At the same time the detailed tests for detection of autoimmune diseases were negative, thus autoimmune aetiology was ruled out. To the best of our knowledge, there are only two other reports of bilateral HSV-related peripheral ulcerative keratitis (PUK) in literature and this was only the third report and therefore posed diagnostic dilemma.^{13,14}

A pertinent question may arise as to how these cases are different from neurotrophic keratitis, so as to qualify them for classification under a separate heading. Suffice it to say, apart from a distinct pathophysiology of causation as described, all the ulcers (excepting one in case 4, where keratoplasty had to be done because of advanced stage presentation) healed rapidly in 3-6 weeks time (Figure 1 e, Figure 2 d, Figure 3 f, Figure 4 c) with local application of Acyclovir 3%/ Ganciclovir 0.15% eye ointment +/- oral Acyclovir tablet. In case of neurotrophic ulcers on the other hand, establishment of healing is extremely difficult.

4. Source of Funding

None.

5. Conflict of Interest

None.

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Author biography

Parthasarathi Roy, Associate Professor

Sarbaraj Nag, Junior Resident

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