

Commentary: Diagnostic markers for suspected herpes simplex virus keratitis – A bridge too far

One of the common indications for optical penetrating keratoplasty (PK) in India is a postinfectious corneal scar. The primary infection can be due to bacteria, fungi, protozoa, or viruses like the herpes simplex virus type-1 (HSV-1). While a healed bacterial or fungal keratitis does not bear any future consequences on the graft, HSV-1 keratitis can recur after PK. Such recurrences in many instances may lead to graft opacity.

Although recurrences can be mitigated with the use of oral acyclovir,^[1] the surgeon has to either confirm or strongly suspect a viral etiology to advise acyclovir prophylaxis. In most cases, it is not possible to infer the causative organism from the morphological appearance of the scar.

HSV-1 can be present in the cornea in three possible ways.^[2] Firstly, the virus can reach the cornea via the anterograde axonal flow from reactivation in the trigeminal ganglion. Secondly, the virus is already present in the cornea and actively replicating but the number of progenies produced is in such small numbers that there is no clinical disease. Lastly, the virus may be in a latent stage in the cornea. During

latency, the viral genome does not replicate or produce any proteins and is noninfectious. From time to time the virus reactivates from the latent stage and causes disease. During latency, the virus expresses messenger ribonucleic acid (RNA) known as latency-associated transcripts (LATs) which are detectable in the cornea.^[3] Identification of HSV-1 DNA, surface antigens (proteins), and LATs in the cornea prove the presence of the virus. These are useful diagnostic markers in atypical clinical presentations or the postinfectious stage when the detection of LATs may correctly identify the cause of the innocuous scar.

In this issue of the Indian Journal of Ophthalmology, researchers from a premier eye institute in north India investigates different molecular methods to identify the presence of HSV-1 in the cornea.^[4] The authors use conventional and real-time polymerase chain reaction (PCR) to detect HSV-1 DNA and LAT gene, respectively, and immunohistochemistry to identify the surface antigen in corneal buttons obtained during PK. They included 30 patients with suspected HSV-1 keratitis and 30 controls with the noninfectious disease. The description of the laboratory techniques in their method-section assures us that due diligence and care was taken to process the samples. HSV-1 DNA, LAT, and HSV-1 antigen were detected in 2/30 (6.7%), 7/30 (23%), and 9/30 (30%) corneal buttons, respectively, of patients with suspected HSV-1 keratitis. All the buttons from the control patients were negative. However, because of the low positivity rate, the authors concede at the end that further studies are required with larger samples to substantiate their findings.

The detection of messenger RNAs (LATs) is fairly challenging, and the findings can be easily marred by quantity and quality of RNA, extraction procedures, RNA integrity, and contamination.^[5] There is also the possibility that the expression of LAT in the cornea is not as abundant or global as it is in the trigeminal ganglion which is the primary site of latency.^[2] In a study on infected rabbits, O'Brien *et al.* were able to detect LAT and HSV-1 DNA in all the samples from the trigeminal ganglion.^[6] In contrast, only 57% of the corneal buttons were positive for HSV-1 and none were positive for LATs. In the present study,^[4] the selection of cases, the interval between the primary infection and surgery, and the use of oral acyclovir are some of the factors that may be responsible for the low positivity rate of HSV-1 DNA and surface antigen as compared to other studies.^[7]

The current role of molecular markers of HSV-1 infection is dependent on the sensitivity of the detection methods like PCR, which the findings of the present study^[4] seem to affirm. HSV-1 LAT encodes many single-stranded microRNAs, which are more long-lived and resistant to degradation than messenger RNAs.^[2] They are easier to quantify in blood, body fluids, and tissue by microarray profiling, real-time PCR, or next-generation sequencing technologies,^[8] thus opening a new and exciting vista of diagnostic capabilities. In India, viral laboratories are few and far between thus viral-based laboratory infections do not feature in the routine care of ocular infections. However, the COVID-19 pandemic has led the health ministry to establish numerous laboratories with PCR facilities across the country, which may be used to detect other viruses like HSV-1 after the pandemic has lessened. Till then most of us need to rely on a sound preoperative clinical examination and send all the corneal buttons for routine histology following

PK. The presence of lymphocytes, multinucleated giant cells, or deep stromal vessels in the corneal sections can indicate the possibility of a viral infection.^[4] Currently, the quest for an easy diagnostic biomarker for HSV-1 keratitis finds an echo in the old Persian proverb “*hanuz dilli door ast*,” but the future can only be promising.

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| Quick Response Code: | Website: www.ijo.in |
|  | DOI: 10.4103/ijo.IJO_3220_20 |
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Cite this article as: Chatterjee S. Commentary: Diagnostic markers for suspected herpes simplex virus keratitis – A bridge too far. *Indian J Ophthalmol* 2021;69:858-9.