Distinguishing infectious versus noninfectious keratitis

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For the purpose of this symposium, the term "keratitis" implies suppurative nonviral and viral keratitis. Corneal ulcers have been described in ancient literature. But even today, despite the availability of a wide range of newer antimicrobials and new diagnostic techniques, infectious keratitis continues to pose a diagnostic and therapeutic challenge. This article focuses on the key diagnostic clinical features of the most common organisms causing infectious keratitis - bacteria, fungi, viruses, nocardia and acanthamoeba - in India. While the clinical features in some cases are fairly straightforward, most cases challenge the clinician. We describe the salient clinical features which can help arrive at a diagnosis to begin appropriate treatment immediately, prior to the laboratory report.

For the purpose of this symposium, the term "keratitis" implies suppurative nonviral and viral keratitis. In general, keratitis could be infectious and noninfectious. Differentiating between them is crucial in managing both. Careful clinical examination, aided by laboratory investigations, could help in correct diagnosis and proper management.

Even though both conditions may involve all age groups, infectious keratitis occurs more frequently in children and adults. To describe precisely the ocular features of these conditions, the clinician must be well trained in slit-lamp biomicroscopy. Other magnifiers like loupes and spectacles may not reveal the depth of the lesion and other associated clinical signs.

Infectious and noninfectious keratitis may overlap each other. Noninfectious keratitis may become infectious by pathogenic or nonpathogenic microbes and may result in sight-threatening complications. Infectious keratitis could also be suppurative and nonsuppurative. Suppurative keratitis is frequently caused by bacteria and fungi. Nonsuppurative infectious keratitis could be viral, spirochaetal, parasitic or immune-related stromal necrosis.

Infectious nonsuppurative keratitis

Frequently seen a few decades ago, it is rarely seen now (e.g., interstitial keratitis due to tuberculosis, leprosy and syphilis). Often they are insidious, chronic and bilateral. There may be obvious associated signs and symptoms of systemic disease. Diagnosis is often clinical, but the laboratory investigations to rule out or confirm tuberculosis, leprosy and syphilis may provide more information to clinch the diagnosis.

The causative agents of infectious keratitis frequently
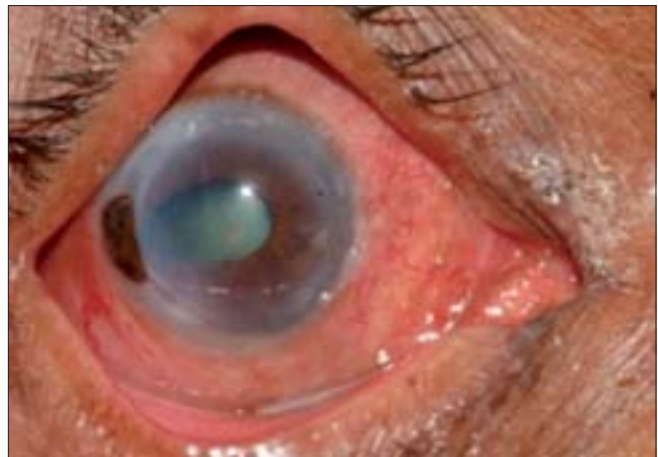
isolated in India are:[1]
1. Bacteria: Gram-positive cocci and Gram-negative bacilli
2. Fungi: Filamentous fungi
3. Viral: Herpes simplex virus
4. Parasite: *Acanthamoeba* species

Non-infectious keratitis

The more common entities of noninfectious keratitis are:[2]
1. Peripheral ulcerative keratitis (PUK) due to auto-immune diseases
2. Phlyctenular keratitis
3. Vernal ulcer or shield ulcer
4. Staphylococcal marginal keratitis
5. Contact lens-related sterile infiltrates
6. Meta herpetic ulcer

PUK [Fig. 1] is rare and diagnosis is often by exclusion. Mooren ulcer, senile marginal degeneration, sclerokeratitis and peripheral corneal melt of rheumatoid origin are some of the few to think about, when the clinician encounters a nonhealing peripheral corneal ulcer. All these are progressive with remissions and relapses. Confirmation of diagnosis

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Figure 1: Mooren ulcer with perforation

may warrant a battery of immunological and bio-chemical investigations like IgM rheumatoid factor, c-ANCA, p-ANCA, circulating antibodies, such as ANA, anti-DNA and anti-SM; which could narrow down the spectrum of etiology.

Vernal keratitis or vernal ulcer is not uncommon. The diagnosis is confirmed by the presence of papillae on the tarsal conjunctiva of the upper lid and Tranta's dots at limbus or pigmentation involving bulbar conjunctiva. It is mostly seen in children and adolescents with the classic symptom of itching. Vernal ulcer is usually unilateral and involves the superior 1/3rd of the cornea. In a few patients, it may lead to plaque formation and the shield ulcer is graded according to the density of the plaque[3] [Fig. 2].

Staphylococcal marginal keratitis is mostly bilateral, involves the lower half of cornea, adjacent to the limbus, having a clear zone of cornea between the lesion and limbus [Fig. 3]. Being uniform in size, discrete and horizontally oval, there may be an oval or round scar due to previous attacks. Most of these patients may have associated blepharitis, meibomitis and rarely acne rosacea.[4]

Phlyctenular keratitis is often noticed in children with a history of recurrent attacks; lesion may show superficial vascularization like pannus or leash of vessels with scarring due to previous attacks. Even though tuberculosis etiology was
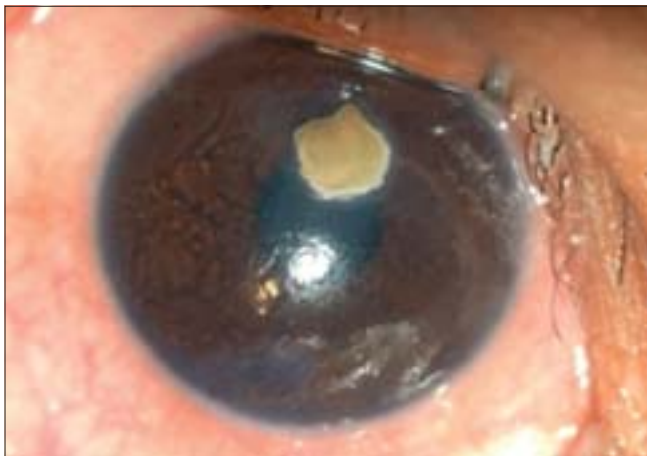
attributed often, other micro-organisms like *staphylococcus* and *candida* can also cause similar lesions.[2] Phlyctenular keratitis represents type IV hypersensitivity response.

Differentiating PUK from other infectious peripheral corneal lesions is mostly based on clinical diagnosis. Mooren ulcer will have a typical lesion in the interpalpebral area, peripheral gutter with edematous or necrotic over-hanging edges [Fig. 4]. Sclera is not involved, which aids in differentiating from rheumatoid and other autoimmune diseases. In 35-40% of patients, Mooren ulcer is bilateral and the reported risk factors are corneal surgery, corneal trauma and hookworm infestation. Natural evolution of Mooren ulcer could be either perforation or conjunctivilization of Descemet's bed resulting in blindness. Mooren ulcer could occur in any sex and age group.[5]

Clinical Diagnosis of Microbial and Viral Keratitis

Why is the clinical diagnosis of infectious keratitis crucial? Even well-established laboratories can grow up to 60-70% of ocular pathogens from the material sent for culture.[6] So, the management of rest of 30-40% of patients with corneal ulcer solely depends on clinical diagnosis, a reality we have to accept even today. Infectious keratitis developing after LASIK poses a problem to make clinical diagnosis due to the level of the lesion and steroid use. Clinicians should be aware of the commonly reported microbes from these patients (e.g., *Nocardia*, *mycobacteriae* and filamentous fungi).[7] The clinical diagnosis of microbial keratitis often relies on a thorough history, especially history of infectious exposure, epidemiological trends and the morphological features of corneal inflammation. Ophthalmologists use clinical clues to recognize ocular surface infection. Some distinctive, though not pathognomonic, signs unique to the causative organism may help to differentiate bacterial, fungal and amoebic pathogens of the cornea.[8]

Bacterial keratitis

All over the world, bacterial keratitis is more common than fungal keratitis, but this does not hold true for India and other tropical countries.[9] In our country, the following risk factors have been identified as leading to corneal ulcer: trauma, xerophthalmia, measles, malnutrition, diarrhea, ocular surface problem, eyelid abnormalities and rarely contact lenses. Trauma to the cornea accounts for 60-68% of cases developing corneal ulcer.[10]
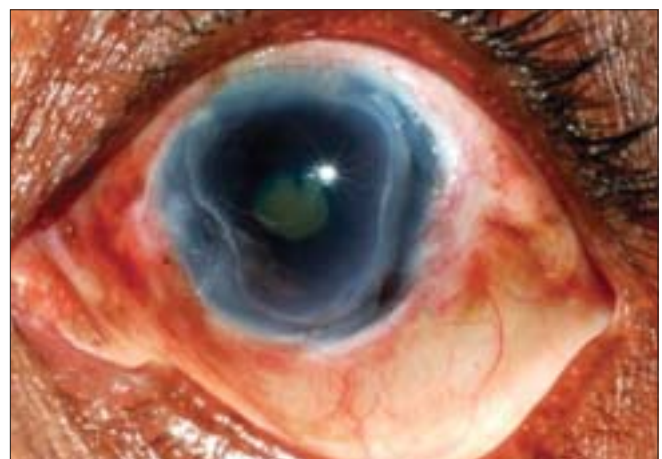

Figure 2: Shield ulcer with plaque

Figure 3: Marginal keratitis

Figure 4: Mooren ulcer

The clinical picture may vary especially when the ulcers have been previously treated. However, a few classical clinical descriptions are useful. For example, Gram-positive organisms tend to produce discrete, small abscess-like lesions and Gram-negative bacteria are more likely to cause diffuse, rapidly spreading necrotic lesions. Watering, pain and vision loss are more severe in rapidly spreading bacterial ulcer caused by *Pseudomonas* and *Streptococcus pneumoniae* species. Indolent ulcers due to *Moraxella* and *Staphylococcus spp.* may be quiet and less symptomatic. Marked lid edema and conjunctival chemosis and purulent exudate are commonly associated with Gram-negative organisms, especially gonococcal infection. Hemorrhagic hypopyon is attributed to either pneumococcal or HSV keratitis. If there is purulent or mucopurulent discharge from lacrimal sac, the keratitis could be due to *Pneumococcus* in 90% of cases[1] [Fig. 5]. Gonococcal ulcer was common in Indian infants but due to improved antenatal and postnatal care, we rarely see this ulcer nowadays.[1]

Among the causative organisms for infectious keratitis, *Nocardia* is uncommon. Trauma with organic matter or dry soil is found to be the major predisposing factor. Typically, the ulcer runs a slow and protracted course. The lesion appears as a cracked windshield or resembling a group of pinhead-size yellowish white infiltrates arranged in a wreath-like fashion which is considered as the classic clinical picture[11] [Fig. 6]. The
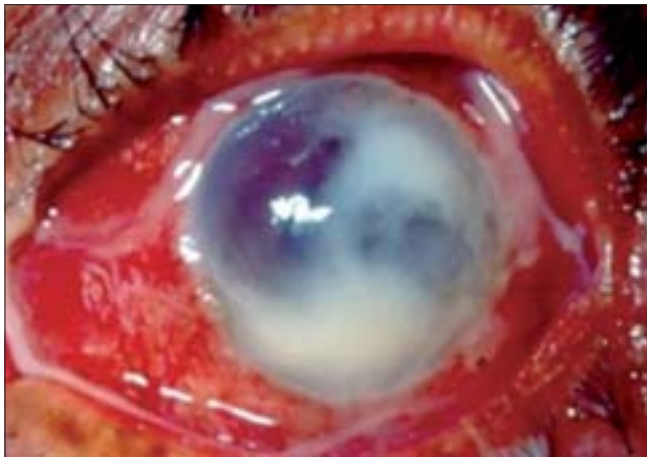
Figure 5: Bacterial ulcer (Pneumococcal)
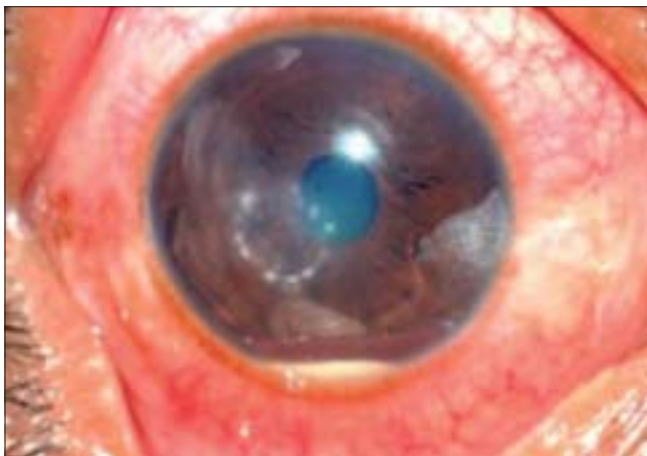
Figure 6: Nocardial keratitis

ulcer remains superficial and may have associated hypopyon. The ulcer does not respond to conventional treatment.

Viral keratitis
HSV
Even though Herpes simplex involves all the layers of cornea, we will limit the discussion to epithelial keratitis only.

HSV causes a spectrum of ocular diseases, but most prominent among them are epithelial and stromal keratitis. Recurrence in the same eye is the hallmark of this common viral infection involving the human cornea.

Epithelial keratitis
Symptoms include photophobia/blurred vision, irritation/pain and a thin watery discharge occasionally associated with cold sores around the lips and nose or genital sores.[12,13] Corneal vesicles in the epithelium are one of the first manifestations of acute HSV infection, which manifest as a fine punctate keratitis or stellate whitish opaque plaques that coalesce into dendritic lesions over 24 h.[13,14] Eruptions of the corneal epithelium due to HSV are characteristically thin, branching dendritic ulcerations, wider, branching dendrogeographic ulcers or map-shaped geographic lesions. The edges of the ulcer become slightly raised due to the presence of edematous epithelial cells.[13] Corneal sensation may be temporarily reduced or absent in 60% of affected patients. Stromal reaction is usually absent or mild and confined to the anterior layers. Most dendritic ulcers will heal spontaneously within 2 weeks. Trophic or metaherpetic ulceration appears as an ovoid lesion which runs a protracted course. The edges are rolled and gray in appearance and do not stain well with rose bengal. The base of the ulcer will stain with fluorescein or rose bengal. The defect may persist for weeks or months carrying with it a risk of melting and perforation. This entity should be thought of when we manage a case of nonhealing corneal ulcer. Sometimes, it is very difficult to differentiate from suppurative keratitis of nonviral origin [Fig. 7]. Presence of old scar or vascularization may help in arriving at a correct diagnosis. History of recurrent attacks also helps.

HZO
Fifty to 72% of patients with periocular zoster will have ocular involvement. The frontal branch of the trigeminal nerve is by far the most frequently involved nerve.[13] Involvement of the nasociliary branch can often herald ophthalmic involvement
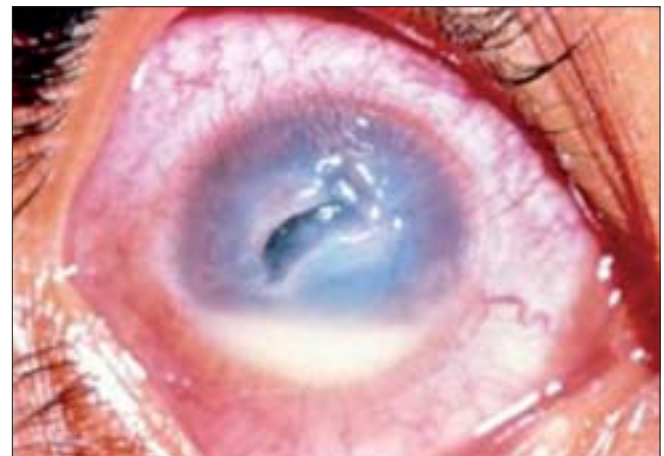
Figure 7: Neurotrophic sterile ulcer

due to its innervation to the eye. The classic Hutchinson's sign (eruptions on the side of the tip of the nose) is evidence of nasociliary involvement and has 85% reliability that the eye will be involved.[13] Herpes zoster begins with a prodrome of severe one-sided headache, malaise, fever and chills, followed by erythema and papules in 2 or 3 days. Occasionally, zoster may develop without vesicles and rarely can affect both sides of the ophthalmic division.[2] Previous attack of chickenpox may be present. When a young patient gets zoster, one should always rule out HIV infection or other immune-compromised diseases.

Fungal keratitis

This is more prevalent in tropical countries and frequently affects young rural men engaged in agriculture and other rural population. The incidence ranges from 35 to 50% in India.[15] Keratomycoses most often picks up healthy cornea exposed due to minor abrasions. Chronic ocular surface problem, steroid use, immunocompromised host, diabetics and contact lens wearers may rarely get fungal ulcer. In 2006, an epidemic of *fusarium* keratitis was reported following the use of contaminated contact lens cleaner.[16] In India, *aspergillus* and *fusarium* species are frequently isolated as causative agents.[15]

Clinical features

Classically, fungal ulcer has been described to commence insidiously and run an indolent course. General features include a thickened epithelium, linear infiltrates often associated with satellite lesions, the presence of an endothelial plaque and posterior corneal abscess, an immune ring infiltrate, a cheesy hypopyon (sometimes hemorrhagic) noted to often wax and wane, and fibrinoid aqueous reaction. The ulcers often appear dry, but most often it is not true. The ulcer base has a raised, wet, soft and creamy grayish-white or yellowish-white infiltrate without mucus or exudates. In case of pigmented fungi, the surface appears dry, tough and leathery [Fig. 8]. In the early stages, a dendritic pattern may be seen which is often misdiagnosed as HSV keratitis[1] [Fig. 9]. Absence of lid edema, minimal conjunctival injection and feathery borders in a healthy adult from rural agrarian population with a recent injury to the cornea with organic matter should strongly favor a diagnosis of fungal ulcer, unless otherwise proved.[15]

Acanthamoeba keratitis

Acanthamoeba keratitis is a painful, sight-threatening and difficult-to-treat corneal infection caused by the parasite *acanthamoeba*.

Acanthamoebae are ubiquitous in nature. At least eight pathogenic *acanthamoeba* subtypes cause keratitis. The first case of keratitis in humans was identified in 1973 in an American farmer with ocular trauma.

The incidence of acanthamoeba keratitis is about 1% among culture-positive infectious keratitis in India.[17] In Europe and the United States, the incidence among contact lens wearers is 1.65 to 2.01 per million contact lens wearers per year by epidemiologic estimation.[18] In India, contact lens wearing is rarely associated with acanthamoeba keratitis.[19]

Clinical features

Suspicion is paramount. It runs a chronic course and diagnosis is often made several weeks after the onset with a poor response
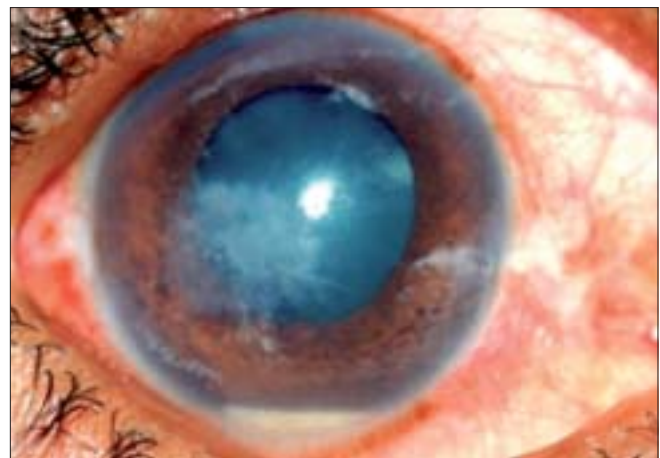

Figure 8: Pigmented fungal ulcer

Figure 9: Early fungal keratitis

Figure 10: Acanthamoeba keratitis

to conventional treatment regimen for an infectious keratitis. It is often misdiagnosed as HSV keratitis, fungal infection or topical anesthetic abuse. Even though pain out of proportion has been described as a prominent symptom by many, it is of the same severity as reported by patients having other types

of keratitis.[20] The disease is usually unilateral, but rarely may be bilateral in contact lens wearers.

The corneal epithelium appears sick, edematous, loose and stroma may be hazy; and sometimes mimics an epithelial keratopathy. Radial perineuritis, one of the early clinical signs, is not a, common feature in noncontact lens wearers.[21] Hypopyon is common. In well-established cases, the dense stromal ring infiltrate at mid-periphery of the cornea, sparing the pupillary area is considered as the diagnostic clinical sign of acanthamoeba keratitis [Fig. 10]. Associated scleral involvement near the limbus could be seen in inappropriately treated cases. Co-infection with bacteria and fungi is not uncommon and is reported as 2-3% in India.[22]

Rare form of suppurative keratitis caused by atypical *mycobacteriae* presents with a deep corneal or plaque-like lesion on the endothelium.

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