Atypical infectious keratitis – a rising scourge

C orneas may be infected by a myriad of pathogens, and in temperate countries such as New Zealand, bacterial infections account for the majority of cases of infectious keratitis. All forms of infectious keratitis have one thing in common – their potential to cause devastating visual loss.

Although relatively uncommon, corneal infections with atypical microbial pathogens (eg. Acanthamoeba, fungal, microsporida, non-tuberculous mycobacteria) are notoriously difficult to diagnose and treat, often resulting in poor visual outcomes.

The past decade has seen a rise in the incidence of atypical infectious keratitis. An outbreak of Fusarium keratitis was described in Singapore in 2005 and was linked to the use of ReNu with MoistureLoc. In 2006, an increase in the incidence of Acanthamoeba keratitis was linked to the use of ADO Complete MoisturePlus. Although product recalls led to a dramatic drop in cases of Fusarium keratitis, the incidence of Acanthamoeba keratitis continues to rise, the cause of which remains uncertain. Indeed, recent data from Greenlane Clinical Centre indicates that the number of cases of Acanthamoeba keratitis presenting annually has doubled in the period 2009-2016 compared to 2003-2009.

Risk factors

Taking a detailed history is crucial when it comes to raising suspicion of an atypical corneal infection. The vast majority of cases of Acanthamoeba keratitis occur in contact lens wearers and is typically associated with swimming, using hot pools/hot tubs or showering with contact lenses in situ. Risk factors also include washing contact lenses in tap water, particularly if sourced from a water tank. A major red flag for fungal infection is trauma involving vegetable matter. Other risk factors include recent travel to a tropical country, chronic ocular surface disease or systemic immune deficiency, and poor contact lens hygiene. Non-tuberculous mycobacterial corneal infections are rare and are usually preceded by a surgical intervention (most commonly LASIK), or corneal trauma.

Up until 2003, microsporidial keratitis was primarily observed in immunocompromised individuals. There was subsequently an increase in reported cases of microsporidia keratitis in immunocompetent individuals in South East Asia. Risk factors include contact lens wear and trauma with exposure to contaminated water or soil.

Diagnosis

Clinical signs alone are usually unreliable in distinguishing the causative organism. In the case of atypical corneal infections, this is attributed to the great variability in clinical presentation. Studies report that over 90% of cases of Acanthamoeba keratitis are initially misdiagnosed as viral, fungal or bacterial keratitis. Corneal epitheliopathy (fig 1a) occurs early in the course of the disease and may have a dendritiform appearance similar to that observed in herpetic keratitis. Subepithelial infiltrates may mimic adenoviral keratitis. Other presentations include ring shaped or focal Stromal infiltrates and corneal melt or perforation. The presence of subepithelial edema is virtually pathognomonic for Acanthamoeba keratitis, as it occurs rarely in other keratitides, but this sign is also uncommon in acanthamoeba and is usually only observed early in the course of the disease.

The stromal keratitis caused by fungal infection (fig 1b) usually resembles bacterial keratitis. Features that are thought to aid in distinguishing fungal keratitis include stromal infiltrates with feathery edges, and satellite stromal infiltrates. In some cases, the overlying epithelium may remain intact despite extensive stromal involvement.

In non-tuberculous mycobacterium keratitis, the infiltrates have may have an unusual, focial, waxy or “cracked windshield” appearance and may develop satellite lesions or a ring infiltrate.

Microsporidial keratitis often mimics herpetic keratitis, presenting with multifocal epitheliopathy, or stromal infiltrates (fig 1c) with surrounding corneal edema and keratic precipitates.

For patients who are on empirical treatment for presumed bacterial keratitis, if there is not at least some sign of improvement within the first four to seven days, viral or atypical causes of the keratitis should be actively considered and the temptation to use corticosteroids should be actively avoided.

Investigation

Tissue sampling and culture remain imperative in the diagnosis of infectious keratitis. Atypical pathogens are often fastidious, requiring specialised culture systems and some cultures may take days to weeks to become positive.

The difficulty in isolating the causative organism in atypical keratitis is reflected by the observation that only 30 to 40% of cultured cases among patients with Acanthamoeba or fungal keratitis have a positive culture. In culture negative cases where there is a lack of a favourable clinical response, a repeat corneal scrape is recommended and, in some cases, a corneal biopsy may be required.

In vivo confocal microscopy (IVCM) is a rapid, non-invasive technique that enables imaging of the living human cornea at the cellular level. IVCM is a useful adjunctive tool when Acanthamoeba or fungal keratitis are suspected. However, the resolution limits of this instrument (approaching one micron) preclude its use in detecting bacterial or viral infections. IVCM has a sensitivity and specificity of approximately 90% for the detection of fungi or Acanthamoeba.

On IVCM imaging, Acanthamoeba cysts may appear as double-walled cysts, signet rings, and bright spots (fig 2a). However, inflammatory cells also appear as similar bright spots, and may easily be confused with Acanthamoeba cysts leading to erroneous diagnosis. The presence of double-walled cysts, signet rings should therefore always be sought.

Fungal hyphae characteristically appear as bright linear branching structures on IVCM images (fig 2b). Microsporidia may be diagnosed on IVCM by the presence of diffuse punctate hyper-reflective inter- and intracellular dots (fig 2c).

Conclusion

Atypical corneal infections pose significant diagnostic challenges, particularly due to the wide variability in presentation, overlapping clinical signs, and difficulties in isolating causative organisms. Early detection of these cases is crucial and relies on having a high level of suspicion based on the history, clinical signs and response to treatment. In particular, the temptation to start corticosteroids should be avoided if there is uncertainty in the diagnosis.

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