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Clinical Commentary

Equine keratomycosis: An international problem

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The fungi are a separate taxonomic kingdom distinct from both plants and animals. Although often inconspicuous, fungi occur in every type of environment and play very important roles in most ecosystems. Fungi have important symbiotic relationships with many types of organisms and tissues. These interactions can be mutualistic or antagonistic, or in the case of commensal fungi are of no apparent benefit or detriment to the host. Fungal hyphae are specifically adapted to growth on solid surfaces and within substrates, and can exert astoundingly large penetrative mechanical forces.

Exposure to fungal organisms in dust and vegetative material (e.g. hay, grasses, shavings, pollen) in a particular geographic region may influence the exposure of horses to particular species of fungal organisms (Brooks and Matthews 2007), but fungal organisms are ubiquitous in the equine environment. Fungal organisms are, therefore, normal inhabitants of the equine ocular surface microflora as the equine conjunctiva and cornea are constantly exposed to these organisms (Brooks and Matthews 2007). They are heterotrophic organisms requiring preformed organic compounds as energy sources, and also as carbon skeletons for organic synthesis. Fungal organisms are characterised by the absence of chlorophyll and include mushrooms, moulds, fungi and yeasts (Brooks and Matthews 2007). They are usually filamentous and multicellular. The filaments are also called hyphae, which are interrupted or divided by cross-walls or septa. Septate filamentous fungi include several species that are common causes of ulcerative fungal keratitis among horses internationally and in the United States (e.g. *Fusarium*, *Aspergillus* and *Penicillium*) (Brooks and Matthews 2007). Each hypha has a surrounding, definitive cell wall made up of chitins, glucans and mannans (Brooks and Matthews 2007). Chitin, which is a structural polysaccharide, is a cell wall component of fungal hyphae that is absent in vertebrate systems (Brooks and Matthews 2007).

Equine keratomycosis is a relatively common, sight-threatening condition in the horse. There are several clinical presentations including ulceration with or without corneal melting (**Figs 1–4**), microerosions (**Fig 5**), fungal plaque (**Figs 6** and **7**), stromal abscess (**Figs 8** and **9**), and iris prolapse (**Fig 10**) (Brooks and Matthews 2007). Infection should be considered a possibility in every horse with a corneal ulcer. *Fusarium* and *Aspergillus* spp. are both common causes of ulcerative fungal keratitis among horses internationally and in the United States (Brooks and Matthews 2007). Fungal involvement should be suspected if there is a history of corneal injury with vegetative material, if a corneal ulcer has received prolonged antibiotic or corticosteroid therapy (or both) with either slight or no improvement, if the tear film is unstable, and if a chronic ulcer fails to vascularise.

Ulcerative keratitis refers to a disruption of the corneal epithelium with varying amounts of stromal loss. The pathogenesis of ulcerative fungal keratitis commonly begins with corneal trauma that results in an epithelial defect and stromal invasion by the commensal fungal organism, or seeding of fungi from a foreign body of plant origin (Brooks and Matthews 2007). If these normally commensal fungi can attach to the cornea via corneal injury they may become pathogenic, and able to invade and colonise the cornea. The key trigger to initiate fungal pathogenesis appears to be that these normally commensal fungi must first adhere to the corneal surface to resist the natural tear film and corneal defence mechanisms that suppress fungal growth (Brooks and Matthews 2007). Tear film instability with or without cornea injury predisposes to this fungal attachment and infection in horses (Brooks and Matthews 2007). Some fungi in horses do appear to be able to adhere to healthy corneal epithelial cells in the absence of normal precorneal tear film layers (Brooks and Matthews 2007).

Stromal destruction in equine ulcerative keratitis results from the release of proteases and other enzymes from neutrophils attracted to the ulcer, and fungi and keratocytes (Brooks and Matthews 2007). Fungi with high pathological potential have the ability to adhere strongly to the epithelial or stromal tissue, and attract large numbers of polymorphonucleocytes (PMNs) that release large quantities of matrix metalloproteinases (MMPs) that allow vertical deep movement in the corneal stroma (Brooks and Matthews 2007). Pathological fungal

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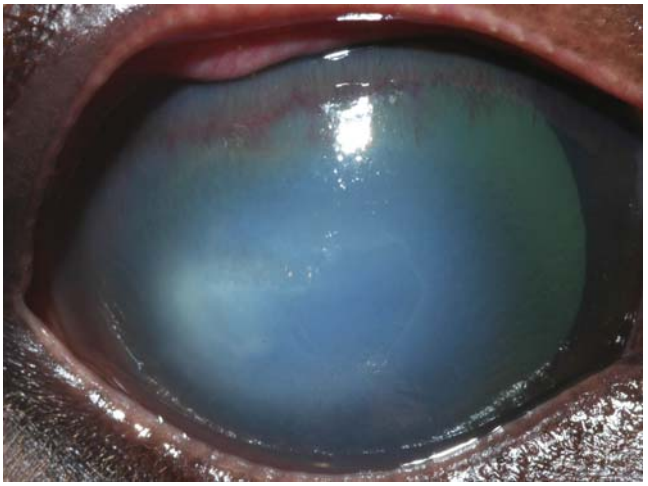

Fig 1: Superficial ulcerative keratitis with cellular infiltrate. Neutrophils are attracted to areas of fungal infection.

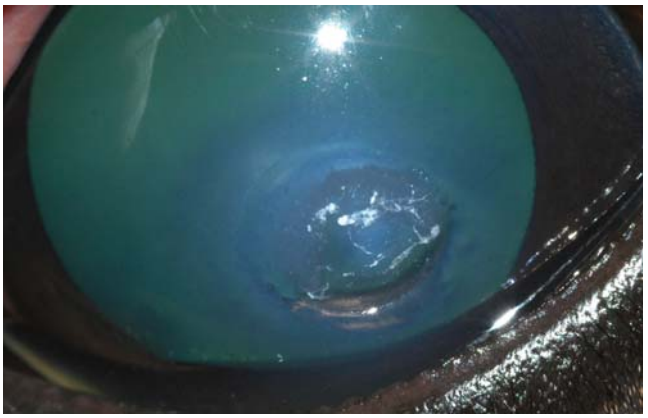

Fig 2: A furrow or 'gutter' is present adjacent to a small fungal ulcer. These furrows indicate an immune or proteolytic reaction related to the ulceration. This situation can deteriorate rapidly and is very serious.

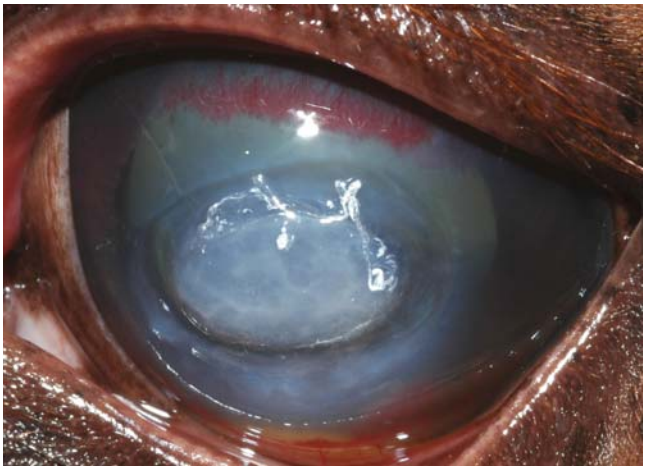

Fig 3: This furrow or 'gutter' is present adjacent to a fungal ulcer that is showing evidence of melting.

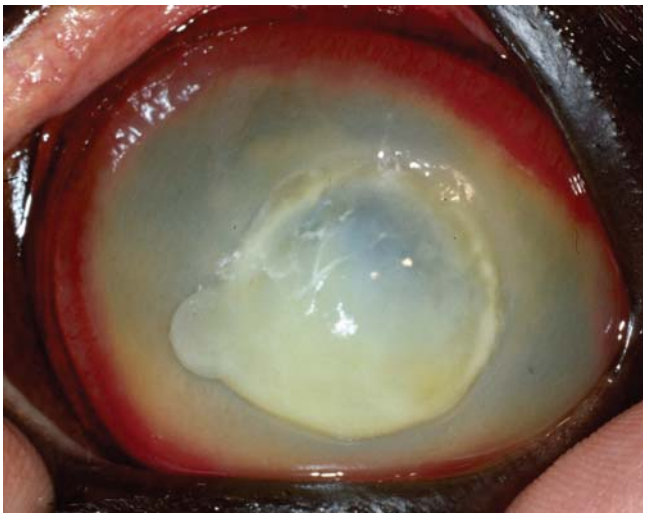

Fig 4: A melting fungal ulcer with intense early limbal vascularisation.

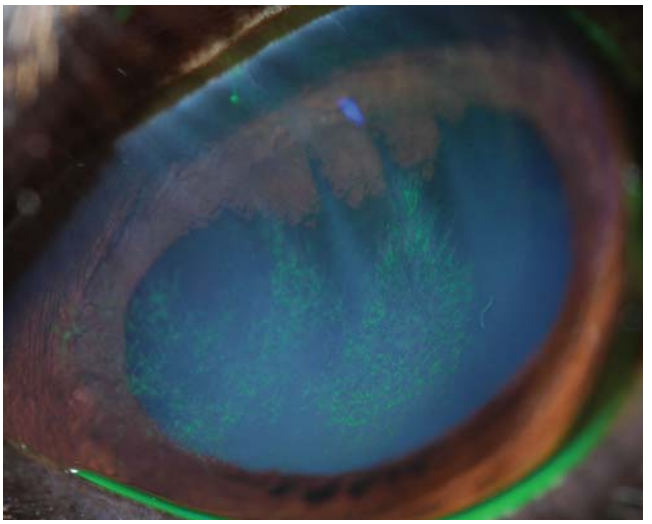

Fig 5: Fungal microerosions are associated with weak, stippled fluorescein stain retention due to partial loss of epithelial cell layering. Microerosions may be the most common and least recognised manifestation of equine keratomycosis.

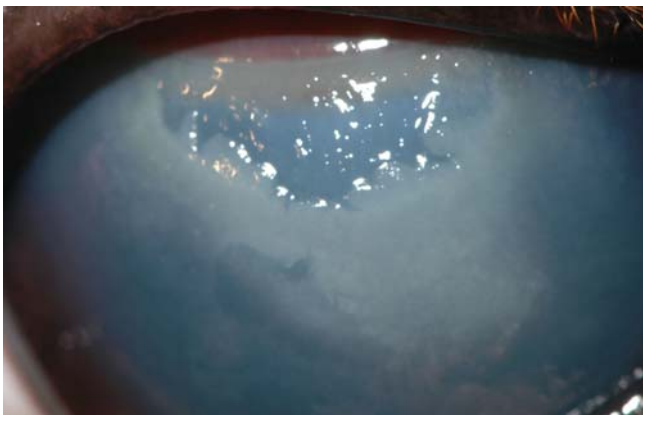

Fig 6: A midstromal depth ulcer with white fungal plaque formation.

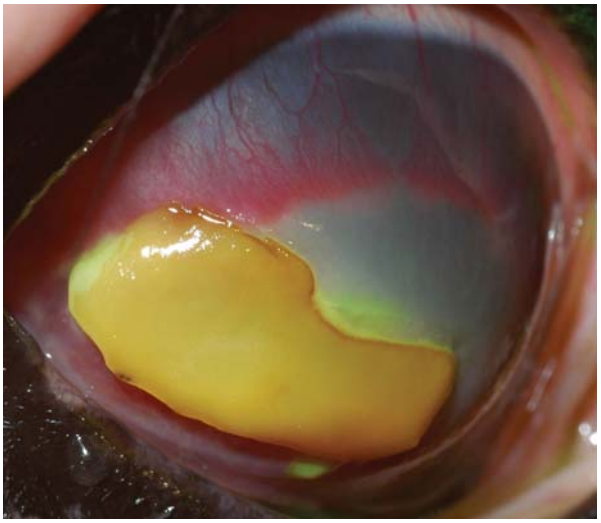

Fig 7: A thick, brown fungal plaque is present covering a stromal abscess. Vascularisation is superficial to the abscess.

Fig 8: A deep stromal abscess at the depth of the corneal endothelium caused by a fungus is present.

Fig 9: A large deep stromal abscess caused by a fungus is present with superficial vascularisation beginning to move over it.

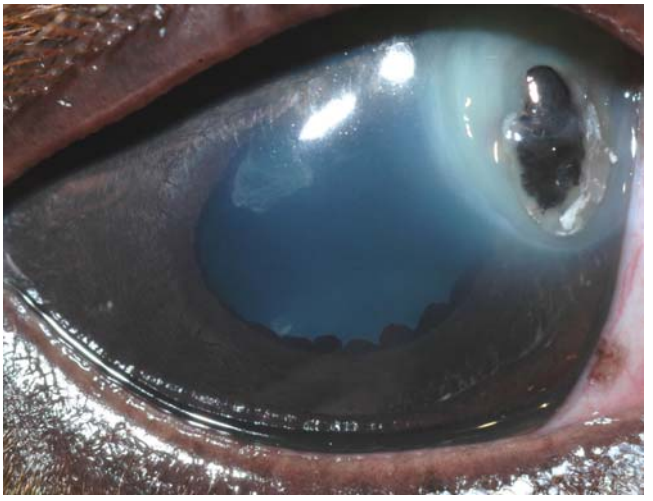

Fig 10: Iris prolapse secondary to a melting fungal ulcer should be surgically corrected.

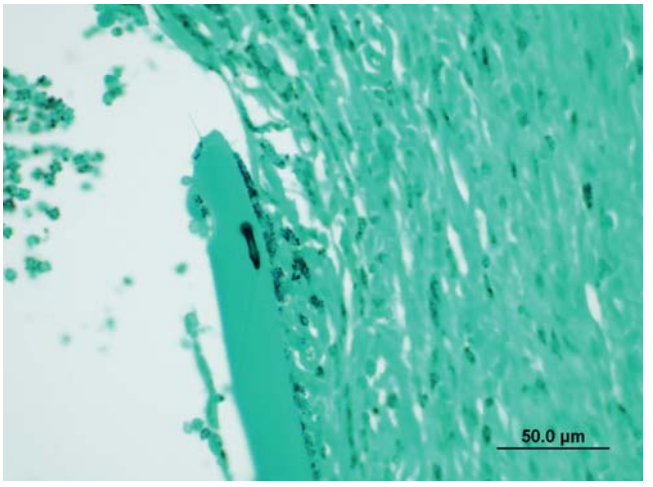

Fig 11: Fungal hyphae in Descemet's membrane. The most pathogenic fungi move vertically in the horse cornea. Some may reach the lens. GMS stain.

organisms have a unique propensity to move or 'tunnel' deep into the stroma towards Descemet's membrane with hyphae frequently being found deep in the corneal stroma of horses (**Fig 11**). Deep fungal corneal invasion can lead to the presence of fungal hyphae in the anterior chamber, lens and iris with a resulting persistent and severe endophthalmitis (Brooks and Matthews 2007). Fungi of low pathology adhere poorly, do not attract PMNs, are associated with small quantities of MMPs, and move laterally or horizontally in the corneal stroma (Brooks and Matthews 2007).

A stromal abscess can result from stromal inoculation with bacteria or fungi through a small or large corneal epithelial defect. The organisms become encapsulated in the corneal stroma after re-epithelialisation of the corneal ulcer over the infection site.

Iris prolapse is defined as corneal, limbal or scleral perforation (or some combination of the 3), with iris protrusion through the wound after trauma or deep

ulceration. These conditions all may be associated with fungal infection.

Medical therapy for ulcerative keratitis, iris prolapse, and stromal abscess varies from case to case and region to region. Miconazole, natamycin, fluconazole, voriconazole, clotrimazole and itraconazole have been used successfully topically to treat fungal ulcers in the horse (Brooks and Matthews 2007). There may, however, be differences in the susceptibility of fungi of the same species to the same medications. An *Aspergillus* in one area may not be susceptible to miconazole, whereas the miconazole may effectively inhibit *Aspergillus* growth in another geographic area. The fungal susceptibilities can also change with time as we have noted in Florida that *Aspergillus* is no longer responsive to natamycin and *Fusarium* no longer susceptible to miconazole. Once the correct medication is identified, however, I would argue that killing the fungi is not always a major problem, but the eye's reaction to the dead fungal hyphae can be very destructive and is often the problem the clinician is attempting to manage.

Aggressive medical and surgical therapy for ulcerative keratomycosis in horses should result in a positive visual outcome and ocular survival in the majority of eyes (Brooks and Matthews 2007). Despite this success, however, therapy is generally quite prolonged, and scarring of the cornea may be prominent. Combined medical and surgical therapy is indicated if ulcers are extremely deep, are not responding to medical treatment, or worsen despite medical treatment. All cases of iris prolapse require surgical repair, with many cases of deep stromal abscesses requiring penetrating keratoplasty (Brooks and Matthews 2007).

It was once believed that equine keratomycosis was primarily a problem of horses living in the warmth and high humidity of subtropical environments. Cases of horses with fungal keratitis in more temperate climates did occur but were thought to be rare and more easily managed. The series of 10 cases from Spain in the current issue (Galán *et al.* 2009) definitively discounts that hypothesis. I am also aware of cases of keratomycosis in horses living in Finland, Canada, Mexico, Denmark, Scotland, England, Spain, South Africa, Dubai, Australia, Japan, France, Germany, Italy, Brazil and Argentina. Keratomycosis can surely be found in many other countries and should be considered in the differential diagnosis for ulcerative and nonulcerative keratopathies in horses. New antifungal and antifibrotic medications continue to be needed. The use of amnionic membrane grafts for ulcerative keratomycosis also has promise to speed healing in horses.

References

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