Fungal keratitis in a mare: case report in Costa Rica

Queratitis fúngica en una yegua: reporte de un caso en Costa Rica

Ceratite fúngica em égua: relato de um caso na Costa Rica

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Abstract
This paper discusses the diagnosis and clinical management of a case of equine keratomycosis. A pregnant Iberic mare was diagnosed with *Aspergillus* subgenus *Circumdati* section *Circumdati,* by direct microscopic examination, cytology, and fungal culture after being treated with a topical antibiotic and steroid drops in her left eye for over a month. The mare developed a melting ulcer and, as a result, topical miconazole 1% was prescribed; while being treated the iris prolapsed, and surgery was suggested but not conducted. After the treatment, the eye was not visual but in the orbit.

Keywords: *Aspergillus*, horse, iris prolapse, keratomycosis, melting ulcer, miconazole

Resumen
Se discute el manejo clínico y diagnóstico de un caso de queratomicosis en un equino. Una yegua Ibérica preñada fue diagnosticada con *Aspergillus* subgénero. *Circumdati* sección *Circumdati* mediante examen microscópico directo, citología y cultivo micológico, después de haber sido tratada por un mes con gotas de corticoesteroides y antibiótico tópico en su ojo izquierdo. Desarrolló úlcera colagenolítica, se prescribió tratamiento con miconazol tópico al 1% y posteriormente presentó prolapso de iris, la cirugía fue sugerida pero no fue realizada. Al final del tratamiento médico, el ojo no es visual, pero está en órbita.

Palabras clave: *Aspergillus*, caballo, prolapso de iris, queratomicosis, úlcera colagenolítica, miconazol

Resumo
Discute-se o manejo clínico e diagnóstico de um caso de ceratomicose em um equino. Uma égua ibérica prenha foi diagnosticada com *Aspergillus* subgen. *Circumdati* seção *Circumdati* por exame microscópico direto, citologia e cultura micológica, após ter sido tratada por um mês com colírio de corticosteróides e antibiótico tópico no olho esquerdo. Desenvolveu úlcera colagenolítica, foi prescrito tratamento com miconazol tópico a 1% e posteriormente apresentou prolapso de íris, cirurgia foi sugerida, mas não realizada. No final do tratamento médico, o olho não é visual, mas está em órbita.

Palavras-chave: Aspergillus, cavalo, prolapso de íris, ceratomicose, úlcera colagenolítica, miconazol

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Introduction

One of the most frequent reasons for an ophthalmic examination in the equine practice is corneal disease. The prominent equine eye contributes to a higher degree of exposure of the cornea (Barnett *et al.* 2004; Clode 2011). Corneal keratitis is frequent and can be ulcerative and non–ulcerative. Both infectious and non-infectious causes can be found in both categories (Clode 2011; Gilger 2013).

Trauma is a common trigger in ulcerative keratitis (Galera & Brooks 2012; Gilger 2013). When the corneal epithelium is damaged, the epithelium takes about five to seven days to restore during a normal healing process (Maggs 2008; Clode 2011). When a nonhealing corneal ulcer is present, bacterial or fungal infections are easier to develop, making the ocular problem more challenging (Clode 2011).

Keratomycosis is a conjunctiva and cornea infection due to commensal fungi. The clinical signs associated with keratomycosis are stromal plaques and abscess, blepharospasm, micro erosions, corneal vascularization, pain, chemosis, photophobia, lacrimation, purulent discharge, miosis, keratomalacia, keratitis, hypopyon, uveitis, iris prolapse, and corneal edema (Galán *et al.* 2009; Brooks *et al.* 2013; Cafarchia *et al.* 2013). Considering that those clinical manifestations are shared with other etiologies, laboratory tests must be used for confirmation.

The aim of this case report is to advise equine veterinarians, mostly from developing countries such as Costa Rica, of the importance of using laboratory tests to provide better prognosis and improve animal welfare before resorting to empirical antifungal treatments.

Case report

On December 11th, 2013 (day 1), a pregnant Iberic mare, semi-stabled from La Ceiba, Orotina, Alajuela, Costa Rica, was evaluated for chronic pain and epiphora on her left eye (Fig. 1). The patient had been treated for several weeks with topical antibiotic and steroid drops (Tobradex: 0.3% tobramycin and 0.1% dexamethasone, Alcon).
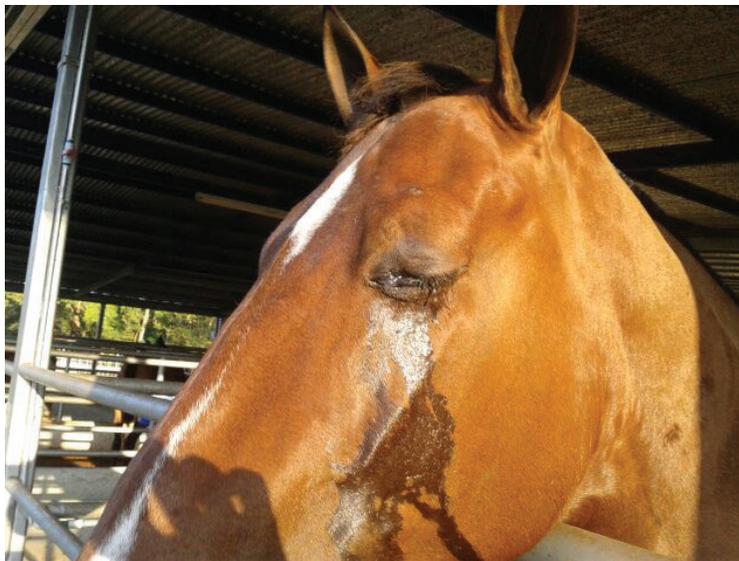

Figure 1. Epiphora and eyelids closed due to severe pain.

Ophthalmic evaluation

On day one, an ophthalmic evaluation was conducted in the morning, using 0.5% tetracaine ophthalmic drops (Alcames, Costa Rica), direct ophthalmoscope (Welch Allyn, Skaneateles Falls, NY), PanOptic ophthalmoscope (Welch Allyn, Skaneateles Falls, NY), and Tono-pen applanation tonometry (Reichert, Inc, Depew, NY). The ophthalmic evaluation consisted of checking the anterior and posterior segments, light responses, intraocular pressure, and fluorescein sodium 1 mg staining strip (Bio Glo, Hub Pharmaceuticals). The left eye (OS) presented abundant epiphora and blepharospasm, and the cornea had superficial erosion positive for fluorescein sodium staining strip (Fig. 2), miosis, and normal fundus. The right eye (OD) was normal. Intraocular pressure was normal in both eyes: OS 30 mmHg and OD 32 mmHg (range 7 - 37 mm Hg) (Utter & Brooks 2011).
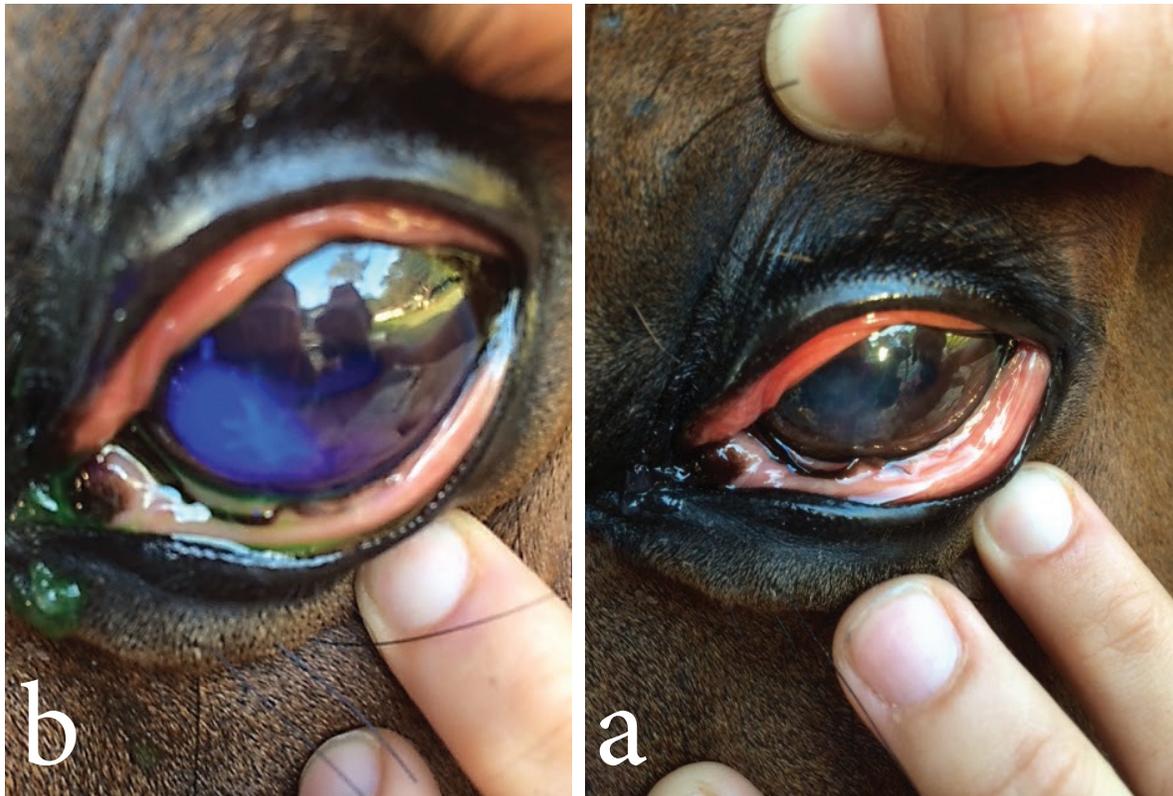
Figure 2. Ophthalmic evaluation of the left eye. a) loss of transparency of the corneal medial aspect, erosion noted with magnification. b) corneal medial aspect positive for fluorescein (corneal ulcer).

By day 3, the left eye presented less epiphora, the pupil was dilated, and the mare was able to open the eyelids wider (Fig. 3).

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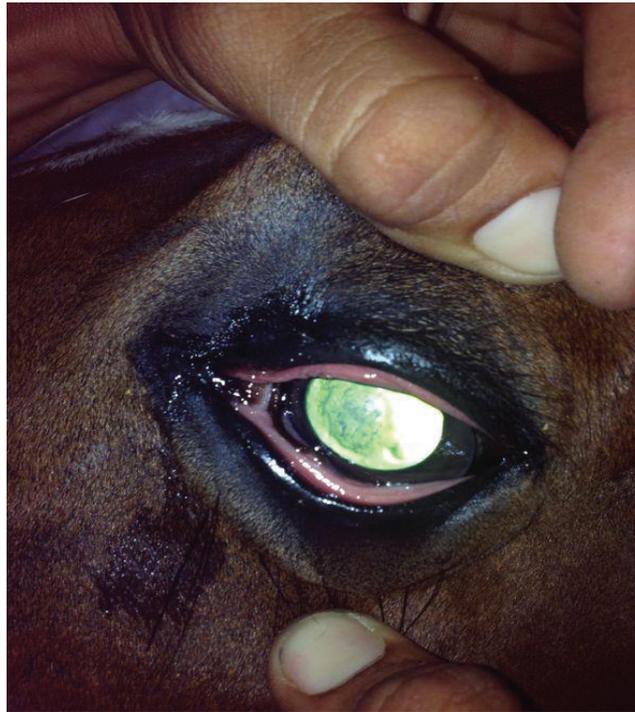
Figure 3. Mydriasis, tapetal reflex (green color), and cornea with furrowing appearance.

On day 6, the mare was able to close the eyelids again. On the cornea, blood vessels started advancing dorsally and the melting process initiated (Fig. 4).
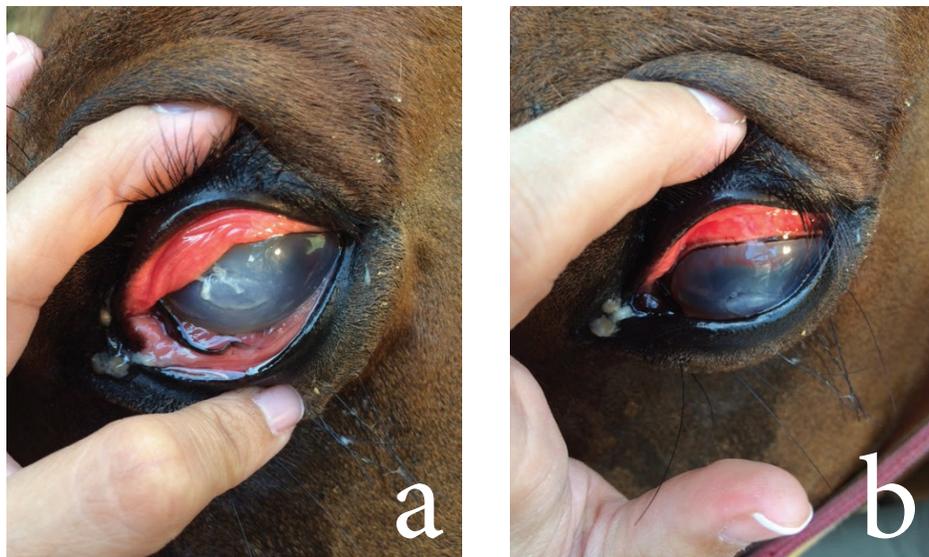
Figure 4. a) Corneal edema and beginning of the melting process b) Note the redness on the sclera and the blood vessels on the dorsal aspect of the cornea.

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By day 8, the melting process was severe (Fig. 5). Since clinical signs worsened and there was no response to antibiotics, corneal scraping and impression smear were immediately taken to the laboratory for fungal tests and cytology. In the following weeks, the cornea continued to get weaker until it ruptured.


Figure 5. Generalized corneal edema. The tip of the melting tissue was used for laboratory tests.

Cytology and mycology results

Samples were processed and analyzed as soon as they arrived at the lab (Diagnóstico Albéitar, S.A.) less than two hours after they were taken. Wright's stain was used for the impression smear. The cytology revealed corneal epithelial cells with slight dysplasia and neutrophilic inflammation. A direct microscopic examination with 10% potassium hydroxide (KOH) made to the corneal scraping showed abundant hyaline septate hyphae of 3-4μm in diameter, some of which showed dichotomous branching at 45° (Fig. 6). Consequently, a hyaline fungal keratitis was diagnosed (Walsh *et al.* 2018; de Hoog *et al.* 2019).

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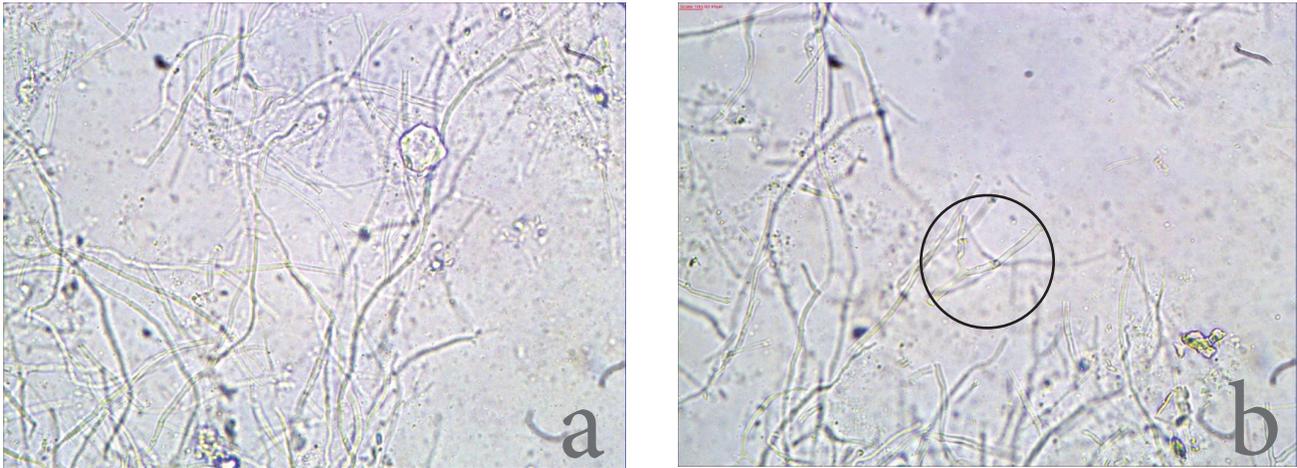
Figure 6. Microscopic direct examination of corneal scraping with KOH 10%, 400x. a. Abundant hyaline septate hyphae. b. Delimited by a circle, hyphae with dichotomous branching at 45°.

Cultures in Sabouraud Dextrose Agar (Oxoid®, Basingstoke, United Kingdom) at 37 °C and 28 °C for seven days yielded positive for a hyaline powdery colony with yellowish conidia, and no sexual stages were present (Walsh *et al.* 2018; de Hoog *et al.* 2019; Samson *et al.* 2019) (Fig. 7).
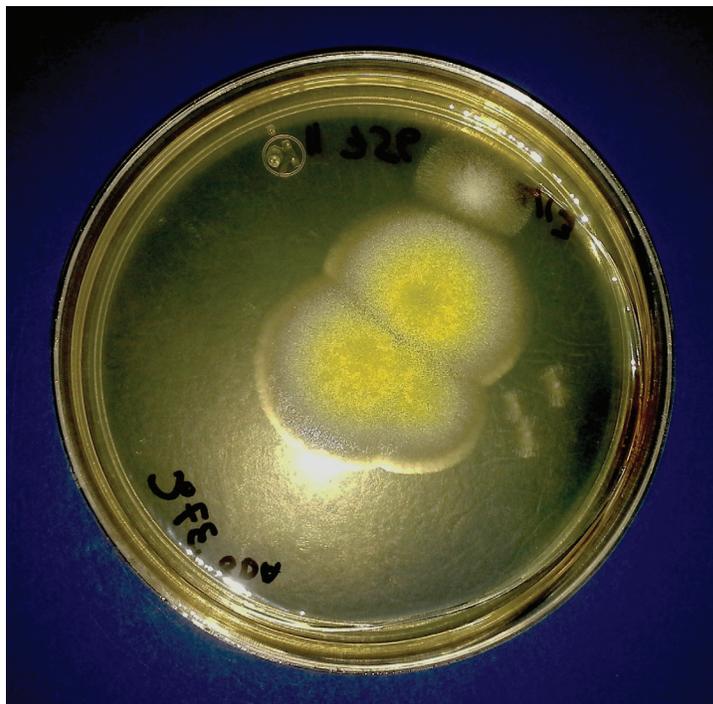
Figure 7. Seven-day culture of corneal scraping positive for *Aspergillus* subgenus *Circumdati* section *Circumdati* on SDA at 37 °C.

The micromorphology analyzed at the Mycology Lab of the School of Veterinary Medicine at Universidad Nacional de Costa Rica (LMIC EMV-UNA) showed a hyaline septate hypha of 3-4 µm in diameter, with erect and unbranched conidiophores and the phialides disposition in the vesicle radiated and biseriate (Fig. 8). Since no molecular methods were accessible at that time in the country, it was identified as *Aspergillus* spp. to genera level. Although the strain is no longer available, it was later identified to section level as an *Aspergillus* subgenus *Circumdati* section *Circumdati* based on the color of the conidia and the disposition of the phialide in the vesicle (Walsh *et al.* 2018; de Hoog *et al.* 2019; Samson *et al.* 2019; Houbraken *et al.* 2020).

Figure 8. *Aspergillus* subgenus *Circumdati* section *Circumdati* radiate conidial head. Lactophenol Cotton Blue Solution, 400x.

Treatment and follow up

On the day of the ophthalmic evaluation, the mare started with topical tobramycin (Tobrex: 0.3% tobramycin, Alcon), diclofenac (3a Ofteno: 0.1% diclofenac, Sophia), atropine (Atropina: 1% atropine, Holliday), and oral phenylbutazone (Fenilbutazona: 1g phenylbutazone, Lisan, no longer available). By day 6, when the melting process started, topical autologous serum, EDTA (Ethylenediaminetetraacetic acid), and ofloxacin (Ofloxacina: ofloxacin 0.3%, Holliday) were added to the treatment.

With the presence of hyaline septate hyphae, a 1% miconazole solution was added to the therapy by day 9, and a conjunctival pedicle graft surgery was recommended to help prevent corneal perforation. As per the owner's decision, the mare continued only with medical treatment.

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The mare was under treatment for almost two months. Although the cornea suffered a perforation with iris prolapse, it eventually healed. To date, the patient's left eye is not visual, but it is in the orbit (Fig. 9).
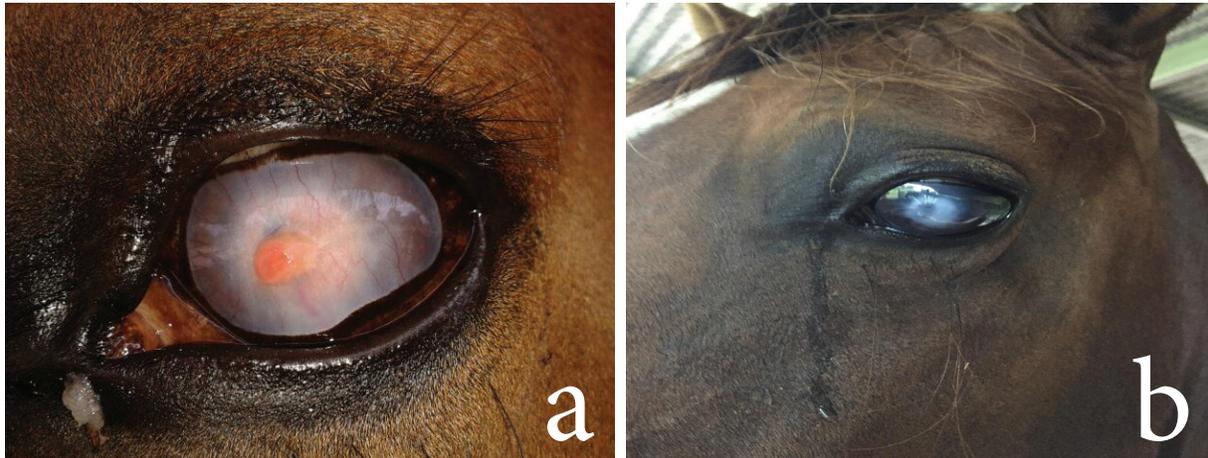
Figure 9. a) blood vessels and ongoing healing process b) scar tissue of the cornea

Discussion

Horses are more likely predisposed to mycotic infections in their eyes than are other mammals because of deficiencies in the innate immune protective barriers of the tear film to develop an adequate response against fungi present in the conjunctiva and the cornea, also because of a lack of integrity and stability of the precorneal tear film, a large corneal surface, and low resting temperature of the cornea (Galán *et al.* 2009; Galera & Brooks 2012; Cafarchia *et al.* 2013; Khosravi *et al.* 2014). Fungal eye infections can be found in the cornea, eyelids, conjunctiva, orbit, and intraocular and can affect the optic nerve as a consequence of trauma due to opportunistic overgrowth or a systemic disseminated disease (Ledbetter 2017). In these cases, the diagnosis should include an exhaustive ophthalmic evaluation and laboratory tests to prescribe the correct treatment.

In normal conditions, the ocular microbiota, mostly made of Gram-positive bacteria, yeast, and filamentous fungi and at a lesser degree of Gram-negative bacilli, remains stable on the eye surface and conjunctiva to prevent pathogen overgrowth. The microbiota related to keratomycosis varies according to geographical areas, seasons, and housing conditions (Galera & Brooks 2012; Khosravi *et al.* 2014). For example, Wada *et al.* (2011) found *Mortierella wolfii* in a 2-year-old Thoroughbred filly in Japan, and no cases involving this fungus had been described causing keratitis anywhere else. This fungus is a prevalent cause of abortion and meningoencephalitis in cattle in New Zealand, Australia, Japan, and England. The authors stated that the possible source could be environmental spores in the silage.

Although bacterial infections in the cornea are treated more frequently than fungal infections, living in tropical weather may increase the probability of developing keratomycosis (Maggs 2008; Gilger 2013; Utter 2015). However, the incidence of fungal keratitis in Costa Rica is either very low or well under-diagnosed since, to our knowledge, this is the first case reported in the country, as reflected in

the keratomycosis cases recorded in LMIC EMV-UNA between 2008 to 2017 (Calderón-Hernández & Urbina-Villalobos 2018). This condition also seems to be sporadic in other countries. After reviewing one-year to twelve-year retrospective studies in the United Kingdom, Spain, the United States, Switzerland, and Japan, the reported cases varied from five to 66 horses (Sansom *et al.* 2005; Galán *et al.* 2009; Utter *et al.* 2010; Brooks *et al.* 2013; Voelter-Ratson *et al.* 2013; Wada *et al.* 2013; Sherman *et al.* 2017). The research by Utter *et al.* (2010) in the mid-Atlantic United States deserves attention due to the large number of registered cases (30 in one year), although these horses were evaluated by a single board-certified veterinary ophthalmologist in comparison to the other papers where subjects were evaluated at Veterinary Teaching Hospitals. It could be deduced that environmental conditions, mostly during the summer in that geographical area, lead to more cases than in any other parts of the world. The studies with the most registered cases (Utter *et al.* 2010 with 30 and Sherman *et al.* 2017 with 66) revealed that the disease is present in ages ranging from one month to 30 years, with no sex predisposition, with eight breeds being represented for the former study and 14 for the latter, with Quarter Horse and Thoroughbred being the most affected ones (20-22% and 20-30% of the cases). In addition, both eyes were equally affected, always in a unilateral presentation. As far as use, both studies indicate horses were frequently exposed to the environment (mainly racing and sports) (Utter *et al.* 2010; Sherman *et al.* 2017).

Several fungal genera are associated with keratomycosis, including *Aspergillus, Fusarium, Candida, Curvularia, Penicillium, Cylindrocarpon*, and *Mucor* (Galán *et al.* 2009; Utter *et al.* 2010; Galera & Brooks 2012; Wada *et al.* 2013; Samanta 2015; Sherman *et al.* 2017; Ledbetter *et al.* 2018), the first two being the most frequently reported and with the worst prognosis (Galán *et al.* 2009; Utter *et al.* 2010; Cafarchia *et al.* 2013; Sherman *et al.* 2017; Roberts *et al.* 2020). Since these genera are also found in healthy eyes (Khosravi *et al.* 2014), a fungal culture must be conducted with histopathology and/or cytology to verify whether the tissue has been compromised with hyphae or yeast. Fungal commensal overgrowth could result from high amounts of conidia in stables, mainly during summer and autumn in temperate countries and throughout the year in tropical areas (Galera & Brooks 2012; Cafarchia *et al.* 2013).

It has been reported and assumed that fungal organisms have a tropism for the glycosaminoglycans in the equine deep corneal stroma close to Descemet's membrane (Utter 2015; Ledbetter *et al.* 2018). In addition, in a study using *in vivo* confocal microscopy, Ledbetter *et al.* (2018) were able to evidence the presence of fungal organisms even when the epithelium is still present, which suggests a similar tropism for the corneal epithelial basement membrane.

When a superficial epithelial lesion exists, the release of proteolytic enzymes from fungi, leukocytes, and keratocytes results in the progression of keratomycosis to deeper layers of the cornea, threatening vision (Wada *et al.* 2013; Ledbetter *et al.* 2018). The use of topical antimicrobials and topical corticosteroids can impair the local immune defenses, and opportunistic pathogens such as fungi can proliferate easily. In addition, collagenolysis can be devastating (Utter 2015).

Different clinical manifestations of keratomycosis include stromal ulcers, superficial fungal keratitis, keratomycosis with surrounding furrows, keratomycosis with a "cake frosting" appearance, and stromal abscesses (Sansom *et al.* 2005). Given that some can exhibit characteristics similar to bacterial infections and that the patient is already on antibiotic therapy, a cornea with a "cake frosting" or

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furrowing appearance (like the present case) must be considered a sign to suspect the presence of fungi organisms to be confirmed with a fungal culture (Sansom *et al.* 2005).

Differential diagnoses include eosinophilic keratoconjunctivitis and keratoconjunctivitis sicca, immune-mediated keratitis, bacterial keratitis, herpes virus keratitis, calcific band and traumatic keratopathy, corneal degeneration, and neoplasia (Galera & Brooks 2012). Regarding the case in question, bacterial, eosinophilic, and neoplastic etiologies were discarded after cytology.

Some of the diagnostic tests used to determine a fungal etiology include culture, cytology, histopathology, polymerase chain reaction, and *in vivo* laser scanning confocal microscopy (Galera & Brooks 2012; Ledbetter *et al.* 2018), all of which, except for the last one, are currently available in Costa Rica at affordable prices. However, depending on the lesion's progression and the availability of the specimen collection, taking the samples and choosing the tests could be a challenge (Ledbetter *et al.* 2018). For example, in a five-year retrospective study using medical records of twenty-one horses with subepithelial keratomycosis, only ten cases of mycotic etiology were cytologically confirmed and only four cases were positive for fungal isolates: *Candida* spp. in one of the cases and *Aspergillus* spp. in three (Brooks *et al.* 2013).

In the present case, *Aspergillus* subgenus *Circumdati* section *Circumdati* was identified as the causative agent. Since this genus can be found as transitory microbiota (Khosravi *et al.* 2014), the etiology was confirmed by culture, the visualization of the parasitic adaptation on the direct microscopic examination of the corneal scraping sample, and associated cellular reaction visualized on the cytology (Walsh *et al.* 2018; de Hoog *et al.* 2019). These diagnostic tests were selected based on the services offered by the closest laboratory since scraping is a very labile sample and it needs to be processed within four hours (Samanta 2015; Walsh *et al.* 2018; de Hoog *et al.* 2019) and also because those exams give important information to confirm the suspected cause.

The key to a successful outcome in keratomycosis cases is an early diagnosis and an aggressive medical treatment for fungi, iridocyclitis, and collagenolysis, with or without surgery. Topical antifungals used to treat this disease include 1% miconazole, 5% natamycin, 0.2% fluconazole, 1% voriconazole, 1% ketoconazole, 1% itraconazole, 0.2% terbinafine, 0.75 - 0.5% amphotericin B, 1% flucytosine, 1% silver sulfadiazine, and 0.1 - 5% diluted povidone iodine. Their effects can vary depending on the geographic region. Most of the times, therapeutic plans are made empirically since antifungal susceptibility testing takes time or cannot be conducted because of the lack of antifungal drugs and the disease progresses rapidly (Galera & Brooks 2012; Voelter-Ratson *et al.* 2013; Wada *et al.* 2013; Utter 2015; Ledbetter *et al.* 2017).

In the present case, topical miconazole 1% was used because, up to now, there is no veterinary or human antifungal eye collyrium registered in Costa Rica, and that was the only option available at the compounding pharmacy at the time. Surgery was also suggested but was not performed as per the owner's decision. Topical miconazole 1% q2h-q6h has been used as a single or compound therapy (with surgery, autologous serum, and/or Atropine) in several cases and has shown fair results as a treatment for *Aspergillus* spp. In relation to keratomycosis in horses, the prognosis depended mostly on the previous medications and an early diagnosis (Utter *et al.* 2010; Wada *et al.* 2011; Brooks *et al.* 2013; Voelter-Ratson *et al.* 2013).

In a ten-year retrospective study including 66 keratomycosis cases caused by *Aspergillus* and *Fusarium*, researchers demonstrated that the case outcomes were not related to the involved fungi, hence there were no significant differences between both genera. The majority of the keratomycosis infections in horses were resolved with eye sparing surgery (46-51%), followed by medical treatment (32-42%), and finally by enucleation (12-17%). Nevertheless, previous antifungal therapy may lead horses to require surgery (85% of the cases), highlighting the importance of selecting the antimycotic until fungal etiology has been confirmed (Sherman *et al.* 2017).

Antifungal resistance is a concerning threat to fighting mycotic diseases such as the one discussed here. New drugs such as luliconazole (an imidazole used to treat keratomycosis in humans) have become a potential treatment for this disease caused by resistant *Aspergillus* or *Fusarium* species in horses, by exhibiting the lowest MICs (Minimum Inhibitory Concentrations) in antifungal susceptibility tests (Roberts *et al.* 2020). However, its availability and price are restrictive to developing nations, highlighting the importance of implementing the proper treatment in the early stages of the disease.

Conclusion

To prevent rejection of unaffordable procedures affecting the animal welfare, steroids must be used with caution, or preferably avoided, on horses since they can promote the growth of resident or transitory fungus and/or bacteria resistant to prophylactic medication. If possible, a cytology, direct microscopic examination, and fungal culture are imperative before implementing an antifungal treatment or when superficial corneal lesions and clinical signs do not improve after a few days of empirical treatment.

Acknowledgments

Conflict of interests

The authors declare no conflict of interests.

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