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Treatment of *Acremonium* sp. keratomycosis – a review of literature

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HIGHLIGHTS

Acremonium sp. keratomycosis is becoming a more threatening pathogen, therefore it is crucial to consider the optimal path for effective treatment and recovery.

ABSTRACT

Corneal infections may be caused by bacteria, viruses, fungi or protozoa. Fungal keratitis, usually associated with *Fusarium*, *Candida* and *Aspergillus*, develops from a saprophytic fungal infection as well, one of the agent being *Acremonium* sp. *Acremonium* infection occurs when a patient is suffering from a penetrating injury, common in ophthalmic patients. Symptoms of *Acremonium*-induced keratomycosis are similar to the usual presentation of a fungal infection – patients complain of decreased visual acuity, ocular pain, redness of the eye, floaters and corneal opacity. While there is no established method of treatment for *Acremonium keratitis*, usual antimycotics and antibiotics intended for keratomycosis are used – fluoroquinolones, azoles and polyenes. If pharmacotherapy does not yield favorable outcomes, surgical forms of treatment should be introduced, such as keratoplasty. If surgical methods are ineffective in infection control, an end-stage solution – enucleation is employed. Although *Acremonium* is an opportunistic fungal pathogen, the infection is generally effectively treated using pharmacotherapy.

Key words: keratitis, *Acremonium*, opportunistic fungal infection

INTRODUCTION

Corneal infections, otherwise called *infectious keratitis*, may be caused by bacteria, viruses, fungi or protozoa. It is associated with systemic or local non-infectious diseases, regarding the ocular surface [1].

Bacterial keratitis commonly occurs as a corneal ulcer and is an outcome of a mechanical injury, mainly concerning the cornea and its periphery – due to corneal trauma or wearing contact lenses, as well as in bullous keratopathy, eyelid laxity and severe dry eye syndrome [2].

Viral keratitis include mainly HSV (*Herpes simplex virus*), HZV (*Herpes zoster* virus) and *Adenovirus* infections. HSV-1 infection may lead to follicular conjunctivitis, epithelial keratitis, HZV may reactivate from the latent virus and cause herpes zoster ophthalmicus (HZO), whereas adenoviruses cause epidemic keratoconjunctivitis (EKC) [1, 3, 4].

Corneal infections caused by protozoa are represented by *Acanthamoeba* keratitis, which is a severe disease that, if not treated appropriately, can lead to a loss of vision. The main risk factor is use of contact lenses, although the affected group of patients includes people who do not wear contact lenses [5].

Keratomycosis, fungal type of keratitis, is most commonly caused by filamentous fungi species such as *Fusarium, Candida* and *Aspergillus* [6]. It is linked to trauma induced by organic material, such as grass, a splinter or a tree branch [7]. Keratomycosis is often in patients with immunodeficiency and after prolonged, locally administered steroid treatment [8]. Another source of infection is decreased hygiene compliance for usage and storage of contact lenses, with lens case contamination ranging from 18% to 85% [9].

Acremonium is a species of a saprophytic fungus, that can as well be an agent of an opportunistic infection. It usually occurs after sustaining a penetrating skin injury, but there is evidence of it taking a form of an ocular infection. The occurrence of acquiring an *Acremonium* infection has increased and affects patients treated with immunosuppressive therapy and those who underwent major surgeries, including transplantation. Steroid therapy is also considered to be an immunodeficiency cause, in cases of traumatic ocular injuries, among other [10].

In the following article, we are to present the *Acremonium* species, causes of its infection in ocular trauma, treatment options and their possible outcomes, which may lead to recovery and regain of vision, or a reinfection that may lead to surgical solutions – keratoplasty and if all available treatment fails – enucleation of the infected eye.

ACREMONIUM SP. CHARACTERISTICS

Acremonium, formerly known as *Cephalosporium*, is a saprophytic fungi species, which is common in the surrounding environment [11]. It is considered as an opportunistic pathogen causing a fungal infection, hyalophycomycosis. Hyalophycomycosis are caused by fungi that are described as hyaline, septate mycelial elements with branched or intertwined hyphae and belong to the filamentous fungi.

Apart from *Acremonium*, other prevalent saprophytes are *Fusarium, Scedosporium, Scopulariopsis* and *Penicillium marneffei* [10]. *Acremonium* consists of over 100 species, but only a few of them are responsible for infections: *A. strictum, A potronii, A. recifei, A. kiliense, A. reseogriseum, A. alabamensis* and *A. falciform* [11]. *Acremonium* may generally cause focal infections, taking the allergic, ocular, mycetoma, invasive and systemic forms. Its colonization might not be always followed by the development of an infection [10].

Nowadays, *Acremonium* poses a greater threat to ophthalmic patients, as it can appear not only in patients that are immunocompromised, but also those who are considered to be otherwise healthy. *Acremonium* infections are frequent in patients who underwent major surgeries, including transplantation, as well as during immunosuppressive therapy or steroid treatment. It has not been yet disclosed why such a trend in the epidemiology of those infections appeared. In the past, *Acremonium*-induced ocular infections were rare, having been reported only a total of 17 cases between 1971 and 2010 worldwide, while 13 of them were reported as cured [10].

In general, fungal keratitis is caused by *Fusarium, Candida* and *Aspergillus*. Due to similarities in morphology, *Acremonium* can be fairly indistinguishable from the *Fusarium* species [12]. *Acremonium* can be isolated on Sabouraud agar, incubated at 30°C [13]. It grows as a colony, which characteristics vary from white, powdery and suede-like to smooth, waxy and velvety, color varying from white to gray to rose, and after being incubated for 4–5 days, the reverse side of the culture plate shows the display of light yellow or light pink [10, 11].

In comparison to the usual fungal keratitis being a consequence of sustaining a corneal injury from a plant material [14], invasive *Acremonium* infection is often linked to a penetrating injury, including ocular trauma [11]. There have been mentioned 4 cases of infectious keratitis related to laser in situ keratomileusis (LASIK), which were performed in the same operating room by different surgeons. All of the referred patients' corneas were examined and revealed the presence of *Acremonium* [15]. It has also been observed that wound integrity is vital when assessing the risk of development of endophthalmitis and intraocular infections [16].

Symptoms of *Acremonium* keratitis are similar to the usual keratomycosis presentation, regarding decreased visual acuity, ocular pain [10, 13, 16–18], redness of the eye [18], floaters [16] and corneal opacity [17].

TREATMENT OF KERATOMYCOSIS

There is a wide range of antibiotics and antimycotics used in therapy of fungal keratitis. In this article we focused on the groups and their possible combinations that are the most effective in treating both keratomycosis and its type caused by *Acremonium*.

Fluoroquinolones

Fluoroquinolones are bacterial agents that act by inhibiting bacterial DNA gyrase, causing the bacterial DNA to become uncoiled and breaking the cell membrane. Demonstrating good intraocular penetration (particularly in the cornea), they are applied topically [19]. Fluoroquinolones are widely used for both prevention and treatment of keratitis. They are often used as first-line monotherapy in bacterial keratitis. Empirical monotherapy with fluoroquinolones (3 mg/ml ciprofloxacin, 3 mg/ml ofloxacin, 5 mg/ml moxifloxacin, 15 mg/ml levofloxacin, 3 mg/ml gatifloxacin or 6 mg/ml besifloxacin) is recommended until culture results are available [4]. It has been shown that fluoroquinolones bind to fungal topoisomerase, which is effective in fungal keratitis treatment [20]. Systemic absorption following topical administration is unlikely, therefore there should be no systemic side effects. Local reactions may occur, including photosensitization or allergies [19].

Polyenes

Natamycin, as well as amphotericin B, belongs to a group of antifungal polyene macrolide antibiotics. Its mechanism of action includes binding to ergosterol in the fungal membrane, creating lethal changes in the membrane, eventually leading to the death of fungal cells [21]. Side effects of topical medication include itching, burning and redness. Natamycin is usually administered topically, however subconjunctival and stromal injections are also possible [22]. Topical natamycin is remarkable as the primary treatment for fungal keratitis, especially in cases of filamentous keratitis. Locally administered natamycin appears to be more effective in treating *Fusarium* keratitis than topical voriconazole. It was also proven that re-epithelialization was significantly faster after using 5% topical natamycin compared to 0.2% chlorhexidine [23].

Amphotericin B has been utilized in fungal infections for over 50 years. Prevailing indications for its use are *Candida* spp., *Aspergillus* spp. and *Cryptococcus* infections, as well as severe and life-threatening fungal infections. Amphotericin B may be administered intravenously in an infusion over 2–6 h, with a risk of nephrotoxicity when the dose exceeds 1 mg/kg [24]. It is not considered a preferred antimycotic drug, due to its adverse effects in systemic use (nephrotoxicity, hepatotoxicity and erythema). Recent studies propose alternative ways of administering amphotericin B, such as intrastromal, intravitreal and intracameral, combined with other typical drugs or topical treatment, although the results of aforementioned approach are not entirely beneficial [25].

Azoles

Fluconazole and voriconazole belong to the group of azole synthetic antifungal drugs. By inhibiting the synthesis of ergosterol (a component of the fungal cell membrane), they inhibit fungal cells' growth and may induce their apoptosis. Azole antifungals are recognized for demonstrating both ocular and systemic forms of toxicities. When administered orally, voriconazole may lead to retinal necrosis, induction of visual disturbances and hepatotoxicity [26].

Oral administration of voriconazole has shown positive outcomes in treatment of fungal corneal infections that did not improve with local treatment using natamycin and amphotericin B. The administration of voriconazole through intrastromal injection at a dosage of 50 µg/0.1 ml demonstrates positive outcomes in addressing deep corneal infections that show resistance to traditional antifungals [27]. Topical voriconazole may be considered an alternative to natamycin in *Fusarium* keratitis treatment. However, this method is less effective and is associated with higher risk of perforation. Combined use of intrastromal voriconazole injections and topical application effectively reduces infiltration size and controls fungal infection [4, 28]. Fluconazole can be administered orally, intravenously, subconjunctivally, or topically. Use of fluconazole in the treatment of *Candida*-induced keratitis demonstrates high efficacy and low risk of toxicity and perforation [26].

TREATMENT OF *ACREMONIUM* KERATITIS

There is no established treatment for *Acremonium* keratitis. It is recommended to start the treatment as soon as possible. Azoles and polyenes are proven to be effective against *Acremonium* [10]. It is recommended to use hourly topical administration of 0.2% fluconazole and 0.15% amphotericin B, along with 0.5% moxifloxacin, in combination with oral fluconazole [11].

If *Acremonium* infection is confirmed, topical administration of 5% natamycin should be administered. Another method involves using topical natamycin along with a drug from the azole class. In the case of a large corneal ulceration (>6 mm), deep ulceration, or an ulceration unresponsive to topical treatment, oral fluconazole can be added to this regimen [11, 12, 29]. Should there be any unfavorable outcomes or recurrent *Acremonium* infections following the surgery or prosthesis removal, it is advisable to use amphotericin B. Successful treatment of immunocompromised patients has been achieved with the use of amphotericin B and ketoconazole [10]. For corneal infections of

mixed etiology, topical antifungals and fluoroquinolones are utilized [12].

Another form of effective treatment is a combination of 0.07 ml voriconazole (50 µg/0.1 ml) administered intrastromally and 0.05 ml of voriconazole (50 µg/0.1 ml) administered into the anterior chamber of the eye. This allows the drug to reach a higher concentration and act on both the cornea and the inside of the eye, which prevents the development of intraocular inflammation – one of the possible complications of corneal infection [18].

If pharmacological methods do not yield the expected improvement, surgical treatment (such as therapeutic keratoplasty) or intravitreal and intrastromal antibiotic injections are necessary. At the end of the aforementioned procedures, voriconazole should be administered intraventricularly. Topical natamycin 5% and oral ketoconazole (200 mg, twice per day) or topical amphotericin B with 1% voriconazole (every hour) and oral itraconazole (400 mg) can be used as postoperative prophylaxis [12, 29].

SURGICAL TREATMENT

When infectious keratitis remains uncontrolled using pharmacotherapy, the following treatment is carried out using surgical methods. Possible solutions regarding the surgery include cornea transplant (including therapeutic corneal transplant and amniotic membrane transplant) and enucleation.

Cornea transplant

Infectious keratitis uncontrolled with pharmacological treatment is one of the indications for a cornea transplant [30]. Corneal transplantation applied in infectious keratitis is a form of infection control [31]. Keratoplasty involves excision of an infected cornea with a margin of 0.5–1 mm larger than the infiltration, removing exudate from the anterior chamber and affixing donor tissue with a 10-0 nylon suture. Prior to the procedure, antibiotic therapy is advised to prevent secondary bacterial infection. In postoperative management following keratoplasty, steroids are utilized, due to their anti-inflammatory properties [30]. Used in a form of adjunctive treatment for keratitis, steroids carry a risk of secondary bacterial superinfection, especially in patients with history of trauma and those who do not properly maintain contact lens hygiene [32].

Therapeutic corneal transplant

Therapeutic corneal transplant (hot transplantation, hot-grafting) is a procedure intended exclusively for emergency treatment [33]. It has been reported that many cases of fungal keratitis (12% to 38%) are treated with such solution. It is proven to be effective in severe fungal keratitis, for visual rehabilitation and protection of the eye [34].

Amniotic membrane transplant

Amniotic membrane graft is widely used in ophthalmology, treatment of chemical burns, surface healing, bullous keratopathy and many others [35]. It promotes epithelialization, and is characterized by its anti-inflammatory, anti-angiogenic and anti-microbial properties. Due to its transparency, it does not impede visual acuity. Its structure is akin to that of cornea and conjunctiva, which promotes the growth of epithelial cells and prevents their apoptosis [36]. In acute fungal keratitis, amniotic membrane transplant has low risk of rejection, but it requires simultaneous, continued antifungal treatment [37].

Enucleation

Enucleation is primarily offered to patients as a solution considered as end-stage in cases of severe ocular trauma [38]. Removing the eye is considered only as a last resort if no other treatment for a serious condition can provide relief – the eye is severely damaged, there is no observed therapeutic effect or patient's vision is severely impaired [39]. Infectious keratitis may be an indication for enucleation when it is considered as unmanageable or in cases of keratitis with endophthalmitis [40].

Enucleation may cause obvious facial deformity, which may lead to poor psychological outcomes and require the help of a mental health professional. It is crucial to thoroughly discuss the procedure with the patient and obtain informed consent prior to surgery. Psychological evaluation may be required to assess and improve patient's readiness. Another part of the preparation stage is choosing a proper prosthetic. The enucleation itself should be executed thoroughly, as the procedure changes the anatomy and physiology of the orbital cavity and any potential errors may have an impact on both the patient and prosthetic fitting [39].

CONCLUSIONS

Recently, *Acremonium* keratomycosis emerged as a severe infection, targeting both healthy and vulnerable patients – risk factors including recent immunodeficiency, major surgeries and prolonged steroid treatment, having a detrimental effect on patient's immune system. Its recurrent appearance is yet to be explained, however it is important to note that, despite becoming a more threatening pathogen, it is a known fungal infection and as such it can be efficiently treated with antifungal drugs. Although there is no comprehensive method, azoles and polyenes are proven to be useful. When antibiotherapy is no longer viable, i.a. due to prolonged time before starting the treatment or failing to properly distinguish the type of pathogen, surgery is an effective alternative. Application of all of the aforementioned treatment options grants the patient the possibility of a full recovery and regaining perfect vision. If these methods

prove to be unsuccessful, the eye will eventually have to be enucleated, in order to prevent the further spread of infection. It is crucial to remember that such procedure is considered as an end-stage solution.

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