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Mini-Review

Contact lens-associated *Fusarium* keratitis: an eye for trouble

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We report a case of contact lens-associated *Fusarium* keratitis and provide an overview of pathophysiology, diagnosis, and treatment. A recent outbreak of contact lens-associated *Fusarium* keratitis has led to increased surveillance for this infection and awareness of risks associated with soft contact lens wear. Fungal keratitis can be misidentified as a viral or bacterial process. Therefore, it is important that clinicians and laboratory personnel are familiar with the clinical presentation and frequency of fungal contact lens-associated infections, including keratitis associated with *Fusarium spp*. In order to optimize patient outcomes and reduce risk of progression to endophthalmitis, *Fusarium* infections must be promptly identified and adequately treated.

Keywords: Contact lens-associated keratitis, corneal ulcer, fungal keratitis, *Fusarium.*

A case report

The patient, a 34 year-old female, presented with a four day history of worsening redness and foreign body sensation in her right eye. The patient wore daily-wear soft contact lenses and had been regularly using a proprietary contact lens solution.

On physical exam, the patient's visual acuity with correction was 20/60 in the right eye and 20/20 in the left. Intraocular pressure was within normal limits. Extraocular motions were full and pupillary exam revealed no abnormalities. Slitlamp examination of the right eye was remarkable for moderate sclera injection with a small amount of mucopurulent discharge. There was a corneal stromal gray-white infiltrate which had a feathery border and an overlying epithelial defect. Moderate anterior chamber reaction was visualized but hypopyon was absent. Dilated fundus exam was unremarkable. The remainder of the patient's physical examination was remarkable for mild scleral injection and the gray-white infiltrate on the right cornea as described **(Fig. 1)**.

The patient was initially treated with levofloxacin 1.5 % eye drops in the affected eye every hour. Scrapings and multiple cultures were obtained on Sabaroud agar, thioglycolate broth, blood agar and chocolate agar. Slides were smeared for Gram stain and Giemsa stain. Microscopic analysis of corneal scrapings identified the presence of filamentous fungi. Shortly thereafter, the corneal culture was typed as *Fusarium oxysporum.*

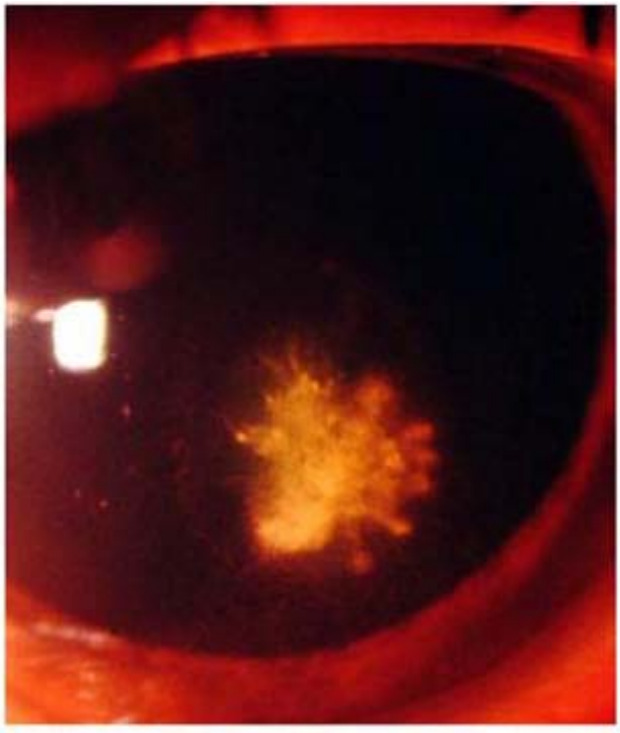

Fig. 1 Slit lamp photograph showing stromal infiltrate.

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Following the diagnosis of fungal keratitis, levofloxacin eye drops were discontinued two days after initiation of treatment. Topical natamycin 5 % was started scheduled every hour for 2 days then tapered slowly over 4 weeks. Oral voriconazole (400 mg every 12 hours for one day followed by 200 mg every 12 hours for a total of 4 weeks) was also initiated for additional coverage. For comfort, a cycloplegic agent, Cyclogyl 1 % was started. The infection clinically responded well to treatment and the patient's symptoms resolved over the course of one month.

Keratitis, or corneal inflammation, is characterized by stromal edema epithelial ulceration and anterior chamber inflammatory reaction **(Fig. 2)** [1]. A number of microscopic agents may be responsible for such infections including specific viruses, bacteria, amoebae, and fungi.Warmer climates have a higher incidence of fungal keratitis than more temperate climates, with studies showing fungal keratitis as accounting for 20 % of cases of microbial keratitis in an institution in south Florida but only 7.8 % of cases in an institution in Pennsylvania [2, 3]. *Fusarium spp.* are the most frequent cause of fungal keratitis in the southern United States and are responsible for a significant amount of morbidity globally [4-8]. *Fusarium spp.* are ubiquitous in soil and organic waste and frequently occur as plant pathogens. In addition, this fungus is classically associated with keratitis following ocular trauma associated with plant or vegetable material [4, 7-11].

Fusarium is not the most common etiologic agent associated with keratitis in those who wear soft contact lenses. However, intense media coverage of the outbreak of *Fusarium* keratitis in 2006 and most recently an outbreak of contact lens-associated *Acanthamoeba* keratitis in May 2007 has fueled increasing awareness of contact lens related keratitis in not only the medical community but the general public as well [12].

Clusters of *Fusarium* keratitis cases were first reported in Singapore and shortly thereafter in Hong Kong in February of 2006 [13-17]. In March 2006, the United States Centers for Disease Control and Prevention (CDC) initiated investigation into increasing incidence of *Fusarium* keratitis cases in the United States [13, 15, 18-22]. Retrospective review by the CDC revealed that cases of *Fusarium* keratitis in the U.S. had been increasing beginning in June 2005, with the number of cases peaking in April 2006 [13]. A case-control study conducted by the CDC identified 164 confirmed cases and subsequently found a statistically significant association between *Fusarium* keratitis infections and users of a proprietary brand of multi-purpose contact lens solution.[13] Further studies and letters also reflected this association and for safety concerns, this solution was removed from the market in the United States on May 15, 2006 [13, 16, 18, 19, 23].

While initial investigation focused on the possibility of solution contaminated at packaging, further investigations failed to detect *Fusarium* in unopened

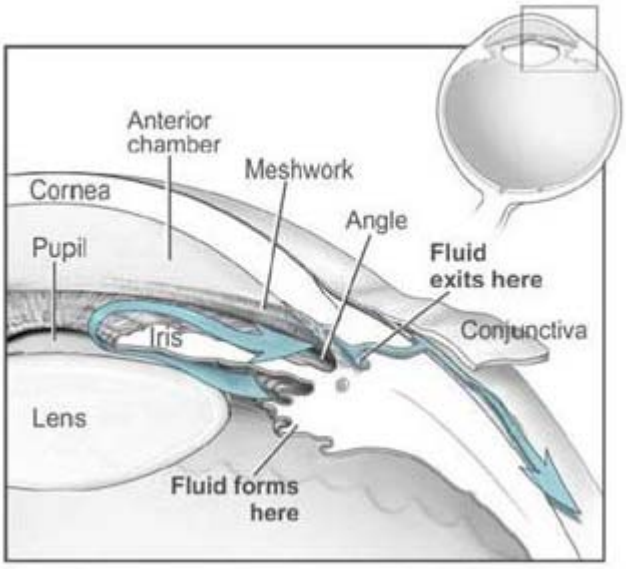

Fig. 2 Normal eye anatomy. (Image courtesy of National Eye Institute, National Institutes of Health, USA).

solution bottles or in samples obtained from the manufacturing facility [20, 24-28]. Additionally, multiple genotypes of *Fusarium* were isolated from corneal scrapings of those with confirmed infections, a finding which has suggested etiologies distinct from intrinsic contamination at the time of manufacturing [20, 24-26, 29].

The relationship of *Fusarium* keratitis to the use of a proprietary contact lens solution is proposed to be multifactorial, involving compliance to proper lens care practices and product formulation. While some solutions have been shown to be fungicidal when used as recommended, poor contact lens hygiene seems to increase risk of *Fusarium* colonization [26, 30-32]. In particular, the practice of "topping off" old solution in contact lens cases with fresh solution was a statistically significant risk factor for the outbreak of Fusarium keratitis occurring in the U.S. in 2006 [13]. The specific formulation of one product is unique in that it contains the antimicrobial formulation, alexidine. Experimentally, when this solution dries on plastic cases it forms a crystalline film which supports increased viable *Fusarium* conidia as compared to multipurpose solutions using other anti-microbial agents [26, 33]. It has also been shown that soft contact lenses have increased absorption of alexidine as compared to other widely used antimicrobial agents, resulting in decreased fungicidal activity of the storage solution, especially with re-use of solution [26, 34].

Among the dozens of fungal species known to cause keratitis, *Fusarium spp*. are particularly aggressive and capable of rapidly invading and destroying corneal tissue [35]. *Fusarium spp.* are multicellular, saprophytic organisms which replicate at 35 °C. They are characterized as filamentous fungi with long, branching, septate hyphae **(Fig. 3)** [4]. Over 100 species have been identified within the genus, with *F. solani* and *F. oxysporum* most commonly associated with fungal keratitis [2, 6, 10, 20, 36, 37]. The case series of contact lens-associated keratitis reported in Singapore in June 2006 identified *Fusarium solani* in 100 % of cases while subsequent reports in the United States identified primarily *F. solani* but also *F. oxysporum* [13, 15, 20, 26].

Pathogenesis

The pathogenesis of *Fusarium* keratitis is not fully understood. However, recent literature has provided information regarding possible mechanisms important in development of keratitis. When considering the pathogenesis of *Fusarium* keratitis, evaluation of both host and agent factors are necessary. The cornea has multiple immunologic defense mechanisms, the most superficial of which is a preocular tear film containing lysozyme, complement, and immunoglobulin. An underlying glycocalyx is associated with mucous glycoprotein and IgA which exists cross-linked to the stromal surface. Langerhans cells are located in the peripheral corneal epithelium and are important in mediating a local immune response to corneal damage [35]. Although keratitis due to *Fusarium spp.* is classically associated with traumatic corneal epithelial damage, changes in the corneal epithelium due to contact lens wear may be sufficient to enable establishment of *Fusarium spp.*

Fig. 3 Conidiophores and conidia of *Fusarium spp.* (Image courtesy of CDC/Dr. Libero Ajello-Public Health Image Library).

infection [7, 8, 32, 38, 39-42]. Thus, as evident in the recent outbreak of *Fusarium* keratitis, poor hygiene practices including topping off old solution with fresh solution and wearing lens overnight are associated with a higher risk of infectious keratitis [3, 5, 13, 15, 26, 30, 32, 39-42].

Experiments involving inoculation of rabbit corneas with fungi have resulted in new insight into the pathogenesis of fungal keratitis. Conidia first bind to the epithelial basement membrame, followed by basement membrane destruction and infiltration of inflammatory cells [43]. In comparison to other organisms causing keratitis, *Fusarium spp.* release small amounts of chemotactic substances. This characteristic limits damage due to host inflammatory response but also contributes to the rapid progression of disease [4, 38, 44]. However, host immune function is still important as polymorphonuclear (PMN) leukocytes are thought to play a key role in stromal degradation. PMN leukocytes release lysosomal substances which are thought to influence the proteolytic activity of *Fusarium spp.*, particularly that of the matrix metalloproteinases [4, 10, 43-45].

Clinical presentation

The clinical presentation of this insidious fungus can vary depending on the extent and stage of the infectious process. Patients with *Fusarium* keratitis may initially present only with redness, photophobia or foreign body sensation. Blurred vision may later accompany obvious corneal lesions as the infection progresses. With invasion of the anterior chamber, increased intraocular pressure may complicate the clinical course. If the infection goes unrecognized or treatment is delayed, *Fusarium* keratitis may progress to corneal perforation and endophthalmitis [4, 20, 21, 38, 46].

A complete history is the cornerstone of any comprehensive clinical evaluation. The interview should specifically focus on use of contact lenses, contact lens practices including duration of use and cleaning practices, exposure to known or common irritants, contact with plant matter, previous history of corneal infections, and recent ocular trauma. Clinicians should be aware that patients may not recall minor ocular trauma. If contact lens-associated keratitis is suspected, it is advisable to ask the patient to offer his or her lenses, storage cases, and most recently used bottle of solution for testing. The type and brand of contact lenses and solution should also be noted.

Investigation with the slit lamp may reveal grayish-white, coarse, granular infiltration of the anterior corneal stroma and epithelium [35]. Infiltrates are described as having feathery "hyphate" margins which may extend into the unaffected cornea with the possibility of satellite lesions.[4, 10, 13]. In cases of keratitis caused by filamentous fungi including *Fusarium* spp., a dry and elevated epithelium overlying an infiltrate is frequently seen [4, 10]. With advanced ulceration and progressive infection, stromal thinning and loss of epithelium may be evident.[1, 4, 47]. A raised dry slough and serrated margins are seen more frequently in fungal keratitis, while hypopyon and fibrinous exudates are observed more frequently in bacterial keratitis [48].

Confocal microscopy, which allows the clinician to visualize the stroma in a single plane of focus, permits an examination of the three-dimensional structure of the cornea [49]. This is useful in differentiation between fungal keratitis due to filamentous fungi such as *Fusarium spp.* and fungal keratitis due to other organisms including *Aspergillus fumigatus* and *Candida albicans* [50]. *Fusarium spp.* proliferate within the cornea in an arrangement parallel to the lamellar plane, while C. *albicans* and *A.fumigatus* appear perpendicular to this plane [43]. A recent case series by Brasnu *et al.* describes *in vivo* confocal microscopy as successful in rapid identification of *Fusarium spp.* as a causative agent of keratitis. Confocal microscopy is emerging as an important tool in clinical decision making and more evidence is needed regarding positive predictive value of confocal microscopy in diagnosis of fungal keratitis [50].

Laboratory diagnosis

Careful evaluation of laboratory data is also essential in the confirmation of this microbe. Both smears and cultures are essential in evaluating keratitis. To obtain corneal material, a Kimura spatula, Bard-Parker blade or calcium alginate swab may be used. Little conclusive evidence-based data is available regarding the most appropriate collection technique for identification of fungal corneal ulcers. One report details greater amounts of mycotic growth when using a calcium alginate swab as compared to a Bard-Parker blade; however, the report described both of these techniques as adequate for establishing diagnosis [50].

After a specimen is obtained, the corneal sample should be lightly streaked in the center of both

chocolate and blood agar plates for culture. In addition to corneal sampling, the clinician may wish to obtain lid and conjunctival cultures for comparison. While cultures are pending, corneal smears are useful in quickly identifying fungal elements and initiating antifungal treatment. If fungal keratitis is strongly suspected but smears and cultures are negative, corneal biopsy may be necessary for establishing a definitive diagnosis [52].

A variety of stains may be used to examine smears for the morphology of fungal elements. The Gram stain is frequently used to differentiate between bacteria, fungi, and *Acanthamoeba* in corneal specimens. However, a recent study provides evidence that potassium hydroxide with calcofluor white is more sensitive and specific in detecting fungal elements in patients with fungal keratitis as compared to Gram stain [53]. Alternatively, some investigators have reported success in detecting fungal elements using lactophenol blue or the Giemsa stain [54]. Lectins bind to the cell walls of fungi, atypical mycobacteria, and *Acanthamoeba* trophozoites and cysts and can be coupled with fluorescein, allowing detection of organisms using fluorescence microscopy [55]. A modified Gomori methenamine silver stain is highly specific for the identification of fungal elements and has been recommended as it enables rapid detection of *Acanthamoeba* as well as fungal elements [39, 56].

Culture of corneal scrapings is more sensitive than examination of smears and is therefore a critical part of the work-up of suspected *Fusarium spp.* Keratitis [47]. Sabouraud's dextrose agar with gentamicin and without cycloheximade, incubated at 25 °C, is frequently cited as a useful culture medium for cases of suspected fungal keratitis [1, 10, 47]. One author reports identification of 97 % of corneal cultures within three weeks when using blood agar at 25 °C and 37 °C, brain-heart infusion at 25 °C, and thioglycolate broth at 25 °C [6]. Chocolate agar placed in a CO_2 jar is useful in ruling out *Haemophilus spp.* or *N.gonorrhoeae* and a non-nutrient agar with *Escherichia coli* overlay may be used to differentiate fungal keratitis from *Acanthamoeba* keratitis [37]. Because the literature describes multiple algorithms for culturing suspected cases of fungal keratitis, more evidence-based data is needed to properly assess the optimal culture media for diagnosis of fungal keratitis.

When plating cultures, a "C" streak pattern should be employed and a positive culture defined as growth in the location of the initial inoculation site [10]. *Fusarium spp*. appear as fluffy elevated white colonies when cultured on solid media and growth of *Fusarium spp.* may be observed as soon as 24 hours after inoculation **(Fig. 4)** [4, 10]. It is likely the future will see novel and more effective diagnostic methods for *Fusarium spp.* keratitis. Such methods include immunochemistry technology as well as polymerase chain reaction (PCR) and rDNA typing [57].

Patient management

Once *Fusarium spp*. keratitis is confirmed, treatment may involve one or more classes of topical, oral or systemic therapy. Although natamycin exhibits relatively poor penetration through the corneal layers, its bioavailability is sufficient for anti-fungal activity and it has been effective in treating *Fusarium spp.* keratitis *in vivo* [58]. A 5 % suspension of natamycin applied hourly during initial treatment and tapered after several days is the usual recommended dosing schedule [58, 59]. Topical amphotericin B, a large polyene, has shown variable activity against *Fusarium spp*. and may be used as a component of initial empirical therapy [4]. Systemic treatment with amphotericin B lipid complex may be more effective than topical treatment when targeting *Fusarium spp* [60, 61].

Imidazoles and triazoles are also important in the effective treatment of *Fusarium* keratitis. The fungistatic mechanism of azoles involves interference in the conversion of lanosterol to ergosterol, resulting in cell membrane disruption [62]. Oral or systemic voriconazole, fluconazole, ketoconazole, or

Fig. 4 *Fusarium spp.* cultured from corneal scrapings.

itraconazole may be administered in conjunction with topical natamycin for infections requiring more aggressive therapy [21, 47]. Topical natamycin 5 % has been shown in one study to be superior to topical itraconazole 1 % in the management of fungal keratitis due to filamentous species including *Fusarium spp*. [58]. Topical and systemic use of voriconazole has been reported as effective in treatment of recent *Fusarium* cases, although several cases refractory to voriconazole have been described [7, 15, 20, 61, 63, 64]. A new triazole available in oral suspension, posaconazole, has been shown to have excellent tissue penetration and has been clinically demonstrated as useful in treating *Fusarium* keratitis and endophthalmitis [61, 65]. Surgical intervention with penetrating keratoplasty may be necessary for cases progressing to corneal perforation; when treating with surgical intervention, care must be taken to remove all organisms in order to avoid reinfection [66].

Conclusion

The 2006 outbreak of *Fusarium* keratitis highlights the need for increased clinical awareness of this aggressive fungal pathogen and differentiation from other contact lens related infections such as *Acanthamoeba* keratitis. In order to optimize patient outcomes and reduce risk of complications including corneal perforation, endophthalmitis, and ultimately vision loss, *Fusarium* keratitis must be promptly identified and effectively treated. This requires a detailed history, an experienced clinician, and a skilled laboratory facility. Above all, patient awareness and education are essential for risk factor modification and early recognition.

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