Int Ophthalmol (2010) 30:103–107
DOI 10.1007/s10792-008-9290-7

CASE REPORT

Fusarium keratitis and endophthalmitis associated with lens contact wear

Julia Proença-Pina · Isabelle Ssi Yan Kai · Tristan Bourcier · Monique Fabre · Hervé Offret · Marc Labetoulle

Received: 2 April 2008 / Accepted: 30 December 2008 / Published online: 10 April 2009

Abstract *Introduction* *Fusarium* keratitis is a severe corneal infection that is usually seen in tropical and subtropical countries after a corneal trauma. In 2005–2006, an epidemic of *Fusarium* keratitis, occurring predominantly among contact lens wearers, was observed in several countries. *Case report* We describe the clinical course of a *Fusarium* keratitis which failed to respond to systemic and local voriconazole treatment, and experienced a progression to a severe keratitis with endophthalmitis, requiring early therapeutic keratoplasty ("à chaud"). After 8 months of follow up, the vision recovered to 20/50. *Discussion* After the 2005–2006 worldwide epidemics, case–control studies pointed out that a new lens care solution, ReNu with MoistureLoc® (Bausch & Lomb™), was likely responsible of numerous cases. Complementary studies underlined that this infection mostly concerned non-compliant patients, i.e., those reusing the solution several times, since this results in a decrease of the antifungal activity due to the uptake of the biguanides into the lens. *Conclusion* *Fusarium* endophthalmitis can result in a devastating disease with a poor visual outcome. An initial antifungal dual therapy may control the infection. In case of failure, an early keratoplasty may be mandatory. For contact lens wearers, education on sanitary good practice is necessary to avoid new epidemics in the future.

Keywords Amphotericin B · Endophthalmitis · *Fusarium solani* · Multipurpose lens care solution · ReNu with MoistureLoc® · Voriconazole

J. Proença-Pina · I. Ssi Yan Kai · H. Offret · M. Labetoulle
Department of Ophthalmology, Bicêtre University Hospital, APHP, University Paris XI, Le Kremlin Bicêtre, Paris, France
e-mail: marc.labetoulle@bct.aphp.fr

T. Bourcier
Ophthalmology Department, Strasbourg University Hospital, Strasbourg, France

M. Fabre
Department of Pathology, Bicêtre University Hospital, APHP, University Paris XI, Le Kremlin Bicêtre, Paris, France

M. Labetoulle (✉)
CHU de Bicêtre, 78 rue du Général Leclerc, Le Kremlin Bicêtre CEDEX, 94275 Paris, France
e-mail: marc.labetoulle@bct.ap-hop-paris.fr

Ocular infections caused by fungal organisms may have vision-threatening consequences. Among them, severe fungal keratitis due to *Fusarium* species may lead to endophthalmitis, which are mainly seen in tropical/subtropical areas, usually following trauma [1, 2]. In late 2005 and 2006, an outbreak of *Fusarium* keratitis was reported all around the world among contact lens wearers. Epidemiologic inquiries suspected the multipurpose lens care solution ReNu

With MoistureLoc® (Bausch & Lomb™) to be associated with numerous cases, leading the company to withdraw marketing of this product.

We report the clinical course of a *Fusarium* keratitis which failed to respond to systemic and local voriconazole treatment and experienced a progression to a severe fungal endophthalmitis.

Case report

In December 2006, a 25-year-old male contact lens wearer was referred to our department with a 1-month history of pain and decreased vision in the left eye. Prior to presentation, he had been treated for a presumed herpes keratitis, using local acyclovir, oral valaciclovir and local steroids. At the time of presentation, the eye was painless. Left initial visual acuity was reduced to hand motion perception. Slit-lamp examination showed a 5-mm round central, whitish stromal infiltrate on the cornea, surrounded by small peripheral infiltrates and an immune ring. There also was a 1-mm hypopion in the anterior chamber (Fig. 1). The right eye was normal.

Since these clinical features could be either due to fungus or acanthamoeba species, QH topical voriconazole 0.1%, PHMB 0.02% and desomedine, and systemic voriconazole (200 mg oral, b.i.d.) were initially associated, after a corneal scraping with biopsies had been performed for microbiological analysis. Cultures of the lens box were positive for *Fusarium solani*, whereas cultures of the contact lens solution (ReNu with MoistureLoc®, Bausch & Lomb™) were negative.

Since keratitis did not improve rapidly, QH topical amphotericin B 0.5% was added. However, the condition continued to worsen, and infectious process reached the inferior limbus (Fig. 2), leading to a therapeutic penetrating keratoplasty 10 days later. During the procedure, we observed that the anterior chamber was filled with coagulated fibrin, with necrosis of the anterior lens capsule, and issue of lens material through a spontaneous capsular break: it was an endophtalmitis and not only a keratitis. After removing of the fibrotic membrane, an extracapsular cataract extraction was performed during the same surgery. The anterior chamber was irrigated with a 5% povidone iodine solution and a 0.005% amphotericin B solution. Postoperative treatment included topical voriconazole 0.1%, topical 0.1% amphotericin B, topical 2% cyclosporine and oral voriconazole. Pathologic examination of the corneal button showed numerous hyphae and cultures grew *Fusarium*. Minimal inhibitory concentrations (MIC) for amphotericine B and voriconazole were 1 μg/ml and >8 μg/ml, respectively. Topical voriconazole was thus rapidly tapered. An important inflammation appeared in the following days, and the graft became vascularized. Peripheral anterior synechia developed inferiorly to the host-donor interface, and posterior extensive synechia appeared quickly (Fig. 3). A post operative ultrasound excluded a fungal invasion of the vitreous.

Topical steroids use was delayed by 6 weeks to avoid aggravation of fungal growth. Heidelberg Retina Tomograph II-Rostock Cornea Module confocal microscopy was performed and showed no *Fusarium* hyphae.

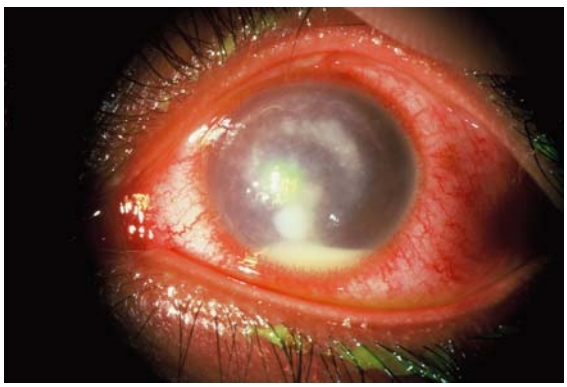

Fig. 1 *Fusarium* keratitis after 1 month of evolution

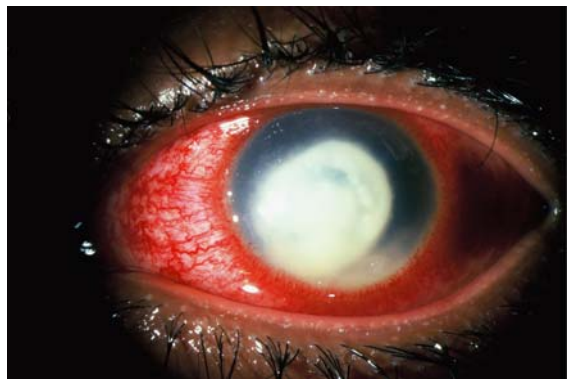

Fig. 2 *Fusarium* keratitis after 10 days of antifungal treatment

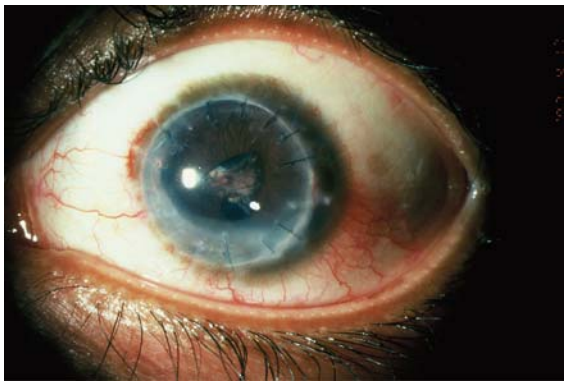

Fig. 3 Six weeks after corneal graft

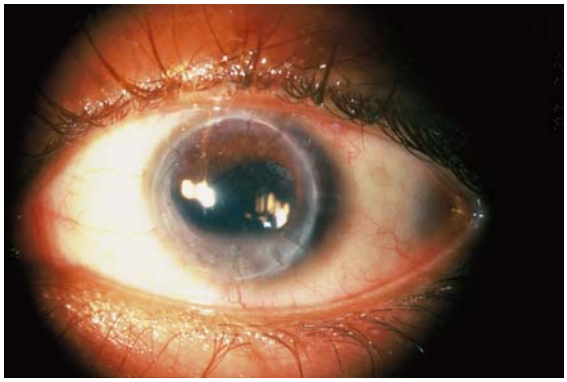

Fig. 4 One week after implantation of a PMMA IOL in the sulcus

The antifungal drops were stopped at 3 months and steroid drops were maintained, permitting a decrease of corneal neovascularization. A PMMA intraocular lens was placed into the sulcus at the 6th month, resulting in a best corrected visual acuity at 20/50 (Fig. 4).

Comments

Fungal keratitis and endophthalmitis are sight-threatening infections that, despite an appropriate therapeutic approach, may lead to corneal graft during the acute phase in about one-fourth of cases [3]. Fungal infections are more prevalent in tropical and subtropical climates, but are rare in temperate countries [4]. Risk factors include ocular trauma, systemic immunosuppression, topical steroid treatment, and soft contact lens wearing. However, fungus is responsible for less than 5% of infections in contact lens wearers [1, 2, 5, 6].

In spring 2006, several articles pointed at an outbreak of contact lens *Fusarium* keratitis in Asia and United States [3, 7–14]. Alfonso et al. noticed that recovery of fungal pathogens among wearers of contact lenses increased from 26.7% to 50% of isolates in 2005 in the Bascom Palmer Eye Institute (BPEI), Miami, and that more than 50% of these fungal infections were due to *Fusarium* species [7]. The authors identified contact lens wear as a risk factor for fungal keratitis. In August 2006, the same team reported that 94% of the confirmed *Fusarium* keratitis treated in BPEI were related to soft contact lenses, and patients were significantly more likely users of ReNu with MoistureLoc® ((Bausch & Lomb™) than controls (69% vs 15%, odds ratio 13.3) [9]. This lens care solution was strongly suspected as being associated with the outbreak of *Fusarium* keratitis in the United States and Singapore. Bausch & Lomb™ stopped supplying the products in the US and Asian markets in April 2006, with a complete withdrawal of the Moisture-Loc® formula on May 2006. However, the first tests established that marketed products were biologically effective against *Fusarium,* and no evidence of *F. solani* contamination was detected at the manufacturing sites [9, 13, 15, 16]. More confounding was the fact that MoistureLoc® was particularly efficient against *F. solani*. So how to explain this outbreak of contact lens related *Fusarium* keratitis? The answer was suggested by the US Centers For Disease Control and Prevention (CDCP) report, indicating that patients reusing lens care solutions were more likely to have *Fusarium* keratitis than those who did not reuse them [9, 17]. This could be related to the uptake of preservatives or biocides into the lens matrix. The antifungal activity of lens care solution containing biguanides as preservatives, such as Alexidine and PHMB, decreases after storage because of the uptake of the biguanides into the lens. In such conditions, the reuse of the solution enhances this phenomenon and decreases the level of biguanides into the remaining solution at each reuse. Indeed, the used ReNu with MoistureLoc® showed less antifungal activity and biocide than the fresh products after a single storage cycle with soft contact lenses [18]. Multipurpose solutions containing POLYQUAD (polyquaternium-1) or a combination of POLYQUAD and ALDOX

(myristamidopropyl dimethylamine) biocides showed a low uptake of biocide and maintained fungicidal efficacy against *Fusarium* [18]. Moreover, release of biocide from lenses after application onto the cornea appeared to be another important factor, since it may damage the ocular surface. Ahearn et al. recently reported that *F. solani* produces coiled penetration pegs in the matrix of hydrophilic soft contact lenses, similar in morphology to those found in HEMA lenses. Viable fungus may remain on the lens despite vigorous rinsing with multipurpose solutions. Zhang et al. showed that *Fusarium* complex survived in stressed drying films of multipurpose solutions, particularly ReNu Moisture Loc®. Levy et al. showed that, under extreme evaporative conditions, the biocidal efficacy of MoistureLoc® is reduced [15], with *Fusarium* being less susceptible to disinfection in the presence of a polymer film of the components present in the MoistureLoc® formulation.

Fusarium is an ubiquitous water- and air-borne fungus which may cause life-threatening infections, besides keratitis and endophthalmitis. The predominant *Fusarium* species inducing human pathogenic are *F. solani*, *F. oxysporum*, and *F. moniliform*. Voriconazole [19], amphotéricine B, posaconazole [20–22], and cetrimide [23] are effective in the treatment of keratitis caused by *Fusarium*, whereas itraconazole and caspofungin are not usually effective [24]. Fungal endophthalmitis is typically indolent, with latency period of weeks to months following the onset of the keratitis. The toxicity of *Fusarium* is related to both its mycotoxin [25] and ability to replicate at 35°C [26], which is the temperature of the cornea. Fungi can invade stromal lamellae, penetrate an intact Descemet's membrane, and then spread into the anterior chamber. Steroids are known to enhance the invasiveness of fungi [27]. *Fusarium* are more alkaline-tolerant than other environmental fungi, and this difference may give *Fusarium* an advantage in their ability to cause ocular infections.

The optimal management of *Fusarium* endophthalmitis is not clearly established, partially explaining why they are still of poor prognosis [26]. Initial treatment of suspected filamentous fungal infections is based on a polyenes, such as 5 mg/ml natamycin suspension or 1.5 mg/ml amphotericin B solution [7], with a high frequency of instillation (QH initially, then according to clinical evolution). Latest antifungal agents, such as voriconazole or posaconazole, are efficient in vitro [19], and oral voriconazole reaches efficient aqueous and vitreous concentration (1.13 ± 0.57 μg/ml and 0.81 ± 0.31 μg/ml, respectively) [20]. In our case, MIC for voriconazole was >8 mg/ml, wheras amphotericin B was more efficient (MIC = 1 mg/ml), which may explain the failure of our initial treatment (i.e., voriconazole monotherapy). Indeed, some authors suggested that an aggressive dual (i.e., voriconazole + amphotericine B) therapy should be considered at presentation of severe fungal keratitis [3]. Clinical and biological diagnosis and monitoring of fungal keratitis is difficult. Besides microbial assessments, high-resolution images of the fungal structures using in vivo confocal microscopy is a valuable tool for diagnosis and monitoring. Brasnu et al. [28], using the Heidelberg Retinal Tomograph II-Rostock Cornea Module (HRTII-RCM), showed a high correlation between images of fungal hyphea and results of cultures. In the future, this exam may be used for an earlier and more accurate diagnosis of fungal corneal infections, as we made in this case.

The timing for surgery is critical. Several authors underlined the importantce of an early keratoplasty ("à chaud") in severe keratomycosis [26, 29], especially when large ulcers affect most of the cornea, or when there is a progression toward the limbus despite medical treatment, or finally in case of impending perforation (descemetocele). In these cases, results are rather positive, with 72.4% of grafts remaining clear after 1-year of follow-up. In contrast, recurrences of the fungal infection may occur into the graft, usually within 3 weeks after surgery [29].

In conclusion, *Fusarium* keratitis can result in devastating consequences and poor visual outcome. It is likely cautious to begin with a dual topical therapy, at least until the results of antifungal susceptibility. An oral treatment may also be associated in case of deep stromal infiltration. Treatment should last between 6 weeks and 3 months.

The timing of surgery is critical and early surgical intervention may play an important role in the prognosis. A therapeutic keratoplasty should be done in case of deep keratitis and in case of failure of initial treatment. Of course, education of patients on contact lens hygiene is mandatory, and probably the best preventive issue, particularly concerning the danger of reusing the solutions.

Acknowledgments Thanks to Dr Antoine Labbe and to Miss Beatrice Dupas for imaging with the confocal microscopy HRTII (Quinze-Vingts National Center of Ophthalmology, Department of Ophthalmology III, Christophe Baudouin).

References

1. Cheng KH, Leung SL, Hoekman HW et al (1999) Incidence of contact-lens-associated microbial keratitis and its related morbidity. Lancet 354:181–185. doi:10.1016/S0140-6736(98)09385-4
2. Schein OD, Ormerod LD, Barraquer E et al (1989) Microbiology of contact lens-related keratitis. Cornea 8:281–285. doi:10.1097/00003226-198912000-00011
3. Iyer SA, Tuli SS, Wagoner RC (2006) Fungal keratitis: emerging trends and treatment outcomes. Eye Contact Lens 32:267–271. doi:10.1097/01.icl.0000249595.27520.2e
4. Bharathi MJ, Ramakrishnan R, Meenakshi R et al (2007) Microbial keratitis in South India: influence of risk factors, climate, and geographical variation. Ophthalmic Epidemiol 14:61–69. doi:10.1080/09286580601001347
5. Mah-Sadorra JH, Yavuz SG, Najjar DM et al (2005) Trends in contact lens-related corneal ulcers. Cornea 24:51–58. doi:10.1097/01.ico.0000138839.29823.57
6. Rosa RH Jr, Miller D, Alfonso EC (1994) The changing spectrum of fungal keratitis in south Florida. Ophthalmology 101:1005–1013
7. Alfonso EC, Cantu-Dibildox J, Munir WM et al (2006) Insurgence of Fusarium keratitis associated with contact lens wear. Arch Ophthalmol 124:941–947. doi:10.1001/archopht.124.7.ecs60039
8. Bernal MD, Acharya NR, Lietman TM et al (2006) Outbreak of Fusarium keratitis in soft contact lens wearers in San Francisco. Arch Ophthalmol 124:1051–1053. doi:10.1001/archopht.124.7.ecr60006
9. Chang DC, Grant GB, O'donnell K et al (2006) Multistate outbreak of Fusarium keratitis associated with use of a contact lens solution. JAMA 296:953–963. doi:10.1001/jama.296.8.953
10. Cohen EJ (2006) Fusarium keratitis associated with soft contact lens wear. Arch Ophthalmol 124:1183–1184. doi:10.1001/archopht.124.8.1183
11. Epstein A (2007) Recent Fusarium outbreak. Eye Contact Lens 33:54. doi:10.1097/ICL.0b013e31802e6236
12. Khor WB, Aung T, Saw SM et al (2006) An outbreak of Fusarium keratitis associated with contact lens wear in Singapore. JAMA 295:2867–2873. doi:10.1001/jama.295.24.2867
13. Rosenberg KD, Flynn HW Jr, Alfonso EC, Miller D (2006) Fusarium endophthalmitis following keratitis associated with contact lenses. Ophthalmic Surg Lasers Imaging 37:310–313
14. Sugar J (2006) The contact lens/fusarium "outbreak". Am J Ophthalmol 142:146. doi:10.1016/j.ajo.2006.04.026
15. Levy B, Heiler D, Norton S (2006) Report on testing from an investigation of fusarium keratitis in contact lens wearers. Eye Contact Lens 32:256–261. doi:10.1097/01.icl.0000245556.46738.14
16. Rosenthal RA, McDonald MM, Schlitzer RL et al (1997) Loss of bactericidal activity from contact lens storage solutions. CLAO J 23:57–62
17. Centers for Disease Control & Prevention (CDC) (2006) Update: fusarium keratitis—United States, 2005–2006. MMWR Morb Mortal Wkly Rep 55:563–564
18. Rosenthal RA, Dassanayake NL, Schlitzer RL et al (2006) Biocide uptake in contact lenses and loss of fungicidal activity during storage of contact lenses. Eye Contact Lens 32:262–266. doi:10.1097/ICL.0b013e31802b413f
19. Marangon FB, Miller D, Giaconi JA, Alfonso EC (2004) In vitro investigation of voriconazole susceptibility for keratitis and endophthalmitis fungal pathogens. Am J Ophthalmol 137:820–825. doi:10.1016/j.ajo.2003.11.078
20. Hariprasad SM, Mieler WF, Holz ER et al (2004) Determination of vitreous, aqueous, and plasma concentration of orally administered voriconazole in humans. Arch Ophthalmol 122:42–47. doi:10.1001/archopht.122.1.42
21. Sponsel WE, Graybill JR, Nevarez HL, Dang D (2002) Ocular and systemic posaconazole (SCH-56592) treatment of invasive *Fusarium solani* keratitis and endophthalmitis. Br J Ophthalmol 86:829–830. doi:10.1136/bjo.86.7.829-a
22. Tu EY, McCartney DL, Beatty RF et al (2007) Successful treatment of resistant ocular fusariosis with posaconazole (SCH-56592). Am J Ophthalmol 143:222–227. doi:10.1016/j.ajo.2006.10.048
23. Mahmoud YA (2007) In vitro and in vivo antifungal activity of cetrimide (cetyltrimethyl ammonium bromide) against fungal keratitis caused by *Fusarium solani*. Mycoses 50:64–70. doi:10.1111/j.1439-0507.2006.01313.x
24. Lalitha P, Shapiro BL, Srinivasan M et al (2007) Antimicrobial susceptibility of *Fusarium*, *Aspergillus*, and other filamentous fungi isolated from keratitis. Arch Ophthalmol 125:789–793. doi:10.1001/archopht.125.6.789
25. Nelson PE, Dignani MC, Anaissie EJ (1994) Taxonomy, biology, and clinical aspects of *Fusarium* species. Clin Microbiol Rev 7:479–504
26. Dursun D, Fernandez V, Miller D, Alfonso EC (2003) Advanced fusarium keratitis progressing to endophthalmitis. Cornea 22:300–303. doi:10.1097/00003226-200305000-00004
27. Nelson PE, Dignani MC, Anaissie EJ (1994) Taxonomy, biology, and clinical aspects of *Fusarium* species. Clin Microbiol Rev 7:479–504
28. Brasnu E, Bourcier T, Dupas B et al (2007) In vivo confocal microscopy in fungal keratitis. Br J Ophthalmol 91:588–591. doi:10.1136/bjo.2006.107243
29. Ti SE, Scott JA, Janardhanan P, Tan DT (2007) Therapeutic keratoplasty for advanced suppurative keratitis. Am J Ophthalmol 143:755–762. doi:10.1016/j.ajo.2007.01.015