

CASE REPORT

Keratomycosis due to *Tintelnotia destructans* refractory to common therapy treated successfully with systemic and local terbinafine in combination with polyhexamethylene biguanide

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Abstract

Purpose To report on a wearer of rigid gas-permeable contact lenses with a keratomycosis due to *Tintelnotia*—a new genus of *Phaeosphaeriaceae*—treated with terbinafine and polyhexamethylene biguanide.

Methods Chart review of a patient with fungal keratitis treated additionally with systemic and topical terbinafine 0.25% after symptoms increased under conventional antimycotic therapy with voriconazole. Antifungal susceptibility had been tested in vitro.

Results After starting an additional treatment with systemic and topical terbinafine, the severe corneal infection was sufficiently resolved. The drug was well tolerated without any neurological, dermatological or gastroenterological problems. Terbinafine revealed a marked in vitro antifungal activity of 0.12 µg/ml. The fungus was identified as *Tintelnotia destructans*.

Conclusions Terbinafine might be considered as a therapeutic option in severe cases of fungal keratitis refractory to common antifungal therapy.

Keywords Fungal keratitis · Terbinafine · Voriconazole · PHMB · *Phaeosphaeriaceae* · *Tintelnotia*

Introduction

Infections of the eye due to moulds are becoming diagnosed more frequently [1, 2]. Fungal keratitis is commonly associated with wearing contact lenses [2–4]. Risk factors for contact lens-associated infectious keratitis are prolonged wearing and poor hygiene [5].

We report on a wearer of rigid gas-permeable contact lenses with keratitis due to a newly described *Tintelnotia destructans*. The infection had been refractory to standard antifungal therapy and developed increasing symptoms. Only a combination with systemic and topical terbinafine and polyhexamethylene biguanide (PHMB) led to recovery of the eye infection.

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Case report

A patient wearing rigid gas-permeable contact lenses had suffered from conjunctivitis for 1 week and decrease of the visual acuity to 20/50. A small paracentral corneal infiltrate was found (Fig. 1), and topical antibiotic therapy was started with levofloxacin 5 mg/ml (Oftaquix[®], Santen Oy, Tampere, Finland) six times per day in addition to scopolamine eyedrops (Boro-Scopol N[®], Dr. Winzer Pharma GmbH, Berlin, Germany) twice a day. As no bacteria or fungi could be cultured from corneal scraping, therapy was extended by additional topical prednisolone 1% hourly (Inflanefran forte[®], Pharm Allergan GmbH, Ettlingen, Germany).

One week later, some satellite infiltrates and an increase of the central infiltrate were observed. Microbiological examination of the contact lens revealed *Klebsiella pneumoniae* and no fungi. Treatment was intensified with topical moxifloxacin 5 mg/ml (Vigamox[®], Alcon Pharma GmbH, Freiburg, Germany) in addition to levofloxacin, both given by turns every hour. As the satellite infiltrates increased (Fig. 2), an additional keratomycosis was suspected and voriconazole 2% eyedrops were administered hourly. The topical steroid treatment was stopped immediately.

Four days later, a hypopyon was observed and visual acuity declined to 20/200 (Fig. 3). Therapy was intensified with intracameral injections of vancomycin, ceftazidime and amphotericin B every 2 days and systemic voriconazole 400 mg daily. Despite this, a viscous, glutinous hypopyon (BB-1-sign [6, 7]) with a retrocorneal cone developed a few days later (Figs. 4, 5). This cone grew and developed

an iris–lens contact (Fig. 6). Over time, several microbiological cultures and PCR tests of corneal scrapings were performed to identify the causative organism; the results remained negative. Using the HRT II–Rostock Cornea Module (confocal laser scanning microscope; Heidelberg, Germany), filamentary structures and hyphal growth patterns consistent with fungal elements were recognized (Fig. 7).

An intracameral extraction of the viscous hypopyon in the form of a cone revealed cultural detection of an unknown hyphomycete and resulted in changing the regimen to topical terbinafine 0.25% and PHMB (Lavanid[®] 0.02%, Serag-Wiessner, Naila, Germany), both given every hour and terbinafine also given every 2 h at night.

Due to the complicated and severe progression, an in vitro susceptibility testing of the still unidentified mould was performed, including several antifungal drugs. Terbinafine showed the lowest rate of minimal inhibition concentration (MIC 0.12 µg/ml) compared to other agents like voriconazole, fluconazole, itraconazole or posaconazole (1/16/1/1 µg/ml); the MIC for PHMB was 1.56 µg/ml [8].

The fungus produced phoma-like pycnidia (Fig. 8) not clearly identifiable by phenotypical and by molecular methods. Sequencing of the ITS (internal transcribed spacer) region, LSU (large subunit) and SSU (small subunit) of rDNA (ribosomal DNA) and comparison with the CBS (Centraalbureau voor Schimmelcultures) database revealed that this isolate belongs to the newly described genus *Tintelnotia* within the family *Phaeosphaeriaceae* and has been identified as *Tintelnotia destructans* [8].

As iris hyperaemia, severe conjunctivitis and corneal neovascularization developed, an additional

Fig. 1 Small paracentral infiltrate at first day of examination



Fig. 2 One week later, satellite infiltrates and increase of the central infiltrate

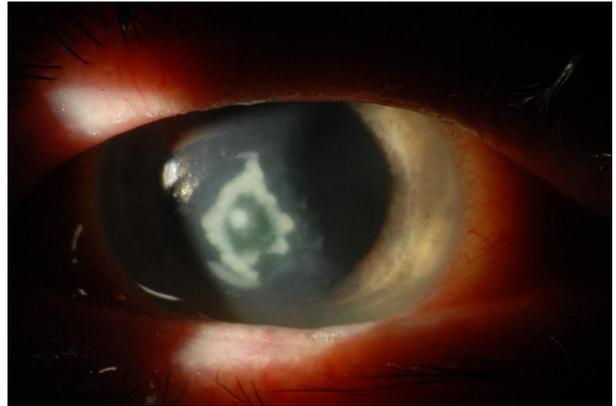


Fig. 3 Increase of inflammation with hypopyon

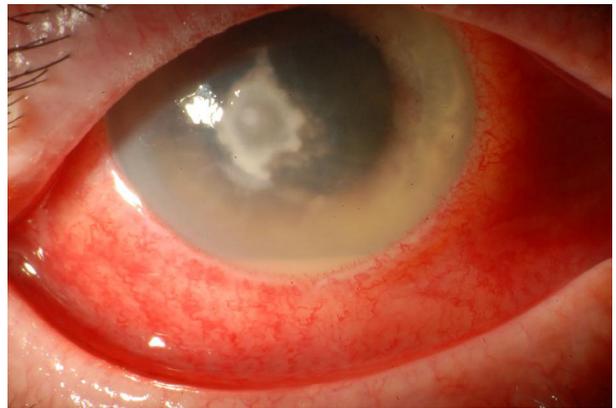
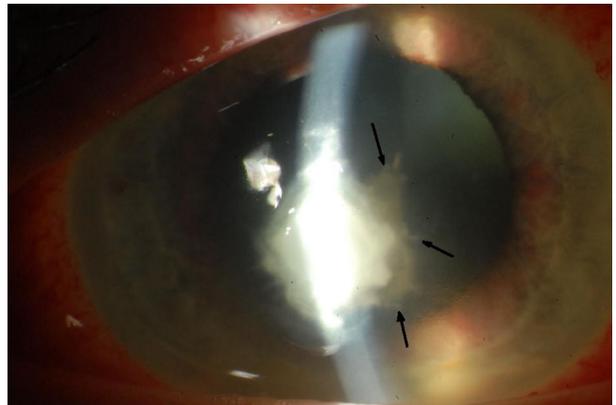


Fig. 4 Viscous, glutinous hypopyon (B.-B.-1-sign) with retrocorneal cone backwards. Arrows at the end of corneal infiltrate



application of topical prednisolone 1% (Inflanefran forte®) three times daily was restarted. Intracameral injections were changed to voriconazole and amphotericin B daily. Systemic treatment was changed to terbinafine (Lamisil®, Novartis, Nuremberg, Germany) 250 mg daily.

Maintaining this treatment, the severe keratitis slowly improved, and intracameral injections and systemic therapy could be stopped 7 weeks after starting. PHMB and topical terbinafine were given daily every other hour for another 2 months. Prednisolone eyedrops were administered over a period of 4 months and then tapered off. No neovascularization

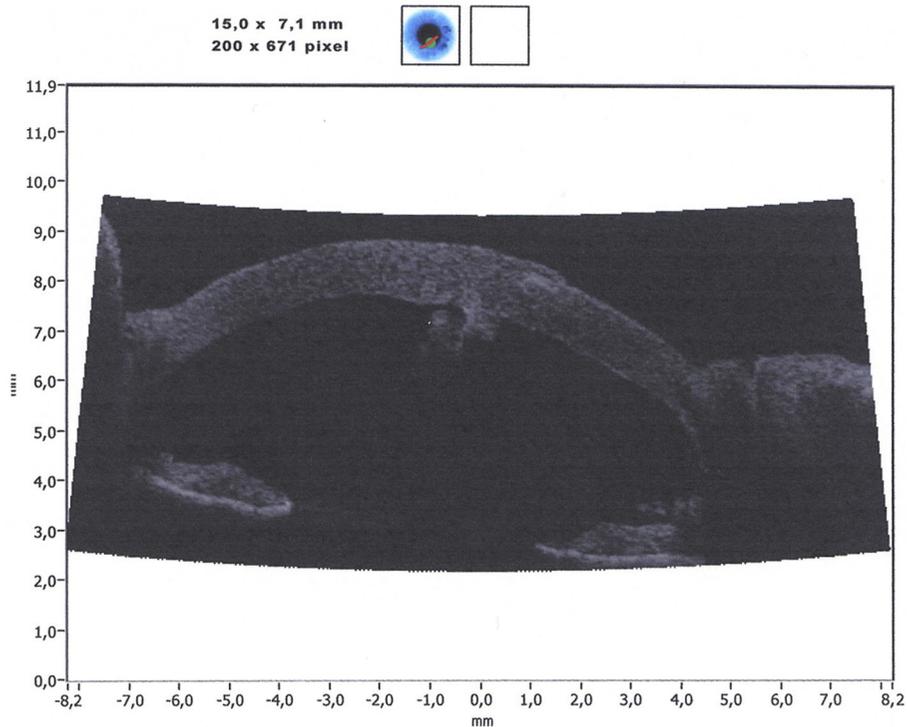
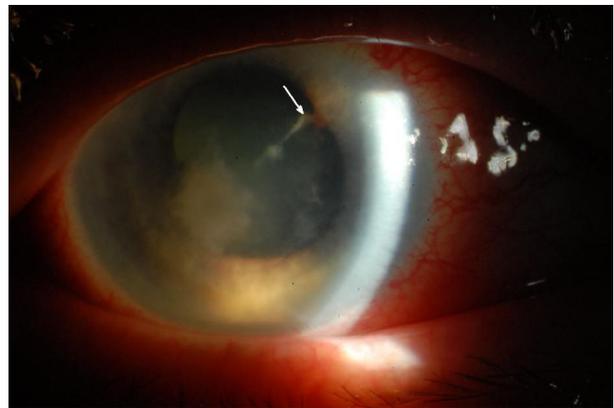


Fig. 5 Viscous, glutinous hypopyon (B.-B.-1-sign) at optical coherence tomography (Visante-OCT, Carl Zeiss Meditec, Jena, Germany)

Fig. 6 Iris–lens contact of infiltration (arrows)



remained and the visual acuity improved to 20/40 (Fig. 9).

Discussion

Fungi increasingly contribute to ocular infections and can cause serious corneal disease which may lead to blindness [1, 2]. Several predisposing factors for

keratomycosis have been identified [5] including wearing contact lenses [2–4], trauma [9], ocular surgery [9] and use of topical steroids [10]. *Fusarium* species are the fungal pathogens identified most frequently in eye infections [1, 2]; nevertheless, there are less common or even new fungal species like those presented in this case. *Tintelnotia destructans* belongs to the family of *Phaeosphaeriaceae* which contains

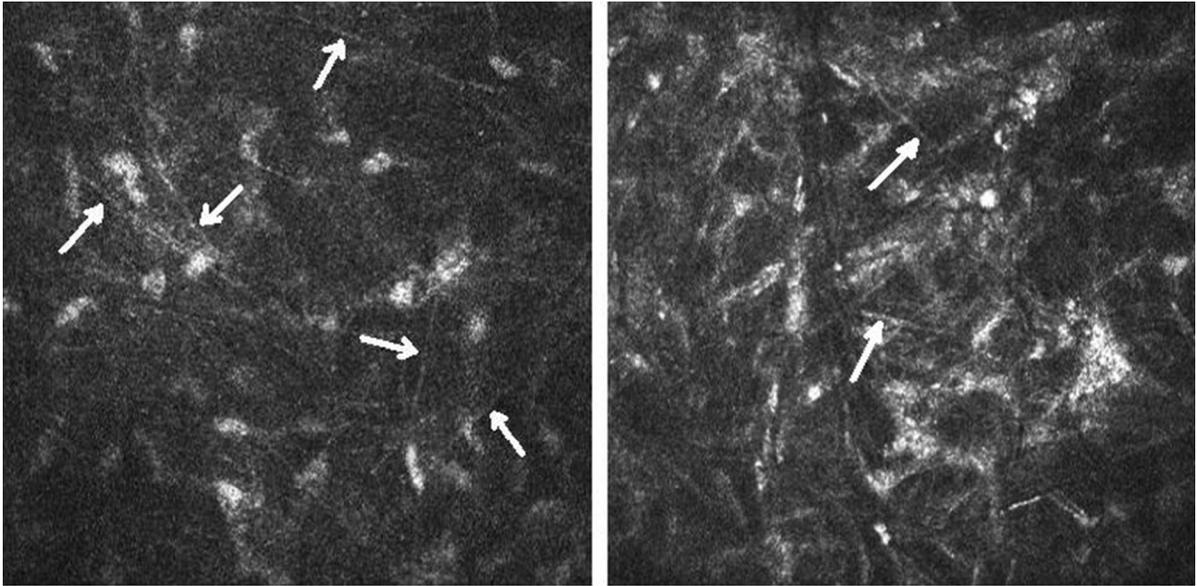
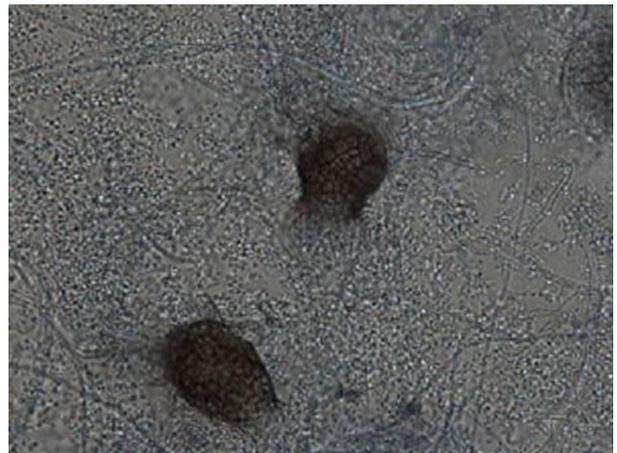


Fig. 7 Hyphal-like growth patterns (arrows) consistent with fungal elements (HRT II—Rostock Cornea Module, Heidelberg, Germany)

Fig. 8 Pycnidia of *Tintelnotia destructans* (lactophenol-cottonblue stain of culture on oatmeal agar)



numerous plant pathogens. Infections in humans are commonly acquired by traumatic inoculation.

A standard therapeutic strategy has not yet been established due to different susceptibilities of various fungi. Some therapeutic options are available including solutions of natamycin, voriconazole and amphotericin B for topical and some for systemic application. In clinical routine treatment, broad-spectrum antibiotics and antimycotics are used in cases not identified microbiologically.

However, new diagnostic options like anterior segment optical coherence tomography (Visante-

OCT, Carl Zeiss Meditec, Jena, Germany) or in vivo confocal microscopy (HRT II—Rostock Cornea Module) can help to identify the causal pathogens [11]. In our case, in vivo confocal microscopy has confirmed the clinical symptoms of fungal infection (viscous, glutinous hypopyon in the form of a cone: BB.-1-sign [6]).

In severe and complicated culturally proven fungal infections, especially in those due to an unidentified species, information on the susceptibility to several antifungal drugs might be highly valuable for optimizing the treatment regime. In our case, terbinafine

Fig. 9 End of treatment, visual acuity of 20/40



showed a promisingly low minimal inhibition concentration compared to other agents, and the clinical improvement after addition of terbinafine to the therapeutic strategy confirms our *in vitro* results. With a molecular mass of 291.43, terbinafine can also penetrate the corneal epithelium [12]. Terbinafine is an allylamine with antifungal activity and is characterized by a wide antifungal spectrum and few interferences with cytochrome oxidase P450, which has been successfully used for the treatment of fungal skin infections [13]. Some studies have also demonstrated its effective use in fungal keratitis in experimental [14] and human cases [15]. For this reason, we have tried the drug as an off-label treatment in this severe case where standard antimycotics (intracameral voriconazole and amphotericin B) have failed. Terbinafine was well tolerated without any neurological, gastroenterological or dermatological side effects. Due to moderate MIC, PHMB was additionally used in this severe case after increase of infiltration under conventional antifungal therapy. PHMB has been successful in keratomycosis due to *Fusarium* species [16].

In the worldwide second case of keratomycosis due to *Tintelnotia destructans*, treatment with systemic voriconazole (2×200 mg p.o.) and voriconazole eyedrops (2%) had been successful following penetrating keratoplasty [17]. One can speculate that in that case, the surgical intervention diminished the amount of fungi and the combination with voriconazole led to a good result, whereas in our patient without an additional keratoplasty a different antimycotic treatment was necessary to eliminate the fungus. Furthermore, our case demonstrates the non-safe use of corticosteroids. An *early high-dose* use of

corticosteroids may be considered as an important risk factor for an impairment of fungal infections, whereas a *delayed additional* use can reduce side effects of corneal inflammation like neovascularization and permanent corneal clouding [18].

Due to high antifungal potency and a low molecular mass, terbinafine eyedrops may be a good alternative treatment also in other cases of fungal keratitis. Further studies should confirm the beneficial use of topical terbinafine before its general recommendation in keratomycosis cases.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with animals performed by any of the authors.

Informed consent The patient has consented to the submission of the case report to the journal.

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