

# Fungal Keratitis Associated with Viral Keratitis

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Microbial keratitis caused by more than one microorganism is rare. It may occur as a coinfection or as a secondary infection superimposed with an existent microorganism.<sup>[1]</sup> Both infectious and immune mechanisms are implicated in microbial keratitis. Herein, we report an unusual clinical case of viral and fungal mixed infection. Written informed consent was obtained from the patient.

A 31-year-old man complained of red left eye for 10 days; accompanied with eye pain, photophobia, and blurred vision for 7 days and exacerbated in the next 2 days. At the beginning, he visited a hospital in Beijing. Corneal smear and the scrapings culture results were negative. Then he was treated as a patient with viral keratitis. He used topical ganciclovir eye gel, interferon, levofloxacin, pranopfen eye drops, deproteinized calf blood extract eye gel, and oral famciclovir tablets. Ocular manifestation was alleviated obviously according to the patient's description and medical record. At 3 days before, he visited our hospital, the patient suffered from heavy cold and recovered after he took over-the-counter cold medications. Unfortunately, he felt severe eye pain and photophobia for 2 days before he was referred to our hospital. He had neither trauma history nor wore contact lenses previously.

The visual acuity of his right eye was 20/20. No significant abnormality was detected in the right eye. While the visual acuity of the left eye was counting finger in front of the eye and could not be corrected. The clinical manifestation was showed in the Figure 1a.

After the patient was admitted, a repeat corneal smear was performed, and the scrapings were sent for bacterial (aerobes/anaerobes), fungal, and *Acanthamoeba* cultures and tested for antibiotic sensitivity. Fungal hyphae and epithelium were found in corneal smear [Figure 1g and 1h]. However, cultures were negative. The patient was diagnosed

with fungal keratitis and viral keratitis based on previous medical history, clinical manifestations, and corneal smear results. The procedure of treatment was divided into four stages.

1. Rapid remission stage lasted approximately 1 week [Figure 1b]. Combined antifungal, antiviral, and anti-inflammatory therapy was administered, including 5% natamycin eye drops (q1h), ganciclovir eye gel (tid), pranopfen eye drops (qid), tropicamide (a cycloplegic compound) eye drops (tid), and oral acyclovir tablets (400 mg, qid). Hypopyon disappeared 1 day after treatment, but fungi were persistent in corneal scrapings 4 days after treatment.
2. Chronic lag stage lasted more than 2 weeks. The patient complained about eye pain at night. Severe mixed conjunctival congestion appeared. Corneal epithelium erosion enlarged, accompanied with sustained stromal edema and aqueous flares [Figure 1c]. The stromal infiltrate improved very slowly. We considered that the toxin released when the hyphae was broken and the toxicity related to topical eye drops, particularly 5% natamycin, may injure the ocular surface. Thus, we gradually reduced the dosage of natamycin from q2h to qid. Pranopfen and tropicamide eye drops was terminated because of ocular surface defect side effects. Antiviral therapy was same. Ocular surface protections

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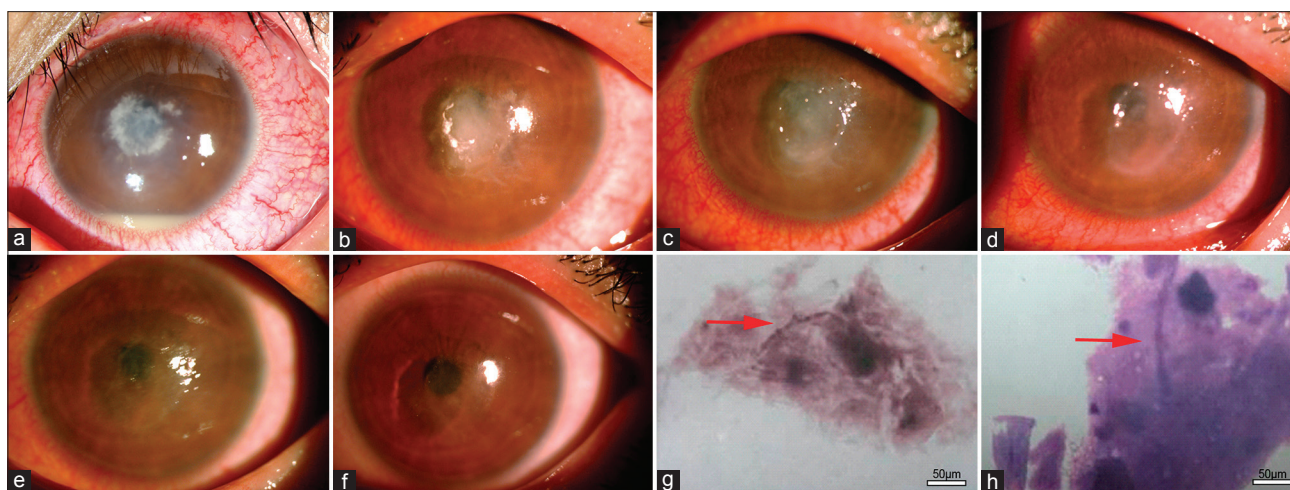
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**Figure 1:** (a) Gray infiltrate with irregular edges involved approximately 5 mm diameter of the cornea. Endothelial plaque, satellite lesions, and hypopyon appeared. (b) Corneal infiltrate and satellite lesions were confluent. (c) Corneal epithelium erosion and stromal edema enlarged. (d) Mixed conjunctival congestion. Corneal infiltrate and anterior chamber inflammation were healing slowly. (e) Conjunctival congestion and corneal edema were alleviated. (f) Corneal nebula involved corneal center. (g-h) Corneal scrapings contained fungi (red arrow). Gram (g) and Giemsa (h) staining, Original magnification,  $\times 400$ , Scale bars =  $50\ \mu\text{m}$ .

was added, such as artificial tears without preservatives, dextran 70 eye drops (qid), deproteinized calf blood extract eye gel (bid), and sodium chloride conjunctival sac wash (bid). Corneal scrapings did not contain fungi 16 days after the patient was admitted.

3. Healing stage lasted approximately 1 week. Conjunctival congestion was still severe. Corneal epithelium defect and infiltrate were healing very slowly, accompanied with mild anterior chamber inflammation [Figure 1d]. The topical treatment of 5% natamycin and ganciclovir was completely withdrawn at the end of this stage.
4. Reparation stage lasted 2 weeks. Corneal stromal edema and inflammation still existed. We carefully observed lesion development for 7 days without recrudescence even withdrew antifungal agent [Figure 1e]. Then topical corticosteroid 0.1% fluometholone eye drops (tid), tobramycin, and dexamethasone ointment (qon) was administered. Oral acyclovir tablets tapered slowly. Conjunctival congestion was alleviated. Corneal infiltrate gradually vanished. The anterior chamber was quiet. When the patient was discharged, the visual acuity of the left eye increased to 20/40 [Figure 1f].

The fungus is a kind of conditional pathogenic microorganism. In a normal conjunctival sac, the positive rate of fungal culture ranges from 2.9%<sup>[2]</sup> to 27.4%.<sup>[3]</sup> Fungal keratitis is the combined result of pathogen and host factors, such as long-term use of broad-spectrum antibiotics, dysbacteriosis in the conjunctival sac, or application of corticosteroids, leading to local hypoimmunity or corneal trauma cases. In general, patients exhibit ocular trauma history, particularly from contact with plants or wood.

In the present case, the patient was a young, healthy office staff without trauma or systemic disease except colds. The corneal smear was negative for microorganism at his first

consultation. Corneal ulceration was diagnosed and treated as viral keratitis. The diagnosis was based on empiric with the clinical manifestation and effective diagnostic treatments. After the patient was referred to our hospital, fungal hyphae were detected. A typical clinical manifestation of mycotic keratitis caused by filamentary fungi showed. It is extremely rare that fungi and virus affected cornea at the same time. Polymerase chain reaction is a sensitive diagnostic method to detect viruses. Unfortunately, we could not get viral sample laboratory test in etiologic diagnose. Considering the medical history and antiviral diagnostic treatment was effective on the 1<sup>st</sup> week after onset, we believed that viral keratitis existed and fungal keratitis might be a secondary infection caused by previous infection. Although the mechanism of mixed infection was hard to determine, we speculated the existed corneal ulcer might be the potential causes of subsequent fungal infection. Meanwhile, the antivirals and antibiotics application aggravated conjunctival sac dysbacteriosis.

Immediate treatment using antifungal with antiviral medicines was necessary. However, the early rapid remission stage turned to the chronic lag stage after many eye drops were used. Why did the severe mixed conjunctival hyperemia, corneal edema, and anterior chamber inflammation persist? At first, we considered eye drops-related irritation. After, we reduced the administration frequency and provided ocular surface protections, the corneal epithelium started to heal, but stromal edema and inflammation persisted for 1 month. Then topical immunopathologic mechanism was considered. Stromal keratitis is immunoinflammatory in nature, and local immunosuppression with topical steroids, along with antiviral coverage, should be involved.<sup>[4]</sup> However, topical steroids not only reduce immune inflammation, but potentially provide conditions suitable for the growth of exogenous fungi and ocular commensals. We carefully observed the lesion development without natamycin and then administered topical corticosteroid. The proper use of corticosteroids

for the treatment of fungal corneal infections has been continuously debated.<sup>[5]</sup> The topical steroid is not prohibited, but should be applied with extremely care. Ophthalmologists should be aware of the uncommon manifestations of keratitis and adjust treatment depending on a patient's condition.

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### **Conflicts of interest**

There are no conflicts of interest.

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