Conidiobolus, a hitherto unidentified pathogen in microbial keratitis

Anita Raghavan, Balakrishna Balaka[1], Narendran Venkatapathy[2], Ram Rammohan[3]

Fungal infections are a significantly increasing cause of ocular and systemic morbidity; the vast majority of cases being ascribed to a handful of species. Fungal keratitis, unlike systemic infections, usually occur in immunocompetent individuals. Rarely, systemic infections can be associated with ocular involvement (e.g., Candida, Mucor, Pythium), or a fungus that predominantly causes systemic disease can affect the eye. One such fungus is *Conidiobolus* which is known to cause muco-cutaneous infections. We report the identification and successful treatment of a case of *Conidiobolus* corneal ulcer in an immunocompetent individual, who had no co-existing muco-cutaneous disease. Identification of this particular fungus and awareness of its potential to cause systemic disease is especially relevant, given its potential for chronic indolent infection of the subcutaneous tissues. To the best of our knowledge, this is the first reported case of a *Conidiobolus* corneal ulcer.

Key words: *Conidiobolus*, diagnosis, keratitis, treatment

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Cornea and Refractive Surgery, Aravind Eye Hospital and Post-Graduate Institute of Ophthalmology, Coimbatore, Tamil Nadu, [1]Cornea and Refractive Surgery, Sri Venkateswara Aravind Eye Hospital, Tirupati, Andhra Pradesh, [2]Aravind Eye Hospital and Post-Graduate Institute of Ophthalmology, [3]Division of Laboratory Services, Aravind Eye Hospital and Post-Graduate Institute of Ophthalmology, Coimbatore, Tamil Nadu, India

Correspondence to: Dr. Anita Raghavan, Aravind Eye Hospital and Post-Graduate Institute of Ophthalmology, Coimbatore - 641 014, Tamil Nadu, India. E-mail: annieram2001@yahoo.com

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Conidiobolus spp. are ubiquitous, cosmopolitan fungi, which occasionally cause human naso-facial mucocutaneous or subcutaneous infections.[1,2] In the immunocompetent host, it causes a progressive mass lesion over the nasal submucosa, nose, eyelids, and over the malar and frontal regions of the face. Occasionally, it can involve the nasolacrimal duct and orbit.[3,4] Although many facial and maxillary sinus cases have involved the lower eyelid, or abut the orbital rim, direct ocular involvement of *Conidiobolus* has not been reported (except for one case of lacrimal sac tumor[5]). Reported infections have mainly been from West Africa, India, Central and South America.[1,6]

Stages of the disease may be classified into:[7]

- Atypical - infection of the facial region (e.g., orbit) other than the nose and maxillary sinus, or in non facial cutaneous sites, diagnosed within 11 months after suspected onset;
- Early Disease – diagnosed before the occurrence of characteristic nodule at the nostril;
- Intermediate Disease; or
- Late Disease

Case Report

We report the first case, worldwide, of a *Conidiobolus* infection, presenting only as a keratitis. A 61-year-old male presented with complaints of pain, watering, and redness of the left eye of 5 days' duration. Diagnosed elsewhere as a fungal corneal infiltrate, he was using Natamycin 5% and Moxifloxacin 0.5% eye drops hourly, Homatropine 2% eye drops twice daily, and Tobramycin eye ointment. He had no prior history of

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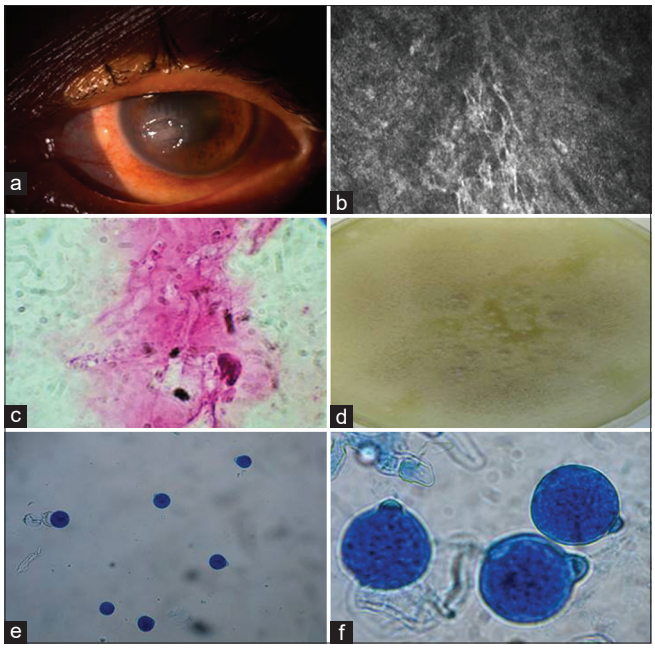

Figure 1: (a) Para-central corneal infiltrate with Descemet's folds. (b) Confocal biomicroscopy showing mid-stromal hyper-reflective, branched, hyphae (Heidelberg Retinal Tomography 3, with Rostock Cornea Module). (c): Gram stain showing irregularly wide, sparsely septate hyphae (100 × Oil Immersion). (d) Dry glabrous colony (Sabouraud Dextrose Agar; 25°C). (e) Blue-stained globose sporangioles (Lacto-Phenol Cotton-Blue; 20×). (f) Blue-stained globose sporangioles with typical papillae (Lacto-Phenol Cotton-Blue; 40×)

ocular disease, was in apparently good health, albeit with well-controlled hypertension. There was no history of trauma, exposure to foreign body, or upper respiratory tract infections; no recent history of nasal blockage, sinusitis; and no evidence of skin infections or peri-ocular lesions.

His uncorrected visual acuity was 6/24 in the right eye and 5/60 in the left eye. Slit lamp biomicroscopy of the right eye was within normal limits, while that of the left eye revealed normal lid contour, with conjunctival congestion. An anterior stromal greyish-white infiltrate with ulceration (4.5 mm × 3.5 mm) and Descemet's membrane folds, was seen in the inferonasal quadrant of the cornea. [Fig. 1a] There was 1+ AC flare, and the lens was cataractous. The initial diagnosis was 'mixed infection' (the ulcer had features of bacterial as well fungal keratitis). *In vivo* confocal microscopy (IVCM) evaluation revealed mid-stromal hyper-reflective, branched, linear structures suggestive of fungal hyphae [Fig. 1b].

Corneal scrapings from the infiltrate were inoculated onto Blood Agar (BA), Sabouraud Dextrose Agar (SDA), and Non Nutrient Agar with *E. coli* overlay. Additional scrapings were taken for smears. The 10% potassium hydroxide (KOH) mount was positive for wide, hyaline, sparsely septate hyphae, and the Gram staining showed poorly staining wide, non septate, branching hyphae [Fig. 1c].

Based on smears and pending cultures, the patient was started on hourly Natamycin 5% and Voriconazole 1% eye drops. Only fungal growth was noted (rapid growth on BA, 24-48 hrs @ 37°C; slower growth on SDA @ 25°C) - starting as dry glabrous, powdery-white with sparse aerial mycelium, becoming light brown with a pale reverse [Fig. 1d]. Lactophenol blue mounts revealed broad irregular hyaline hyphae with rare septation, and large blue-stained globose sporangioles (conidia) with typical basal papilla [Fig. 1e and f]; rare thick-walled zygospores (without conjugation beaks) were also seen. There were no villose or multiplicative secondary conidia. Based on these macro- and micro-morphological criteria, the isolate was identified as *Conidiobolus incongruus*.

Since this uncommon fungus is usually associated with morbid infections of the subcutaneous tissue or sinuses, the patient was referred to a physician for systemic evaluation, and to an oto-rhino-laryngologist. Clinical evaluation was normal; computerized tomography showed no sinus abnormalities, except for a right concha bullosa with focal paradoxical curve of right middle turbinate. White blood cell count was 5200/mm^3 (51% neutrophils); ESR was 07 mm; serology was negative for Hepatitis B surface antigen, HCV, and Human Immunodeficiency Virus (HIV).

Most cases reported from India have been Atypical disease, where Amphotericin-B has been used (in combination with other anti-fungals).[7-9] Therefore, Natamycin was replaced with Amphotericin-B, 0.15% hourly. Itraconazole eye ointment 1% t.i.d. and tablet Ketoconazole were added, while Voriconazole was continued. Over the next 2 weeks, the infiltrate healed slowly, and 30 days after institution of tapered therapy it had resolved completely. Corrected visual acuity improved to 6/9 N8.

Discussion

Conidiobolus spp. and *Basidiobolus sp.* belong to Class Zygomycetes.[1] Conidiobolomycosis or rhino-facial entomophthoramycosis invariably involves the mucosa and subcutaneous tissues of the nose. They are more predominantly observed as a sinusitis in adult males, spreading into subcutaneous fat. Sources are contaminated water, soil, leaf litter, or via insect vectors.[1] Rare cases of disseminated infection in immunocompromised hosts have been reported.[1] As of 2015, only 198 well-documented cases of Conidiobolomycosis have been reported.[7] Except for one case of lacrimal sac tumor (secondary to traumatic entry of soil into the eye),[5] no cases of purely ocular involvement have been reported. A rare occurrence in India, about 40 cases of Conidiobolomycosis have been reported.[10]

Conidiobolomycosis is very difficult to treat, and Itraconazole or potassium iodide has usually been first-line choices. Combination of anti-fungals (potassium iodide, Miconazole, Co-trimoxazole, Ketoconazole, Itraconazole, Amphotericin-B, Terbinafine) have been used successfully.[2,6-9] In our case, the *Conidiobolus* infection was restricted to the cornea, the ulcer healed slowly but completely within a month (with Amphotericin-B, Voriconazole, and Ketoconazole), with no signs or symptoms of extraocular spread.

This may be the first reported incident of *Conidiobolus* keratitis. Morphologically, in smears, *Conidiobolus* looks similar to Mucor or Rhizopus, exhibiting wide, ribbon-like aseptate hyaline hyphae. Although, in culture the colony grows rapidly, there is absence of aerial mycelia and most often remains flattish, waxy or glabrous. The presence of unique globose conidia with characteristic prominent papillae, were confirmatory for *Conidiobolus sp*.

Given the potential for serious sinus and maxillo-facial infections, and the need for systemic anti-fungal therapy, identification of the fungus is particularly relevant. More importantly, the drug of choice is probably Amphotericin-B, and not the more commonly administered Natamycin. Our patient did not respond to the administration of Natamycin and Voriconazole, but did so only after the addition of Amphotericin-B.

Conclusion

To the best of our knowledge, this is the first reported case of a *Conidiobolus* corneal ulcer.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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