**Conidiobolus**, a hitherto unidentified pathogen in microbial keratitis

Anita Raghavan, Balakrishna Balaka¹, Narendran Venkatapathy², Ram Rammohan³

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

*Conidiobolus* spp. are ubiquitous, cosmopolitan fungi, which occasionally cause human naso-facial mucocutaneous or subcutaneous infections. 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. 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). Reported infections have mainly been from West Africa, India, Central and South America.

Stages of the disease may be classified into:

- **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

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

Cite this article as: Raghavan A, Balaka B, Venkatapathy N, Rammohan R. *Conidiobolus*, a hitherto unidentified pathogen in microbial keratitis. Indian J Ophthalmol 2020;68:1461-3.
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 at 37°C; slower growth on SDA at 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 zygosporous (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/mm³ (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). 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.[2] Except for one case of lacrimal sac tumor (secondary to traumatic entry of soil into the eye),[3] no cases of purely ocular involvement have been reported. A rare occurrence in India, about 40 cases of Conidiobolomycosis have been reported.[4]

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.[5-9] 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 extracutaneous 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 asetate 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.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Mendoza L, Vilela R, Voelz K, Ibrahim AS, Voigt K, Lee SC. Human fungal pathogens of mucorales and entomophorales. Cold Spring Harb Perspect Med 2015;5. pii: a019562. doi: 10.1101/cshperspect.a019562.
2. Prabhu RM, and Patel R. Mucormycosis and entomophthoramycosis: A review of the clinical manifestations, diagnosis and treatment. Clin Microbiol Infect 2004;10:31-47.
3. Ramesh A, Deka RC, Vijayaraghavan M, Ray R, Kabra SK, Rakesh K, et al. Entomophthoramycosis of the nose and paranasal sinus. Indian J Pediatr 2000;67:307-10.
4. Michael RC, Michael JS, Mathews MS, Rupa V. Unusual presentation of entomophthoramycosis. Indian J Med Microbiol 2009;27:156-8.
5. Bittencourt AL, Marback R, Nossa LMB. Mucocutaneous entomophthoramycosis acquired by conjunctival inoculation of the fungus. Am J Trop Med Hyg 2006;75:936-8.
6. Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: Pathophysiology, presentation, and management. Clin Microbiol Rev 2005;18:556-69.
7. Blumentrath CG, Grobusch MP, Matisiegui PB, Pahlke F, Zoleko-Manego R, Nzenze-Afene S, et al. Classification of rhinoentomophthoramycosis into atypical, early, intermediate, and late disease: A proposal. PLoS Negl Trop Dis 2015;9:e0003984.
8. Gugnani HC. Entomophthoramycosis due to conidiobolus. Eur J Epidemiol 1992;8:391-6.
9. Foss NT, Rocha MR, Lima VT, Velludo MA, Roselino AM. Entomophthoramycosis: Therapeutic success by using amphotericin B and terbinafine. Dermatology 1996;193:258-60.
10. Chowdary A, Randhawa HS, Khan ZU, Ahmad S, Khanna G, Gupta R, et al. Rhinocutaneous mucoromycosis due to *Conidiobolus coronatus*. A case report and an overview of the disease in India. Med Mycol 2010;48:870-9.