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Letter to the Editor

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Corneal abscess caused by *Filobasidium uniguttulatum*. Case report and literature review on cryptococcal keratitis

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Sir,

Cryptococcus spp. is an anamorphic basidiomycetous yeast genus containing currently 70 species, with *C. gattii and C. neoformans* as the most frequently isolated species in human infections [1]. *C uniguttulatus* was firstly identified in 1934 by Wolfram and Zach as *Eutorulopsis uniguttulata* in the infected fingernail of a patient [2]. Then it was redescribed as *Cryptococcus neoformans* var. *uniguttulatus* in 1952 because of its morphological similarities with this species, and being finally considered a new species in 1970 [3]. This fungus presents a worldwide distribution (along with other *Cryptococcus* species such as *C. albidus* or *C. laurentii*) and it has been identified from various environmental sources [4]. *C. uniguttulatus* (or its sexual state *Filobasidium uniguttulatum*) has been detected in crop and droppings of pigeon lofts, so feral pigeon can be considered as carriers of this *Cryptococcus* species with an important role in the epidemiology of the infection [5]. In this manuscript, we report the first case of keratitis caused by *F. uniguttulatum*.

A 56-year-old patient attended the emergency department for severe pain in the left eye during the past 24 hours. He presented reduced vision and bullous keratopathy in the left eye as a consequence of a lens implantation in anterior chamber two years earlier. He had undergone intraocular lens (IOL) explant, as well as phacoemulsification and lens implantation in a sac as a previous step to endothelial transplantation seven months before. The patient did not present any additional comorbidities or potential exposure to cryptococcal conidia such as contact with doves or pigeon nests. Biomicroscopic examination showed intense ciliary hyperemia, corneal abscess of 2.5 mm between nasal and lower temporal fields (Figure 1A) and organized hypopyon of 2 mm. A corneal abscess culture was obtained and empirical treatment was prescribed with reinforced vancomycin and ceftazidime eye drops (5%, 50 mg/ml, 1 drop/hour the first 24 h and 1 drop/48 h later), one application/24 h of ciprofloxacin ointment (0.3%, 3 mg/g) and 500 mg/24 h of oral ciprofloxacin.

Samples were cultured on chocolate, 5% trypticase soy with 5% of sheep blood (Becton Dickinson, Franklin Lakes, NJ, USA) and saboraud agar with chloramphenicol. Abundant yeasts were observed in the Gram staining and, after 48 h, growth of white mucous colonies was observed saboraud agar. These colonies were identified by API® 20 C Aux (API system, Montalieu, France) as *Cryptococcus spp.* Antifungal susceptibility was studied using the colorimetric panel of broth microdilution in Sensititre® YeastOne® (Thermo Fisher Scientific, Massachusetts, USA). The strain showed the following MICs to all tested antifungals: fluconazole (MIC = 128 mg/L), itraconazole (MIC = 1 mg/L), voriconazole (MIC = 4 mg/L) and liposomal amphotericin B (MIC = 4 mg/L). Since there are no established cut-off points and no ECOFFs for species other than *Cryptococcus neoformans* and *Cryptococcus gattii*, the results could not be interpreted. After the results of the culture, the abscess was re-evaluated and biomicroscopy showed a slightly reduced size abscess with increased inflammatory reaction. Optical coherence tomography (OCT) confirmed the presence of a 470 µm deep abscess with inflammatory plastron and corneal central thickness of 711 µm (Figure 1A). Antibiotic treatment (reinforced vancomycin and ceftazidime eye drops, and oral ciprofloxacin) was replaced with one drop/4 h of voriconazole eye drops (10 mg/ml).

The internal transcribed spacer (ITS) 1, the 5.8 S ribosomal RNA gene, and ITS-2 were sequenced in order to confirm the species identification, obtaining a sequence of 461 bp. The sequence was introduced in BLAST® and identificated as *Filobasidium uniguttulatum* (sexual state of *Cryptococcus uniguttulatus*) with 99,35% of concordance with reference strain "MN309713.1", and it was submitted in GenBank® with access number "OQ236158.1". The following week, biomicroscopy

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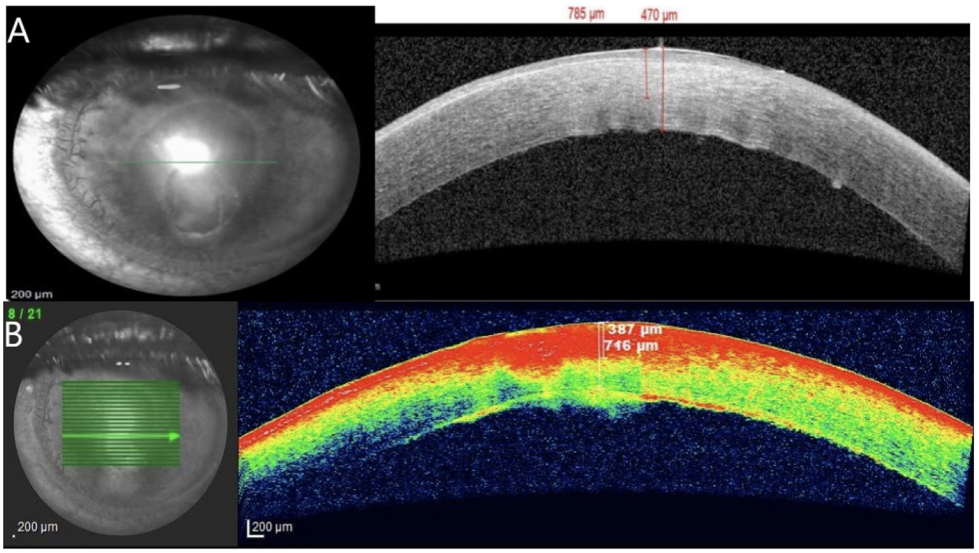

Figure 1 **A: Biomicroscopy (left) shows: +++ corneal abscess of 2.5 mm with endothelial plastron and organized hypopyon of 2 mm. The OCT-anterior segment image (right) shows a 470 micron deep extension with diffuse corneal edema (785 microns) and an endothelial fibrin plastron. B: BMC image: less active abscess. Corneal edema is somewhat greater but the relative depth of the abscess is . There is no more anterior chamber reaction, the endothelial plastron has disappeared, leaving only some residual endothelial PRK.**

showed mild improvement of his condition with a slight decrease of the abscess observed on OCT (Figure 1B, from 470 to 387 µm), and 200 mg/24 h of oral itraconazole for 3 weeks was added to the topical treatment. Finally, after 6 weeks of treatment with voriconazole eye drops, absence of infection signs and persistence of residual paracentral bulla were confirmed.

C. uniguttulatum has been isolated causing mild infections as onychomycosis in Type 2 diabetes Mellitus patients, but also severe infections as meningitis or ventriculitis in both immunocompromised and immunocompetent patients [3, 6-8]. It is a very rare cause of human infection, with only 2 cases of meningitis and 1 of ventriculitis caused by this microorganism. In this case report we described the first eye infection caused by this yeast in the scientific literature. Colonization with *C. uniguttulatus* could occur, so it is important to evaluate each case separately, to see if there is an established infection and to start treatment early if required [9]. We performed a literature review by searching "*Cryptococcus* keratitis" in PubMed®. Up to now, 5 cases of keratitis caused by cryptococcal species have been reported in the scientific literature (table 1). All patients presented risk factors related to eye diseases and/or procedures such as penetrating keratoplasty (most found risk factor with 3 patients), bullous keratopathy, previous eye injury or lens implantation, among other. Topical antifungal was used as monotherapy only in one patient, whereas two patients required combined treatment with intrasomal injection and topical treatment of different antifungal. In two patients, resolution of the infection was reached after penetrating keratoplasty and no antifungal treatment.

Since therapeutic approach can vary from species to species, an accurate identification is needed in these infections. Clinical specimens should be incubated on selective fungal agar at 30–37°C (such as Sabouraud or Bird Seed agars) and then, correct species identification could be obtained in some cases by biochemical tests such as API 20 C Aux (API system, Montalieu, France). However, in most cases, species identification requires sequencing of internal transcribed spacer (ITS) 1 + 2 regions of rDNA and/or D1/D2 domains [4]. In recent years, the introduction of mass spectrometer MALDI-TOF has brought some lights in this field as a promising tool for the rapid identification of uncommon fungus. In fact, Danesi P *et al.* used this method with satisfactory results in the identification of species different from *C. neoformans* and *C. gatti*, including 9 strains of *C. uniguttulatus* [15].

Management of keratitis must be individualized, considering several factors such as the available drugs or local microbiological profile, among others. Natamycin is usually the first drug of choice for fungal keratitis, but voriconazole could be used in other cases, included keratitis caused by rare pathogens [16]. Emerging treatment options such as "photodynamic therapy" and newer methods for the delivery of existing drugs can become a turning point for better management of recalcitrant and progressive cases. Most isolates of non-neoformans

Table 1 Summary of cryptococcal keratitis in the scientific literature

Year [reference]	Risk factor	*Cryptococcus* species	Treatment
1990 [10]	Penetrating keratoplasty 2 months earlier	*Cryptococcus neoformans*	Topical miconazole
1998 [11]	Rigid gas permeable contact lens. Onychomycosis	*Cryptococcus laurentii*	Penetrating keratoplasty, then enucleation
2005 [12]	Penetrating keratoplasty 7 months earlier	*Cryptococcus albidus*	Repeat penetrating keratoplasty
2015 [13]	Eye injury after being hit by a plant	*C. albidus*	Topical fluconazole and amphotericin B, and intrasomal injection of amphotericin B
2019 [14]	Lattice corneal dystrophy. Penetrating keratoplasty 5 years earlier	*Cryptococcus curvatus*	Topical amphotericin B and fluconazole, intrasomal voriconazole and penetrating keratoplasty
2022, present report	Bullous keratopathy phakic anterior chamber lens implantation 2 years earlier. IOL explant + phacoemulsification and lens implantation in a sac as a previous step to endothelial transplantation seven months before	*Filobasidium uniguttulatum*	Topical voriconazole and oral itraconazole

cryptococci reported in the literature were not tested for antifungal susceptibility, while available studies suggest that this species seems to be more resistant to antifungals than *C neoformans*. In addition to being intrinsically resistant to echinocandins, previous clinical isolates of *C. uniguttulatus* were found to be resistant to flucytosine and fluconazole, as well as with a decreased susceptibility to itraconazole and voriconazole [3,4,7,8,17]. However, all the cases responded favourably to liposomal amphotericin B. Optimal treatment of *C. uniguttulatus* infections is unknown due to the limited literature. Therefore, susceptibility studies are necessary for the correct eradication of the infection and to avoiding the emergence of resistance.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

REFERENCES

1. Gassiep I, Douglas J, Emeto TI, Crawley K, Playford EG. Cryptococcal infections over a 15 year period at a tertiary facility & impact of guideline management. Mycoses. 2018 Sep;61(9):633-638. doi: 10.1111/myc.12783.
2. Kwon-Chung KJ. Perfect state of *Cryptococcus uniguttulatus*. Int J Syst Bacteriol. 1977;27: 293–9. Doi: 10.1099/00207713-27-3-293
3. Pan W, Liao W, Hagen F, Theelen B, Shi W, Meis JF, Boekhout T. Meningitis caused by *Filobasidium uniguttulatum*: case report and overview of the literature. Mycoses. 2012 Mar;55(2):105-9. doi: 10.1111/j.1439-0507.2011.02054.x.
4. Arendrup MC, Boekhout T, Akova M, Meis JF, Cornely OA, Lortholary O; European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group; European Confederation of Medical Mycology. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast infections. Clin Microbiol Infect. 2014 Apr;20 Suppl 3:76-98. doi: 10.1111/1469-0691.12360.
5. Rosario I, Soro G, Déniz S, Ferrer O, Acosta F, Padilla D, Acosta B. Presence of *C. albidus, C. laurentii* and *C. uniguttulatus* in crop and droppings of pigeon lofts (Columba livia). Mycopathologia. 2010 Apr;169(4):315-9. doi: 10.1007/s11046-009-9262-0.
6. Manzano-Gayosso P, Hernández-Hernández F, Méndez-Tovar LJ, Palacios-Morales Y, Córdova-Martínez E, Bazán-Mora E, López-Martinez R. Onychomycosis incidence in type 2 diabetes mellitus patients. Mycopathologia. 2008 Jul;166(1):41-5. doi: 10.1007/s11046-008-9112-5.

7. Animalu C, Mazumder S, Cleveland KO, Gelfand MS. *Cryptococcus uniguttulatus* Meningitis. Am J Med Sci. 2015 Nov;350(5):421-2. doi: 10.1097/MAJ.0000000000000564.
8. McCurdy LH, Morrow JD. Ventriculitis due to *Cryptococcus uniguttulatus*. South Med J. 2001 Jan;94(1):65-6. PMID: 11213945.
9. Khawcharoenporn T, Apisarnthanarak A, Mundy LM. Non-neoformans cryptococcal infections: a systematic review. Infection. 2007 Apr;35(2):51-8. doi: 10.1007/s15010-007-6142-8.
10. Perry HD, Donnenfeld ED. Cryptococcal keratitis after keratoplasty. Am J Ophthalmol. 1990 Sep 15;110(3):320-1. doi: 10.1016/s0002-9394(14)76362-7.
11. Ritterband DC, Seedor JA, Shah MK, Waheed S, Schorr I. A unique case of *Cryptococcus laurentii* keratitis spread by a rigid gas permeable contact lens in a patient with onychomycosis. Cornea. 1998;17(1):115-8. doi: 10.1097/00003226-199801000-00017.
12. de Castro LE, Sarraf OA, Lally JM, Sandoval HP, Solomon KD, Vroman DT. *Cryptococcus albidus* keratitis after corneal transplantation. Cornea. 2005;24(7):882-3. doi: 10.1097/01.ico.0000157404.34774.1a.
13. Huang YH, Lin IH, Chang TC, Tseng SH. Early diagnosis and successful treatment of *Cryptococcus albidus* keratitis: a case report and literature review. Medicine (Baltimore). 2015;94(19):e885. doi: 10.1097/MD.0000000000000885.
14. Ting DSJ, Bignardi G, Koerner R, Irion LD, Johnson E, Morgan SJ, Ghosh S. Polymicrobial Keratitis With *Cryptococcus curvatus*, *Candida parapsilosis*, and *Stenotrophomonas maltophilia* After Penetrating Keratoplasty: A Rare Case Report With Literature Review. Eye Contact Lens. 2019 Mar;45(2):e5-e10. doi: 10.1097/ICL.0000000000000517.
15. Danesi P, Drigo I, Iatta R, Firacative C, Capelli G, Cafarchia C, Meyer W. MALDI-TOF MS for the identification of veterinary non-*C. neoformans-C. gattii Cryptococcus* spp. isolates from Italy. Med Mycol. 2014 Aug;52(6):659-66. doi: 10.1093/mmy/myu031.
16. Sharma N, Bagga B, Singhal D, Nagpal R, Kate A, Saluja G, Maharana PK. Fungal keratitis: A review of clinical presentations, treatment strategies and outcomes. Ocul Surf. 2022 Apr;24:22-30. doi: 10.1016/j.jtos.2021.12.001.
17. Bernal-Martinez L, Gomez-Lopez A, Castelli MV, Mesa-Arango AC, Zaragoza O, Rodriguez-Tudela JL, Cuenca-Estrella M. Susceptibility profile of clinical isolates of non-*Cryptococcus neoformans*/non-*Cryptococcus gattii*. Cryptococcus species and literature review. Med Mycol. 2010 Feb;48(1):90-6. Doi: 10.3109/13693780902756073.