

Successful Treatment of *Cryptococcus albidus* Keratitis with Voriconazole 1% Drops and Oral Itraconazole

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Abstract

The *Cryptococcus* genus, include a wide group of yeast, which species are usually found in water and plants. *C neoformans* and *C gatti* are considered pathogens for humans and animals, whoever *Cryptococcus laurentii*, *C albidus* and *C curvatus* are considered as potential environmental pathogen for both.

We describe one fungal keratitis caused by *Cryptococcus albidus*, in a male 41 years old, diagnosed previously with diabetes type 2, and ocular surgery for cataract extraction 7 years before, actually he presented a corneal ulcer in right eye diagnosed before as herpetic keratitis unresponsive to Aciclovir, after de first ocular observation in our hospital in Cornea Service, and samples for culture taken, the final diagnosis was *Cryptococcus albidus* keratitis, the treatment with antimycotic drugs, topic voriconazole 1% and oral itraconazole 100mgs each 12 hs was administered. The corneal ulcer was healed in 3 weeks and the FBCVA was 20/30.

Keywords: Cryptococosis, *Cryptococcus albidus*, Corneal ulcer, Keratitis

Introduction

Cryptococcus is a fungal yeast genus within many species of wide world distribution, located mainly in dust, mud, and water, that has pathogenic species for man and animals as *C neoformans* and *C gatii*, causing a fungal pulmonary, cutaneous or disseminated disease named cryptococosis, some no-*neoformans* species in this genus are mentioned as opportunistic in ocular infections by Gugnani since 1978 [1]. The genus *Cryptococcus* include the formerly yeast named *Cryptococcus albidus* or *Naganishia albida* in the new nomenclature, it is an opportunistic yeast that has been associate to diverse systemic human infections like peritonitis in normal and immunocompromised individuals, in some cases with fatal consequences [2-4].

In rare ocular infections, *Cryptococcus albidus* has been isolated in scleritis (5), and even related as fastidious organism retrieved from one case of uveitis (6) in all this publications it have been described as an opportunistic ocular fungal infection, with a good or torpid evolution after treatment.

Objective

We present a case of *Cryptococcus albidus* in a diabetes mellitus

patient keratitis, with early diagnosis, and good response at medical treatment.

Case Report

A male 41 years old, with diabetes mellitus diagnostic and no well medically controlled, developed red eye, epiphora, foreign body sensation and moderate pain in right eye, one week before to assist at medical attention, the first diagnosis made by an ophthalmologist was herpetic keratitis, and administered oral acyclovir 400mgs each 12 hours, and topical one drop of 0.3% ciprofloxacin each four hours.

After one week of treatment and no response, the patient decided to be attended in our eye care hospital. At the first visit in Cornea Service, at slit lamp examination: In both eyes sowed post-surgical cataract and intraocular lenses madden 7 years ago, by patient reference, and actually in good conditions. Left eye no showed abnormalities.

Actual illness: In right eye was observed hyperemic conjunctiva+++, inflammatory reaction 360 grades around the limbus, diffuse epitheliopathy, severe anterior chamber reactions, and cornea ulcer of 1.5 X 1 mm in left inferior quadrant with dense sur-

rounding infiltrate. (Figure 1), initial best corrected visual acuity (BCVA) was 20/250. The diagnosis was bacterial ulcer in inferior quadrant in right eye, and the medical treatment administered was topical drops of netilmicin 0.3% (Netira® Sifi laboratories, Italy) and moxifloxacin 0.5% (Vigamoxi® Alcon laboratories, USA) alternatively each 2 hours.

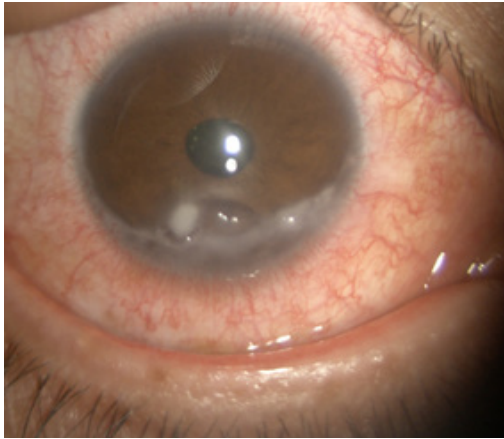


Figure 1: In right eye, was observed diffuse cornea epitheliopathy, and an ulcer of 1.5 X 1 mm in inferior quadrant (arrow) with dense surrounding infiltrate

Corneal scrap was made for cultures, the laboratory report was; The periodic acid Schiff stain revealed; scarce levaduriform cells and in Geimsa stain abundant polymorphonuclear leucocytes. In cultures at 24 hours after, was reported Staphylococcus epidermidis, 3 days after was observed 5 colonies of Cryptococcus albidus (identified by VITEK 2 Biomerieux, France). The treatment mentioned above, was changed for Voriconazol 1% ocular drops prepared from intravenous solution (V-FEND® Pfizer, Germany) and netilmicin 0.3% one drop alternatively each 2 hours.

Five days after, at slit lamp examination: Cornea infiltrate was less dense, the cornea ulcer was healed, anterior chamber was normal (Figure 2), Tyndall negative, and at the medical treatment was added oral Itraconazole 100 mgs each 12 hours, Maxus® drops and Thealoz Duo® (Thea laboratories, France).



Figure 2: Five days after, in the same eye, cornea infiltrate was less dense, the cornea ulcer was healed, and anterior chamber was normal

One month after with the antimycotic treatment, the ulcer was well healed. There was only a light scar instead of the ulcer, with some infiltrate in stroma. The Visual Acuity in right eye was 20/30, with a stable evolution, all medication was retired, but netilmicin 0.3 % drops 3 X 12 hs was left for one week more, to avoid a possible subsequent bacterial infection.

The colonies of Cryptococcus albidus, was observed in the cornea strikes in agar chocolate, and blood agar. In agar Sabouraud-Emmons, was observed as moist beige colonies (Figure 3) that in wet India ink mount showed a thin capsule (Figure 4) and no dark coloration in Black bird seed agar media (Figure 5). The final identification of Cryptococcus albidus was made by PCR, performed in Medical Microbiology and Infectious diseases (C70). Canisius Wilhelmina Hospital (CWZ) in The Netherlands confirming the Cryptococcus albidus by Meis J MD, PHD.

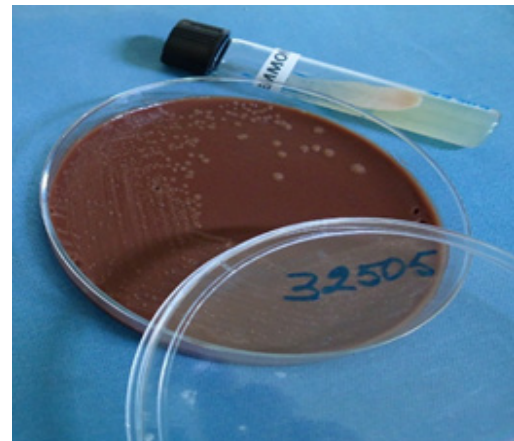


Figure 3: White-Beige color colonies in agar chocolate and Sabouraud-Emmons media, after 48 hours of incubation at 27 c



Figure 4: India Ink wet mount 400X in light microscope, the cell capsule was thin, and it had diverse size (arrow)

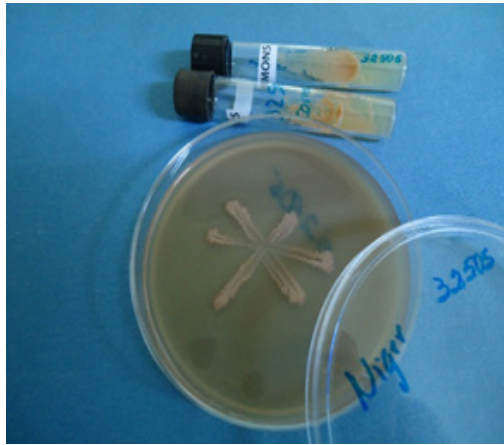


Figure 5: *Cryptococcus albidus* (*Natrashia albida*) after 15 incubation days at 27 grades (centigrades) in Niger seed medium

Discussion

In *Cryptococcus* genus is included a wide group of yeast, which species are usually found in water and plants. *C. neoformans* and *C. gatti* are considered pathogens for humans and wild birds or domestic animals, like cats and dogs causing *Cryptococcosis* in humans, a pulmonary, cutaneous or disseminated infection. Whoever *Cryptococcus laurentii* and *C. albidus* are considered as potential

environmental pathogen yeast for both.

In a brief review, we found 3 published ophthalmic cases caused by *Cryptococcus laurentii*, and *C. albidus*, Garelik, et al. described one immunosuppressed case by AIDS with a *Cryptococcus albidus* sclera ulcer, treated with topic and systemic amphotericin B and oral Itraconazole, with no visual compromise and BCFV 20/20 [5].

Drancourt, et al. in an uveitis etiology causes revision found a *Cryptococcus albidus* infection in 1520 cases studied, with no described treatment or evolution, and one case published by Custis, et al. was suspected by bloodborne pathway infection, diagnosed as chorionic uveitis that developed an endophthalmitis [6,7].

However, corneal involvement of *Cryptococcus* is very rare. Four previous cases of *Cryptococcus laurentii*, *C. albidus* or *C. curvatus* keratitis was found published in the search of the literature (PubMed page media), the first case described by Ritterband, et al. 1998 a diabetic man 51 years old, diagnosed with an onychomycosis, CL user, and posterior keratitis caused by *Cryptococcus laurentii* and *Fusarium solani*, the initial treatment was topical natamycin 5% y oral fluconazol 200mg/day and Amphotericin B intravitreal as last treatment, finally the patient was enucleated [8].

In a brief review the ocular non-*neoformans* *Cryptococcus* cases was described in Table 1

Table 1: Ocular infections caused by non-*neoformans* *Cryptococcus*

| Author/year reference | Sex/ Age years | Initial diagnosis/ Surgical treatment | Medical treatment | Evolution FBCVA | Infectious agent |
|---|----------------|---|--|---------------------------------------|---------------------|
| Custis PH, et al ;1995 (7) | F/61 | Chronic uveitis, Endophthalmitis | Oral Fluconazole 200/12hs, 5 months | After five months HM | <i>C. laurentii</i> |
| Ritterband DC, et al;1998 (8) | M/51 | DM, LC wearer onychomycosis, keratitis | topical natamycin 5% y oral fluconazol 200mg/day and Amphotericin B 0.05µ 0.1ml intravitreal as last treatment | Enucleated | <i>C. laurentii</i> |
| Garelik JM, et al;2004 (5) | F/16 | AIDS, Scleral ulcer | Topic, systemic amphotericin B, Itraconazole 100/12 hs | Two weeks 20/20 non visual impairment | <i>C. albidus</i> |
| Fernandez de Castro LE, et al ;2005 (9) | F/69 | Fuchs Cornea Distrophy and post- KP infection | Submitted to a second KP, Non antimycotic treatment | Stabilization 20/40 | <i>C. albidus</i> |
| Drancourt M, et al; 2008 (6) | Serial case | Chronic uveitis | Not described | Not described | <i>C. albidus</i> |
| Huang YH, et al;2015 (10) | M/45 | Vegetal trauma keratitis | Topic, and intra-stromal 100µg/0.1ml amphotericin B. topic and oral fluconazole | Three months 20/40 | <i>C. albidus</i> |

| | | | | | |
|-------------------------------|------|---|---|--|-------------------|
| Jen Ting DS, et al; 2019 (11) | F/54 | After 3rd PK For last keratitis: 2nd PK CL-related by <i>S maltophilia</i> and <i>C parapsilosis</i> keratitis. After 6 years <i>Cryptococcus curvatus</i> keratitis | After 3rd PK For last keratitis: Amphotericin B 0.15% drops/2 hs. Oral Fluconazole 400 mg/24 hs. Topical voriconazole 1% 4/24hs, Voriconazole intra-stromal 50µ-0.1ml X2 at /72 hs. | Seven years after the first diagnostic 20/30 | <i>C curvatus</i> |
| Current case | M/41 | Herpetic initially. Bacterial and, Mycotic keratitis as final diagnosis | Netilmicin 0.3% Voriconazole 1% drops, oral Itraconazole 100mgs/12 hs. | 30 days, 20/30 | <i>C albidus</i> |

DM = Diabetic mellitus, LC = gas permeable contact lens PKP= penetrating keratoplasty, AIDS = Acquired Immune Deficiency Syndrome, ND= not described

The second keratitis case was a female patient 69 years old diagnosed initially with Fuchs cornea dystrophy described by Fernandez de Castro, the patient was submitted to PK and as post-surgical complication was observed with *C albidus* keratitis by suspected donor to host transmission. The first corneal tissue was retired and a second donor tissue was transplanted, after, the patient eye was stabilized without signs of inflammation or recurrence, with an acceptable BCVA 20/40 visual acuity 24 months after the second surgery [9].

The third corneal infection case published was an early diagnosis and good response to treatment described by Huang YH, et al. in a 45 year old non immunocompromised man, he referred a red left eye [10]. At slit lamp examination was observed deep corneal infiltration. *Cryptococcus albidus* was detected by molecular test by dot hybridization assay. For treatment was used stromal amphotericin B reaching gradual improvement.

The fourth keratitis case recent published by JenTing was for a PK in a female patient diagnosed with lattice dystrophy, the first PK was infected by the use of contaminated LC with *Stenotrophomonas maltophilia* and *Candida parapsilosis*, with good response to antimicrobial therapy [11]. Six years after the patient was diagnosed with a *Cryptococcus curvatus* keratitis, treated with Amphotericin B 0.15% drops/2 hs, oral Floconazole 400 mg/24 hs by five months, the CDVA achieved then was 20/25. For a recurrence of *Cryptococcal* keratitis, within four weeks, after the discontinuation of antifungal treatment, the patient was treated once again with topical voriconazole 1% 4/24hs, and application of six voriconazole intra-stromal 50µ-0.1ml injections, that have failed in the eradication of *Cryptococcal* infection. Finally the patient was submitted to the 3rd PK and an antimycotic treatment of topical amphotericin B 4/day for 5 months and oral fluconazole 400 mg once daily for 3 months, the infection was resolved and CDVA was 20/30.

Our case was diagnosed in early stage and responded well to voriconazole 1%, and oral Itraconazole 100 mg/12 hs. Was prescribed too netilmicin 0.3% drops each two hours alternatively, because the isolation of *Staphylococcus epidermidis* susceptible to netilmicin and voriconazole 1µ in the cornea sample. Finally the

patient reach an acceptable final visual acuity 20/30.

Non-neoformans species of *Cryptococcus* lacks phenoloxidase enzyme for melanin synthesis and when grown in Niger seed agar medium produce white-gray colonies, in contrast to *C neoformans* that produces black colonies. The cells forming colonies was tested for india ink test, the round mucosal walls are thin in our isolate. We take the 95 % accuracy in Vitek 2 (Biomeraux, France) test for the identification. The PCR genomic identification was in our case the gold standard test for identification.

Conclusion

The early clinical diagnosis, confirmed by cultures and after by genomic PCR as *Cryptococcus albidus* keratitis, in the corneal samples was isolated too *Staphylococcus epidermidis*, for medical treatment were administered voriconazole drops 1%, netilmicin 0.3% drops, and oral Itraconazole 100 mgs 12 hs. The patient reached a good evolution in a short time (one month) and good final visual acuity 20/30.

Acknowledgment

In memoriam to Marino Alcantara Castro QFB who passed away for Covid19.

Disclosure

The authors declare no conflict of interest in any of the drugs or method cited.

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