



## Case report

# Chorioretinal paracoccidioidomycosis treated with intravitreal voriconazole and therapeutic vitrectomy

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## ARTICLE INFO

## Keywords:

Paracoccidioidomycosis  
Fungal uveitis  
Ocular  
Chorioretinal  
Intravitreal voriconazole  
Pars plana vitrectomy  
Tractional retinal detachment

## ABSTRACT

**Purpose:** To report a case of aggressive chorioretinal paracoccidioidomycosis requiring treatment with systemic antifungal agents, frequent intravitreal voriconazole injections, and surgical excision.

**Observations:** A Brazilian man in his mid-30s with a history of chronic, biopsy-proven cutaneous paracoccidioidomycosis, chronic sinusitis, and perichondritis secondary to paracoccidioidomycosis presented with profound vision loss. He was found to have significant vitreous inflammation and a large chorioretinal lesion in the posterior pole concerning for ocular involvement. He was treated initially with combined topical and systemic steroids as well as systemic antifungals and antibiotics, then with serial intravitreal voriconazole injections resulting in a significant reduction of intraocular inflammation and subretinal fluid. The residual tractional retinal detachment from the chorioretinal lesion was addressed surgically by pars plana vitrectomy.

**Conclusion and importance:** Intravitreal voriconazole can be an effective adjuvant treatment for the vitreous inflammation and subretinal fluid associated with chorioretinal paracoccidioidomycosis. Surgical intervention may be indicated in cases complicated by tractional retinal detachment.

## 1. Introduction

Paracoccidioidomycosis is a chronic fungal infection primarily affecting the lungs, lymph nodes, skin, and mucous membranes.<sup>1,2</sup> It is contracted through inhalation of the spores of *Paracoccidioides brasiliensis*, an organism endemic to much of South and Central America with high incidences noted in Brazil, Colombia, Argentina, and Venezuela.<sup>3,4</sup> Ocular involvement is rare and most frequently involves the eyelid and conjunctiva,<sup>5,6</sup> with rare cases of choroidal granulomas and endophthalmitis.<sup>7–10</sup> We describe a case of ocular paracoccidioidomycosis presenting with a large chorioretinal lesion and describe successful treatment with serial intravitreal antifungal injections and surgical excision.

## 1.1. Case report

A Brazilian man in his mid-30s presented to the emergency department with a 2-week history of floaters and worsening vision in his left eye, as well as redness and swelling of his right ear (Fig. 1). His medical history was notable for chronic right-sided maxillofacial sinusitis and perichondritis secondary to biopsy-proven paracoccidioidomycosis

diagnosed 15 years prior with intermittent flares on maintenance therapy of itraconazole 100 mg twice daily (BID) for the last 3 years. Two months prior to presentation, he ran out of itraconazole and was unable to obtain refills in the setting of the COVID-19 pandemic.

Snellen visual acuity at distance was 20/20 right eye (OD) and 20/200 left eye (OS). Intraocular pressures were 18 mmHg OD and 15 mmHg OS. Examination of the right eye was unremarkable. Slit lamp examination of the left eye was notable for 1+ conjunctival injection, corneal endothelial dusting with a Krukenberg spindle, and 1+ anterior chamber cell and pigment. There were no iris nodules, synechiae, or transillumination defects. Posterior segment examination revealed 1+ vitreous cell and 0.5+ inferior haze with a 4 disc-diameter elevated circular whitish-yellow subretinal lesion along the distal inferotemporal arcade with subretinal fluid and exudates extending to the fovea (Fig. 2A). There were numerous mid-peripheral small-to-medium white lesions with indistinct borders. Optical coherence tomography (OCT) confirmed a serous retinal detachment surrounding the lesion and involving the fovea. Fluorescein angiography (FA) showed early hypofluorescence over the lesion with late hyperfluorescence without evidence of neovascularization. Review of systems was notable for a perichondritis flare with increased pain, edema, and erythema of his

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<https://doi.org/10.1016/j.ajoc.2021.101187>

Received 2 February 2021; Received in revised form 21 May 2021; Accepted 3 August 2021

Available online 11 August 2021

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Fig. 1. External photograph of right ear at presentation.

right ear.

He was started on oral intravenous 200 mg BID and trimethoprim/sulfamethoxazole 160/800 mg BID, given his history of excellent response to systemic therapy in the past. Additionally, topical prednisolone acetate was added four times a day (QID). One month later, oral prednisone was started at 20 mg/day; this dose was chosen during the early stages of the novel coronavirus pandemic with concern for the risk of immunosuppression, but was escalated to 40 mg/day three weeks later due to persistent subretinal fluid. Over the next three months, the ear redness/swelling improved and the chorioretinal lesion gradually reduced in size on systemic therapy (Fig. 2B). However, the patient self-discontinued oral prednisone due to concerns over a rash. Due to persistent vitreous inflammation and macular traction with associated subretinal fluid, the patient was started on intravitreal voriconazole 100 µg injections. He underwent 14 injections, as frequently as twice a week, over the subsequent three months, which resulted in near-complete resolution of the vitreous inflammation and further consolidation of the border and reduction in the size of the chorioretinal lesion with some decrease in the surrounding subretinal fluid (Fig. 2C). The persistence of subretinal fluid was attributed to vitreoretinal traction from the chorioretinal lesion, so the decision was made to proceed with a pars plana vitrectomy. Intraoperatively the regressed lesion was strongly attached to the underlying choroid with surrounding retinal contraction and macular dragging. A biopsy was attempted, but the lesion was too friable to grasp any tissue. The retina could not be flattened without releasing the retinal traction from the lesion, so a retinotomy was performed 360° around the lesion allowing the retina to flatten intra-operatively, endolaser was applied to seal the retina around the excision site, and the eye was filled with silicone oil (Supplementary Video). Undiluted samples of vitreous fluid were negative for fungal stains by cytopathology, and fungal cultures remain negative to date. One month post-operatively, vision was 20/100 under silicone oil, and over the next few months, epiretinal fibrosis developed with retinal folding from the optic nerve to the retinotomy lesion, with some persistent subfoveal fluid (Fig. 2D). The retinotomy was confirmed to be well sealed by OCT, further indicating the source of the subretinal fluid was traction from the recurrent macular fibrosis. Four months after his initial vitrectomy, he underwent a repeat vitrectomy to remove the recurrent epiretinal fibrosis. The dense fibrosis was difficult to peel from the underlying retina leading to traction and limited detachment of the retina intra-operatively, perfluoron liquid was used to flatten the retina, and silicone oil was replaced. One week post-operatively he had significant improvement in subretinal fluid (Fig. 2E) and a vision of 20/400.

Supplementary video related to this article can be found at <https://doi.org/10.1016/j.ajoc.2021.101187>

## 2. Discussion

Paracoccidioidomycosis is the most common systemic mycosis in Latin America.<sup>1</sup> Diagnosis can be made by microscopic examination and cultures from skin, sputum, blood, and lymph node specimens. Histology reveals a characteristic pilot's wheel appearance: a single mother cell surrounded by multiple peripheral daughter cells.<sup>1</sup> Serological testing is most often used for guiding clinical response to treatment.<sup>3</sup> In our case, the diagnosis of ocular paracoccidioidomycosis was made based on the combination of his history of biopsy-proven systemic infection as well as negative laboratory work-up for other potential causes of similar chorioretinal lesions (e.g. syphilis, TB, HIV, sarcoidosis). Vitreous biopsy and culture did not show evidence of the organism; however, he had already received 7 months of systemic and intravitreal treatment at the time of the biopsy, which may have limited their diagnostic utility. Regardless, the initial biopsy-proven diagnosis in Brazil and a positive response to treatment strongly suggest paracoccidioidomycosis as the most likely etiology of the chorioretinal lesion.

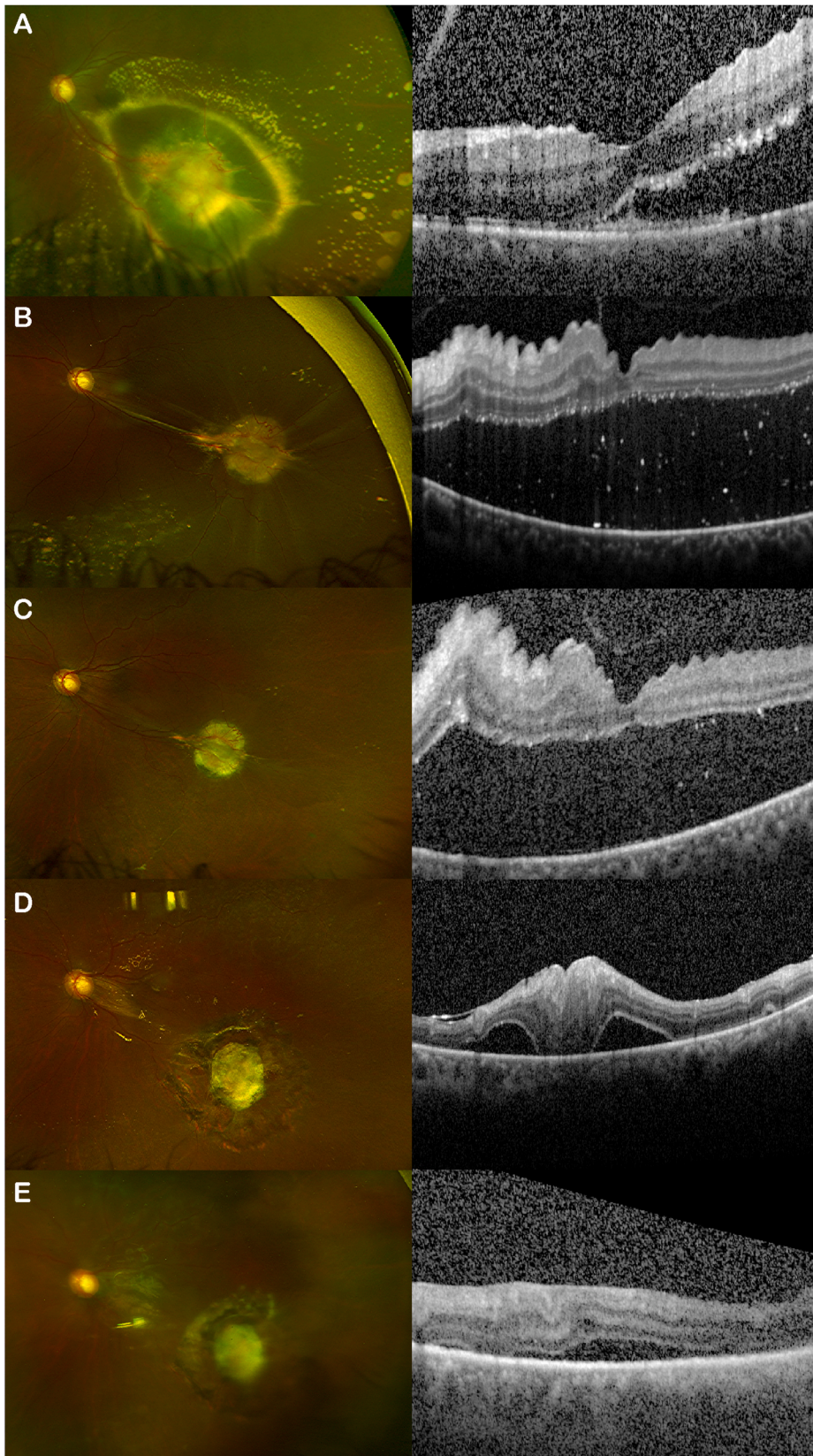
Pharmacologic options for systemic disease include: sulfonamide derivatives, which act as competitive antagonists of *para*-aminobenzoic acid to prevent folic acid synthesis; azoles, which inhibit the microsomal P450 dependent enzyme lanosterol 14 $\alpha$ -demethylase involved in fungal cell membrane synthesis; and amphotericin B, which binds to ergosterol in the fungal cell membranes forming pores and increasing permeability.<sup>11</sup> For mild-to-moderate cases, sulfonamides and azoles have been shown to be equally effective, and in cases of central nervous system (CNS) involvement, the outcomes with sulfadiazine and amphotericin B are comparable.<sup>11</sup> Typically dosed at 1 mg/kg/day,<sup>2</sup> amphotericin B has a high toxicity profile including cardiac arrhythmia and renal failure.<sup>3</sup> Itraconazole 200–400 mg/day<sup>2</sup> is often considered the drug of choice given the low relapse rates and favorable toxicity profile.<sup>3</sup> Finally, trimethoprim/sulfamethoxazole dosed at 60–240/800–1200 mg BID,<sup>2</sup> is generally inexpensive, has good CNS penetration, and, given the similarity of appearance to ocular and CNS toxoplasmosis, is an effective treatment for both conditions.<sup>7</sup> Cure rates for systemic paracoccidioidomycosis with these treatments ranges from 50 to 70%,<sup>3</sup> however mortality from disseminated ocular paracoccidioidomycosis with CNS involvement may be greater than 20%.<sup>7</sup> There is also a high relapse rate ranging from 15 to 30%,<sup>3</sup> often requiring lifelong therapy.<sup>2</sup>

There are no controlled studies that compare treatment options for ocular paracoccidioidomycosis.<sup>11</sup> Isolated chorioretinal involvement is infrequent, with only a few reports existing in the literature. Bovo et al. described a case of multifocal chorioretinitis, which responded well to oral trimethoprim-sulfamethoxazole 160–800 mg.<sup>8</sup> The choroidal lesions formed atrophic scars and the subretinal fluid slowly resorbed over the course of 6 months. Bonomo et al. described a case treated with amphotericin B with flattening of the chorioretinal lesion and resolution of the serous retinal detachment over 3 months.<sup>9</sup> Finamor et al. described a case of advanced chorioretinal disease in a patient with AIDS (CD4 count 25 cells/mm<sup>3</sup>).<sup>7</sup> Despite partial response to treatment for suspected toxoplasmosis (sulfadiazine and pyrimethamine), there was rapid progression to retinal detachment and neovascular glaucoma requiring enucleation. The final diagnosis of paracoccidioidomycosis was made during histopathologic evaluation of the enucleated eye.

To our knowledge, serial intravitreal voriconazole injections, as well as surgical excision, have never been described in the literature previously. The combination of the juxtamacular location, profound intra-ocular inflammation and large subretinal fluid collection prompted aggressive treatment to prevent further vision loss. Intravitreal voriconazole was chosen because it has broad coverage and, along with amphotericin B, has been shown to achieve high local antifungal

activity.<sup>12</sup> We chose voriconazole over amphotericin B because the patient seemed to respond positively to oral itraconazole with resolution of his ear lesion and improvement in the chorioretinal lesion size. Despite resolution of the intraocular inflammation, there was a plateau in the

subretinal fluid improvement due to traction from the chorioretinal lesion requiring pars plana vitrectomy with surgical release of traction. Post-operatively, after 2 surgeries, the patient's vision improved to 20/400 under silicone oil with a significant reduction in macular



**Fig. 2.** Wide-field fundus photographs and optical coherence tomography of the macula at various time points during the clinical course. A) Initial presentation with vitreous inflammation and chorioretinal lesions. B) Following three months of systemic antifungal and corticosteroid therapy, and prior to intravitreal therapy, with a plateau in lesion size reduction. C) Following three months of serial intravitreal voriconazole injections (14 total) with resolution of vitreous inflammation and lesion consolidation. The persistent subretinal fluid was attributed to vitreoretinal traction. D) Three months after pars plana vitrectomy for tractional retinal detachment with improvement in subretinal fluid. Four months after the initial surgery, he underwent repeat intervention to release the epiretinal fibrosis. E) One week post-operatively he had a significant reduction and near resolution of subretinal fluid.

subretinal fluid (Fig. 2E).

While chorioretinal involvement with paracoccidioidomycosis is rare, our case demonstrates success with aggressive management with systemic therapy and subsequent intravitreal antifungal injections and pars plana vitrectomy. We hope that this case may expand the therapeutic arsenal available to clinicians beyond the traditional medical management that have previously been described in the literature. This case also highlights the vision-threatening consequence of treatment interruption and diagnostic delay in a patient with limited access to eye care during a pandemic.

### 3. Conclusions

We report a rare case of ocular paracoccidioidomycosis presenting with an isolated chorioretinal lesion that was refractory to standard therapy and provide the first report of serial intravitreal voriconazole injections to prevent further vision-threatening complications. We also demonstrate the utility of vitreoretinal surgical intervention to address the tractional retinal detachment from the chorioretinal lesion. We hope this case illustrates the additional medical and surgical options available to treat vision-threatening chorioretinal paracoccidioidomycosis.

#### Patient consent

Written consent from the patient was obtained for publication of this report.

#### Funding

No funding or grant support.

#### Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

#### Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

#### Research ethics

Written consent to publish potentially identifying information, such as details or the case and photographs, was obtained from the patient(s) or their legal guardian(s).

#### Declaration of competing interest

None.

#### Acknowledgments

None.

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