

**Title: Bevacizumab for treatment of choroidal neovascularization secondary to Candida chorioretinitis**

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## **ABSTRACT**

**Purpose:** To report a case of juxtafoveal choroidal neovascularization in a patient with candida chorioretinitis successfully treated with intravitreal bevacizumab. **Methods:** Case report. **Results:** A 45-year-old woman previously treated for candida chorioretinitis, presented with reduced vision in the left eye. The patient was investigated with ophthalmoscopy, fluorescein angiography, and optical coherence tomography (OCT). Following initial treatment, fundus examination, fluorescein angiography, and OCT of the right eye revealed a secondary juxtafoveal classic choroidal neovascularization. Following a single intravitreal injection of bevacizumab, the patient had excellent visual recovery, with absence of subretinal or intraretinal fluid in the OCT. **Conclusions:** Bevacizumab was effective in treatment of choroidal neovascularization associated with Candida chorioretinitis.

**KEY WORDS:** Candida; chorioretinitis; choroidal neovascular membrane; bebacizumab.

## **INTRODUCTION**

Candidemia can lead to metastatic ocular infection with potential serious and sight threatening consequences.[1] Intravenous drug use, systemic immunosuppression, uncontrolled diabetes, parenteral hyperalimentation, malignancy, organ transplantation, surgically-induced abortion and recent major surgery are known risk factors for candidemia.[1]

Endogenous endophthalmitis and chorioretinitis are the two main presentations of ocular candidiasis. The former is characterised by vitritis and fluffy balls affecting the inner retina extending into the vitreous, whilst the latter typically manifests as focal deep creamy chorioretinal lesion with pathology restricted to the chorioretinal layers without direct vitreous involvement.[1] In cases of endophthalmitis, hypopyon, scleritis and optic-nerve involvement may occur.[2]

In the acute phase of chorioretinitis, colonies of candida can settle in the space between the retinal pigment epithelium (RPE) and Bruch's membrane. Once the acute phase of chorioretinitis ends, fibrosis and scarring may ensue which can disturb the RPE architecture and promote development of choroidal neovascularization (CNV) which is a rare and usually late sequelae. Although uncommon, it is an important potential complication of Candida infection with probable devastating visual outcome.[3]

Various treatment strategies have been used in the past to treat CNV secondary to candida chorioretinitis, including laser photocoagulation,[4] photodynamic therapy,[5] and submacular surgery.[6] However there are no previous reports about the use of intravitreal bevacizumab in the treatment of CNV secondary to candida chorioretinitis.

We describe a case of CNV secondary to Candida chorioretinitis, which resolved with a single intravitreal injection of bevacizumab alone.

## **CASE REPORT**

A 45 year-old woman was referred by her general practitioner to eye clinic with three days history of pain followed by reduced vision in her left eye, one day after the use of an intravenous drug. Apart from a longstanding exophoria, there was no other ocular history of note. She was a known intravenous drug user. On examination, the best

corrected Snellen visual acuity was 6/5 in the right eye and 6/60 in the left eye. Pupillary reflexes were normal. Anterior segment was unremarkable with normal intraocular pressure in both eyes. Posterior segment examination of the left eye revealed mild vitritis and an elevated chorioretinal lesion adjacent to fovea with associated subretinal fluid (Figure 1). Right eye showed no abnormalities.

A clinical diagnosis of candida chorioretinitis was made based on patient's background and clinical findings. Full blood count, liver and renal function, blood culture, liver and cardiac ultrasound did not reveal evidence of any other foci of fungal infection. HIV and Hepatitis B testing were also negative, although she was positive for hepatitis C virus. She underwent vitreous biopsy and was treated simultaneously with intravitreal amphotericin B and oral voriconazole (200 mg BD). The vitreous tap did not find any microorganism or fungi. However, she had a good clinical response to treatment, which was supportive of the clinical diagnosis with dramatic improvement of visual acuity to 6/6 in the left eye after six weeks of treatment.

After two months, she presented with worsening of her visual acuity in the left eye (6/12) after stopping the treatment with voriconazole. At that time the clinical examination disclosed a mild amount of subretinal fluid with a small subretinal haemorrhage (Figure 2).

Fundus fluorescein angiography and optical coherence tomography (OCT) demonstrated the presence of a classic juxtafoveal choroidal neovascularisation (CNV) associated with the scarring of the previous candida chorioretinal lesion (Figure 1).

A single intravitreal injection of bevacizumab (1.25/0.05 mg/ml) was administered in the left eye, which resulted in complete resolution of the fluid within 1 month and improved visual acuity to 6/7.5 in the left eye. Vision remained stable at 14 months after the treatment at her last follow-up with no further evidence of reactivation of CNV or chorioretinitis.

## **DISCUSSION**

The incidence of chorioretinitis and endophthalmitis in patients with culture proven candidemia ranges from 2 - 26% and 0 - 6%, respectively.[1,7] Factors associated with poor visual outcomes include, presenting visual acuity, central location of the lesion, presence of secondary CNV, retinal detachment, and insufficient or delayed treatment.[8,6,9]

The mainstay of treatment in ocular candidiasis is systemic antifungal medication such as voriconazole and fluconazole, associated to intravitreal injection of antimycotic agents (amphotericin B or voriconazole) which could be combined with pars plana vitrectomy.[2] Currently, there are no established treatment strategies for CNV in the context of candida chorioretinitis. Historically, various modalities have been employed including conservative approach i.e. observation, laser photocoagulation or surgery in selected cases, all having some limitations.[3-6]

Laser photocoagulation has been reported to bring the neovascular process related to candida albicans chorioretinitis under control,[3] although its therapeutic effects could be compromised by enlargement of the scars and scotomata. Additionally laser treatment has been associated with persistent and recurrent CNV.[4]

Tedeschi et al treated a case of macular choroidal neovascularization secondary to Candida endophthalmitis with photodynamic therapy (PDT) which stabilised vision and arrested progression of CNV.[5] The thrombogenic effect of PDT is thought to be responsible for halting the neovascular process, although this may have to be combined with systemic therapy to increase its long term success rate. The effect of PDT could be limited by its collateral damage to the surrounding tissue, hypoperfusion and RPE atrophy from PDT leading to reduction in final VA.[10]

Surgical excision of the neovascular membrane has also been described in the literature. Recchia et al studied the outcomes of submacular surgery for CNV secondary to candida endophthalmitis. This small case series included 5 eyes of 3 patients who underwent submacular surgery. Substantial visual improvement was noticed in 4 eyes of 3 patients, although this was limited in the 2 eyes with preexisting submacular fibrosis.[6]

Corticosteroids have a role in treating inflammatory CNV by inhibiting the actions of inflammatory elements, reducing the secretion of proangiogenic factors and reducing vascular permeability,[10] although their use in the setting of fungal infection is very controversial.

In an animal model, intravitreal corticosteroids combined with amphotericin B was compared to amphotericin B alone. The authors found significantly clearer vitreous in eyes receiving corticosteroids and there was no enhanced fungal activity, contrary to general belief that steroids can potentiate fungal proliferation.[11]

Vascular endothelial growth factor (VEGF) expression has been seen to play a role in the pathogenesis of the inflammatory CNV. It has been demonstrated that excised inflammatory CNVs overexpressed VEGF by immunohistochemistry.[12] Multiple reports have been published on the use of intravitreal anti-VEGF agents in the management of inflammatory CNV mainly focusing on the non-infectious uveitis. Despite some promising results with anti-VEGF agents in treating inflammatory CNV, the current data is limited by lack of comparative studies, and

further data from prospective controlled studies are required to fully determine the role of anti-VEGF therapy for the inflammatory CNV.[13]

Although, intravitreal anti-VEGF has been widely used for inflammatory CNVMs, there are only a few anecdotal reports in the context of CNVM secondary to infectious and particularly fungal chorioretinitis. Successful outcomes have been documented in CNVM related to ocular toxocariasis following three consecutive injections of ranibizumab. [14, 15] Favorable results have also been associated with Intravitreal bevacizumab for treatment of choroidal neovascularization secondary to toxoplasmic retinochoroiditis.[16] The use of Ranibizumab combined with vitrectomy has been found to be beneficial in patients with tractional retinal detachment secondary to retinal neovascularization due to endogenous fungal endophthalmitis in intravenous drug users.[9] Similarly a single intravitreal injection of ranibizumab alone has also been used in the treatment of choroidal neovascular membranes secondary to fungal endogenous endophthalmitis with good outcomes.[17]

In our case a single intravitreal injection of bevacizumab was effective in resolving the CNV secondary to candida chorioretinitis, maintaining vision for a follow-up of 14 months (to our knowledge, the longest follow-up in the literature without recurrence of the disease) after the initial bevacizumab injection. This is the first described case of CNV secondary to candida chorioretinitis treated with intravitreal bevacizumab alone. Anti-VEGF treatment is a useful addition to our armamentarium when treating CNV associated with infectious aetiologies.

#### **COMPLIANCE WITH ETHICAL STANDARDS**

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None of the authors have any proprietary interest in the materials described in this study.

This report is limited to secondary use of information previously collected in the course of normal care (without an intention to use it for research at the time of collection) and therefore excluded from REC review.

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**LEGENDS TO FIGURES:**

**Figure 1.** Serial fundus photography and OCT examination from presentation and pre and post intravitreal injection of bevacizumab showing resolution of the subretinal fluid with evolving scar. A: Lesion at presentation. B: 1 month after presentation, post-treatment with oral voriconazol and intravitreal amphotericin B. C: 5 months after presentation, presented with new onset subretinal fluid, and confirmed classic choroidal neovascular membrane in the fundus fluorescein angiography. D: 1 month after treatment with a single injection of intravitreal bevacizumab. E: OCT and colour fundus photograph of the last follow-up visit 20 months after presentation.

**Figure 2.** Fundus fluorescein angiography demonstrating the presence of classic choroidal neovascularisation in the left eye. Earlier frames are showed in the left.