Candida endophthalmitis following penetrating keratoplasty in patient with negative donor rim; a case report with review of literature for diagnosis and treatment of fungal endophthalmitis

Abstract

This is a case of young patient presented with granulomatous anterior and posterior uveitis, which turned to be fungal endophthalmitis after penetrating keratoplasty. Her symptoms were undetected because she was on systemic and topical steroids. The patient is a 25 years old Caucasian female, previously medically free of any disease, who was admitted to the Eye Clinic at the Jordan University Hospital, Amman, Jordan, for left penetrating keratoplasty and severe keratoconus. After an initial improvement in her vision and a smooth postoperative course, she presented with drop of vision, photophobia, and non-specific eye pain. On examination she was found to have anterior granulomatous uveitis. She was started on systemic steroids and the topical steroids were increased in intensity. The initial systemic workup for granulomatous anterior uveitis was negative. However, culture of the aqueous was positive for *Candida galabrata*, but the donor rim was negative. Later the patient developed vitritis despite being on systemic fluconazole and topical amphotericin B. She was treated with intravitreal amphotericin B. The vitritis improved, but vitreous opacities developed which deteriorated her vision. A pars plana vitrectomy was done. Her final visual acuity remained poor because of opacified graft. The patient's unfortunate case represents a *Candida* endophthalmitis after penetrating keratoplasty despite being medically a healthy person.

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Introduction

Corneal transplantation is considered a proved way of treatment of various corneal disorders [1]. Fungal keratitis and endophthalmitis

Keywords

Candida Endophthalmitis;
Penetrating Keratoplasty;
Negative Donor Rim.

is a rare but well known complication that occurs post transplantation [2]. It had an incidence of 1.4 per 10000 transplants. Culture can detect presence of fungal keratitis and endophthalmitis [2]. Fungal infections of post keratoplasty can lead to severe complications [1].

Candida chorioretinitis typically presents as several, small, creamy white, circumscribed chorioretinal lesions with overlying vitreous inflammation. In certain cases, these chorioretinal lesions may be surrounded by hemorrhage, giving them the appearance of a white-centered hemorrhage. Within the area of the lesion, the retinal vessels may be sheathed, and the vitreous opacities resemble fluffy balls, and they may be linked to each other by strands giving them the string of pearls appearance. In case the infection is not detected the disease advances, epiretinal membranes may develop, leading to vitreoretinal traction and retinal detachment. The lesions often heal with treatment, but chorioretinal scarring may be developed in the areas of prior inflammation. Two thirds of patients have bilateral disease, and more than one half of patients have vitreous involvement. Iridocyclitis often is present, and fungal infection of the iris and ciliary body is rare [3].

Case report

A 25 year old female patient diagnosed with keratoconus in both eyes, with mild degree in the right eye and severe one in her left eye. The right eye was doing well with rigid contact lens obtaining a visual acuity of 0.7. However, her left eye had a visual acuity of CF 1m, which did not improve with contact lens or glasses. The keratometric reading was 70 and 77 diopters in the left eye for which a penetrating keratoplasty was indicated.

She was medically healthy person and was not on any medications. An uneventful penetrating keratoplasty was done in her left eye. Her immediate postoperative visual acuity was 0.2. She was started on topical prednisolone acetate every two hours

and topical ofloxacin every four hours. She had a smooth postoperative course, so her topical steroids were tapered and a visual acuity of 0.4 was gained. Few months later the patient developed a drop in her vision and severe anterior uveitis, which was thought that it is a rebound uveitis due to tapering of her topical steroids. As a result, the topical steroid was increased in frequency to every one hour, and after a fair response, the patient was started on oral steroids prednisolone acetate of 1mg/kg.

The patient showed a good response initially and her visual acuity improved, but she went back with a drop in her visual acuity. After examination her visual acuity, she was found to have granulomatous anterior uveitis with mutton fat keratic precipitate. Her B scan was negative for vitritis. A workup was done including chest X-ray, Purified Protein Derivative (PPD) skin test for tuberculosis, CBC with differential, Angiotensin Converting Enzyme level, Cytoplasmic Antinuclear Cytoplasmic Autoantibody, While waiting for the results, which turned to be negative, the oral steroids were maintained. Later, the patient developed a white fluffy matter in the anterior chamber, with more severe inflammation. An aqueous tap was done for gram stain, fungal and bacterial culture and susceptibility tests. Culture of the donor bottom was done which turned to be negative. There was budding yeast in the gram stain and the culture turned to be positive for *Candida glabrata*. The patient was referred to the infectious disease unit and was started on oral fluconazole and topical amphotericin B (50mg/ml). During follow up, a breached anterior capsule was noted with opacified lens. A history of trauma was present, which was denied by the patient latter.

A lens aspiration with intraocular lens implantation and culture of the aqueous was obtained again. It turned to be positive for *Candida glabrata*. The patient was maintained on oral fluconazole and topical amphotericin B. The patient visual acuity improved to 0.2. Four months later, the patient developed mild discomfort and drop in her visual

acuity to counting fingers (CF) at 1m. A posterior uveitis developed vitreous tap for fungal culture and susceptibility and intravitreal amphotericin B of 0.1ml (50mg/ml) was given. The vitreous culture turned to be negative. The patient improved initially and the vitritis subsided but vitreous opacities developed and a thick retro-lental membrane developed and the IOL lens was displaced anteriorly, so the visual acuity was decreased to hand motion (HM). A pars plana vitrectomy was done and a second vitreous culture was done and intravitreal amphotericin B was given. During the surgery, there were thick vitreous opacities with very adherent posterior hyaloid but the retina looked healthy. The fungal culture was negative again. Although her smooth postoperative recovery, her visual acuity remained HM due to opacified graft.

Discussion

Although fungal keratitis and endophthalmitis post keratoplasty is very rare, it has a very poor prognosis [1, 3]. Patients who develop *Candida* endophthalmitis have risk factors like intravenous drug abuse being the most common one, other risks include; long standing indwelling catheters, postpartum women, premature infants, patients undergoing hyperalimentation, history of recent abdominal surgery, and patients with debilitating diseases like diabetes mellitus, post organ transplantation or malignancies [1, 3].

The symptoms of *Candida* endophthalmitis may include loss of vision which may be unrecognized in cases of endogenous endophthalmitis, visual acuity may not be affected if the lesion is peripheral, red eye, and photophobia, pain, floaters or scotoma may be present. *Candida* endophthalmitis typically presents as several small well demarcated peripheral creamy lesions surrounded by vitreous inflammation, Roth spots, which are areas of chorioretinitis surrounded by hemorrhages, may be present. The nearby vessel may be sheathed. The vitreous

may be involved and vitritis typically present as ill-defined balls of inflammation connected together by strands resembling strings of pearls. In unrecognized cases epiretinal membrane develops resulting in vitreous traction and epiretinal membrane formation. Healed chorioretinal lesions leave scarred areas which may be complicated by choroidal endovascular membrane. The infection is bilateral in two third of patients and vitritis is present in half of the patients. Iridocyclitis is usually present and hypopyon may develop, although presence of infection of the iris or the ciliary body is rare.

Most cases of fungal endophthalmitis are due to *Candida albicans* [1, 3]. *Candida glabrata* is also a common ocular pathogen with increasing frequency and predilection for eyes with corneal transplant [4]. Most reported cases were also associated with a positive culture of the donated cornea. In half of the cases there is a latent period of several months before the fungal infection is recognized and due to delay in diagnosis, most cases required re-grafting [4-8]. The most commonly isolated yeast in infectious keratitis is *C. albicans* [8]. Also, *C. glabrata* related infections are documented and such cases are difficult to treat because *C. glabrata* is resistant to most antifungal agents used in treatment of *C. albicans* [4]. Differential diagnoses include postoperative endophthalmitis, acute retinal necrosis, acute complications of sarcoidosis, toxoplasmosis, leukemia, interstitial keratitis and tuberculosis. The diagnosis of fungal endophthalmitis should be suspected in any immunocompromised patient present with vitritis and chorioretinitis.

The diagnosis of fungal infections in the ophthalmic practice requires the presence of pathology. A presumptive diagnosis is possible when the fungus is isolated by culture from any part of the body; like blood, cerebrospinal fluid, urine, sputum associated with presence of classical intraocular findings. In suspected cases of endogenous endophthalmitis, cultures with direct examination for fungi using Giemsa, Gomori-Methenamine-Silver (GMS) and

Periodic-Acid Schiff stains should be requested. In the present study, the presence of the fungal infection was documented by culture [8]. *C. glabrata* was isolated on two different occasions using aqueous sample for culture. Fungal culture on Sabourauds dextrose agar can be positive in 44% to 70% of clinically diagnosed cases. Vitrectomy samples are more yielding than vitreous needle samples[9], any growth should be considered as significant rather than contamination and the samples should be kept for 4-6 weeks to insure that slow growing fungi are not missed [8].

A modern technique of diagnosis of fungal endophthalmitis is using polymerase chain reaction (PCR). PCR is a rapid and high sensitive method and helps in early differentiation between bacterial and fungal endophthalmitis. PCR was used successfully to identify *Candida* species from intra ocular fluids [10]. In addition, DNA microarray is a modern rapid helpful method of diagnosis [11]. *Candida* species grows well on Sabourauds dextrose media at room temperature and 37C without cycloheximide as white and pasty colonies after incubation 2-4 days. A simple wet preparation can reveal the presence of yeast cells. Germ-tube test can be used to differentiate between *C. albicans* and other *Candida* spp. ChromCandida agar is frequently used to confirm the presence of all clinically common *Candida* species [12].

Various drugs are used in the treatment of fungal endophthalmitis. Drugs include, amphotericin B, fluconazole, ketokenazole, miconazole, flucytosine, itraconazole and caspofungin. But the best initial treatment for endogenous fungal endophthalmitis has not been established. However, both amphotericin B and fluconazole are recommended [13]. Systemic amphotericin has been the drug of choice because of its broad spectrum activity, but the penetration of the vitreous cavity is limited, and doses of 5 to 10 mg intravitreal amphotericin is commonly used. Retinal toxicity was reported in animal models with such doses [13]. Fluconazole

and flucytosine have good intraocular penetration, but *Candida* species have already high resistance to flucytosine. A recent drug is voriconazole which is administered systematically, has a good intra vitreal penetration and is not retino toxic when given intra vitreal in a concentration up to 25 mg/ml [14]. Antifungal susceptibility test *in vitro* using minimum inhibitory concentrations (MICs) does not always correlate with *in vivo* values, for that reason the MIC of fungal drugs *in vitro* should only be used as a guideline [15].

The echinocandines (caspofungin, micafungin and anidulafungin) are new drugs that work by inhibiting D-glucan synthase, which is an essential enzyme involved in fungal wall synthesis. They have activity against most species of *Candida* and *Aspergillus*. Caspofungin and amphotericin B are equally effective in candidemia and fungal endophthalmitis, but fewer side effects were reported with caspofungin compared to amphotericin B [16]. Gauthier *et al.* [14], reported a case of *Candida* endophthalmitis that failed to respond to caspofungin due to poor penetration into the vitreous. The role of caspofungin in the treatment on *Candida* endophthalmitis remains limited. Al Assiri *et al.* [17], recommended routine culture of the donor corneal rim at the time of surgery to detect potential source of late onset fungal infections like *C. glabrata*. Visliser *et al.* [18], concluded that positive donor rim cultures are uncommon but carry an unacceptably high risk of post graft fungal infection. This process can be reduced with prophylactic antifungal treatment in positive cultures [19]. We have used amphotericin B topically and intravitreally in our patient and showed a good response. Grueb *et al.* [13], found that topical and intracameral application of amphotericin B is sufficient and safe in the therapy of *C. glabrata* endophthalmitis post keratoplasty in 26 old man.

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