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First Report of Intraocular Madurella Infection Following Phacoemulsification

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Abstract Purpose: To report the first case of post phacoemulsification endophthalmitis secondary to Madurella fungal infection. Method: A case report. Case Presentation: A 51-year-old female referred for post-operative chronic endophthalmitis. She complained of right painless reduced visual acuity (VA). She had undergone uneventful bilateral phacoemulsification with lens implantation four weeks earlier. Her clinical conditions were normal until after about four weeks postoperatively when she presented with signs of right eye endophthalmitis. She then underwent right eye vitreous aspiration needle tap and intravitreal antibiotics. Removal of the intraocular lens was done subsequently. Examination revealed a vision of counting fingers due to hypopyon and 4+ anterior chamber cells associated with fibrinous white exudate in capsular remnant, grade 4 vitreous inflammation with flat retina on ultrasonography. Urgent vitreous biopsy, vitrectomy, removal of the capsular bag, and intravitreal vancomycin and ceftazidime had been performed. White exudates were adherent to the capsular bag, the posterior surface of the iris, and the ciliary processes with sparing of the retina and optic nerve. Gram-positive cocci and fungus of *Madurella sp* were isolated via the vitreous biopsy. Initially the patient responded well to antibiotics but one month later had a recurrence. Revision vitrectomy and intravitreal voriconazole injection was performed. Oral and topical antifungals were tapered over three months with judicious steroid use. At six weeks post-operatively, her best corrected VA was 6/18, N18. Conclusions: Chronic and recurrent endophthalmitis following phacoemulsification may be due to *Madurella* fungus. Complete removal of the capsular bag and discrete areas behind the iris and the ciliary processes where fungal hyphae may hide is mandatory. *Madurella* tends to be locally invasive and spares the retina and optic nerve. It responds well to systemic itraconazole and intravitreal voriconazole.

Keywords: *Madurella, phacoemulsification, endophthalmitis, infection*

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1. Introduction

Madurella is a type of dematiaceous filamentous fungus that is found in soil. It is particularly found in tropical and subtropical areas of Africa, India, and South America. *Madurella* is pathogenic in humans and mainly causes mycetoma, specifically eumycotic mycetoma [1].

In ophthalmology, Madurella species is responsible for fungal keratitis [2,3,4]. However, so far, no intraocular infection caused by Madurella species has been reported previously following phacoemulsification surgery.

Endophthalmitis is not common, however it can cause a serious and sight-threatening condition due to intraocular inflammation, secondary to a non-infectious process, or by an infectious organism. It is a term used to describe the intraocular inflammation that involves the vitreous, together with the anterior chamber of the eye. Endophthalmitis may involve other adjacent ocular tissues such as the choroid, retina, sclera, or cornea [5]. In tropical regions, fungal endophthalmitis that developed after cataract surgery may present more acutely, usually within four weeks after surgery [6]. Fungal species that inoculate in the aqueous may progress posteriorly, involving the vitreous. Patient commonly present with painful reduced vision, eye redness, and hypopyon. In order to establish the diagnosis, vitreous samples should be obtained for culture. Early diagnosis and intensive management with suitable and appropriate antimicrobial therapy, as well as surgical intervention, are crucial for optimal visual outcomes.

2. Case Report

A 51-year-old, Chinese female, who was in good health, was referred by a private ophthalmologist for post-operative chronic endophthalmitis. She complained of right eye painless, blurring of vision commencing four weeks after uneventful bilateral phacoemulsification with lens implantation. The left eye was asymptomatic. On examination, her right visual acuity was counting fingers with no relative afferent pupillary defect. Her left eye

vision was 6/6, N5. On examination of her anterior segment, a hypopyon of 1 mm with anterior chamber cells of 4+ and fibrinous white exudate in the capsular remnant was observed (Figure 1). She was aphakic as the intraocular lens had been removed by the referring physician who noted white plaque at the nasal haptic-optic junction. There was no fundus view. B scan showed vitritis with a flat retina.

She had been previously treated with topical antibiotics and intravitreal and intracameral antibiotics were given twice. Subsequently, a topical and systemic steroid therapy produced a positive response, but a relapse occurred during steroid tapering. All previous cultures had been negative, including fungal culture. The left eye was pseudophakic with no evidence of inflammation.

Urgent vitreous biopsy, pars plana vitrectomy, removal of the capsular bag together with an intravitreal vancomycin and ceftazidime was immediately performed under general anaesthesia (GA). Oral steroids were discontinued. Gram staining of the vitreous biopsy revealed gram-positive coagulase-negative cocci but *Madurella* species was identified in the vitreous plate five days later. According to the microbiologist, *Madurella* was isolated in Sabouraud glucose agar. The colonies had flat and leathery look at first, were white to yellow to yellowish-brown in colour, then became brownish, folded and heaped with age, with the formation of aerial mycelia. Brown diffusible pigment in the cultures is one of the characteristic features. This type of mould has an optimum temperature of 37 degrees Celcius for growth.

The administration of the antibiotics and topical steroids improved the clinical picture of the patient, and visual acuity rose to best corrected visual acuity (BCVA) of 6/48. Given this clinical improvement, anti fungal medications were not administered to the patient. However, one month after vitrectomy, she reported floaters and blurred vision lasting one day. The hypopyon had returned with Grade 4 vitreous inflammation.

She was then scheduled for vitreous washout and intravitreal antibiotics, including 0.1 ml voriconazole 0.1% and 10ug in 0.1 ml amphotericin B under GA. Intraoperatively, purulent material adherent to the iris and ciliary processes was seen. There was no vasculitis or retinal or optic nerve involvement. Oral itraconazole 200 mg bd, topical voriconazole 1%, vancomycin 2.5% and moxifloxacin 0.5%, was administered as gram-negative rods were seen subsequently on aqueous humour tap. The anti-fungal medication was tapered slowly over three months while monitoring her renal and liver function regularly. These remained normal. Topical steroids were commenced at low doses after 2 weeks, stepping up judiciously with close monitoring of subjective complaints and clinical findings.

Post-operative complications included elevated intraocular pressure (IOP) of 26 mmHg responsive to topical timolol and brimonidine; and cystoid macula oedema (CMO) responsive to topical nepafenac.

At three weeks postoperatively, her unaided vision had improved to 6/36, N18, and at nine months post-operatively, her best corrected vision improved further to of 6/6, N6 with quiet fundus and resolved cystoid macula oedema (Figure 2). Correction of aphakia was scheduled for three months after the anti-fungal was discontinued without recurrence.

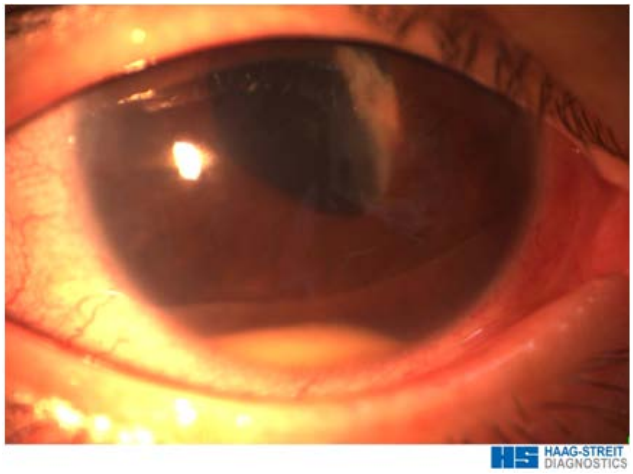

Figure 1. Anterior segment photograph of the right eye of the patient during the initial presentation to our centre. Hypopyon of 1 mm with cells of 4+ and fibrinous white exudate in the capsular remnant (black arrow) had been seen

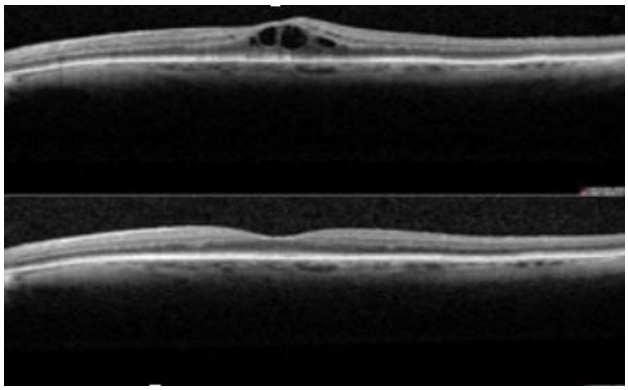

Figure 2. OCT of the right macula that showed CMO as a post-operative complication (above) and after six weeks of follow up (below)

3. Discussion

Endophthalmitis is a complex and potentially serious intraocular inflammatory disease. Postoperative exogenous endophthalmitis is known as the most common form of endophthalmitis. The incidence of postoperative endophthalmitis is approximately 0.093%, and generally it is secondary to bacterial infection. Only three per cent of all cases is due to fungi [7,8]. Out of all culture-positive postoperative endophthalmitis cases, fungi have been isolated from 21.8%, and *Aspergillus* spp. and *Candida* spp. are the most commonly responsible for fungal endophthalmitis [9,10]. To our best knowledge, *Madurella* endophthalmitis has never been reported.

In fungal endophthalmitis, a late, indolent inflammation associated with relatively less severe symptoms, with fibrinopurulent anterior chamber exudate, vitreous snowballs, and opacities are commonly found at presentation. These signs and symptoms rarely become evident until several weeks after the operation [11,12]. The infection might be masked by the use of corticosteroids, as the condition can lead to a dramatic,

sudden increase in intraocular inflammation and ocular discomfort. A period of symptom relief as long as one month without anti- fungal medications followed by a rapid relapse of one day is typical of fungal intraocular infections. *Madurella* is a genus of fungus of the Hypomycetes class that has rarely been isolated in eye infections. It has only been reported isolated in cases of fungal keratitis [17]. *Madurella*-related keratitis tends to be limited to the anterior segment and initially does not extend to the retina or optic nerve. This seems, indeed, to be the the case of our patient, whereby despite dense vitreous inflammation, the optic nerve and retina remained unaffected. This is in contrast to endogenous infections by yeast organisms such as Candida. The fungal balls were very adherent to the ciliary processes and they formed an adherent plaque which despite careful dissection during the first surgery persisted on the posterior surface of the iris and reactivate the infection. However, at the initial presentation, the purulent anterior segment inflammation made it difficult to determine the causative organism as Gram-positive cocci were also isolated from the "pure" vitreous biopsy. It could represent multiple infections in the one eye.

In cases of keratitis secondary to *Madurella* infection, a study done in North India showed that 56% caused by ocular trauma involved vegetative matter [18]. This is most probably due to the habitat of these dematiaceous fungi which is commonly found in soil and decomposing plant material. In this study, the eyes were treated with hourly 5% natamycin suspension based on the clinical assessment and microbiological smear results. Topical voriconazole 1% (Vozole, Aurolab, India) was used for larger and deeper fungal corneal ulcers.

Madurella infection in humans is more commonly seen in contaminated wounds, and, in these cases, eumycetoma is the most common disease. Eumycetic myetoma may occur at any site involving traumatized skin [19], and a combination of medical and surgical treatment is the management of choice. Azoles are the drug of choice in this disease since they are effective against a broad range of yeasts and moulds. Laboratory investigation, specifically fungal culture is important to confirm the diagnosis. However, negative cultures do not exclude the diagnosis, since 20 to 30% of endophthalmitis cases are culture-negative. Cultures are positive in approximately 90% of vitrectomy specimens, 50 to 70% of vitreous aspirates, and 40% of aqueous aspirates [20]. Despite the conflicting culture results in this patient, a fungal rather than a bacterial aetiology has been suspected due to the late onset and chronic, relapsing nature of disease while on antibiotics, and finally, the response to anti-fungal medications.

The role of corticosteroids in fungal endophthalmitis remains a matter of debate. In a study by Meredith et al. in 1996, the usage of intraocular corticosteroids was associated with an increase in inflammatory reaction, an increase in the development of opaque corneas, an increase in moderate to severe choroidal inflammation, and an increase in retinal necrosis [13]. According to Manzouri et al. 2001, the current practice is to stop the use of anti-inflammatory medicine until either the fungi has been confirmed, a suitable antifungal drug is used, or the practicality of that antifungal drug against the organism involved has been strongly proven, based on the patient's biological response [21]. Thus, the decision to administer corticosteroids in the treatment of severe endophthalmitis must be made with caution. In our patient, intravitreal steroids were avoided. The usage of topical steroids was also closely monitored even when there was no more inflammation in our case.

As recommended by previous literature, a combination of vitrectomy and antifungal agents appears to be highly effective for exogenous fungal endophthalmitis [14,15,16]. The advantages of early vitrectomy in managing fungal endophthalmitis more favourable visual and structural outcomes [22]. Vitrectomy helps in removing organisms from the capsular bag and the ciliary processes, disrupting the vitreous scaffold that allows fungal hyphae to propagate, and prevents inflammatory membranes from occuring, for instance, in cases of Aspergillus endophthalmitis [23]. Alternatives to vitrectomy include repeated intravitreal injections of antifungal agents such as voriconazole and amphotericin B [24]. However, this repeated intravitreal therapy tends to be long-drawn, time-consuming and uncomfortable for the patient. Inflammatory membranes and vitreous debris can affect vision for a long time and may even need surgical removal later. Hence, a decision was made for this patient to have vitrectomy immediately on both occasions.

The treatment of fungal endophthalmitis does not end with the vitrectomy, but systemic anti-fungal therapy from the azole group such as itraconazole, voriconazole, posaconazole and ketoconazole needs to be continued post-operatively for at least 4-6 weeks [25,26].

Our patient received three months of oral itraconazole 200 mg twice daily (SporanoxTM, Pfizer, Inc) and topical voriconazole 2% QID which had to be prepared from a standard vial containing 200 mg voriconazole. The usage of itraconazole is supported by a consistent bulk of data, but this substance was not available in our centre [27].

Complications encountered in this case were increased in intraocular pressure (IOP) and cystoid macular oedema (CMO). Elevated IOP is a common complication of vitrectomy surgery. A study done by Weinberg et al. concluded that the increase of intraocular pressure tends to develop within the first 21 days after pars plana vitrectomy.

In our patient repeated surgery was a further risk factor. And yet, repeated episodes of inflammation increased the risk of anterior synechiae for which steroids could not immediately been administered given the aetiology (i.e. fungal) of the inflammation.

CMO occurred in this patient as a consequence of the inflammation, fostered by the repeated operations in a limited interval of time (1 month). The nature of fungal infection also hinders steroid therapy. The patient received nepafenac, which is a topical non-steroidal anti-inflammatory drug that proved to be effective in post-cataract CMO in diabetic patients [28]. In our case, CMO resolved after the inflammation was controlled.

A secondary lens, in our case will need to be scleral fixed due to the pupil irregularity and anterior synechiae. Her visual potential is good given that infection by *Madurella* was predominantly anterior despite the dense vitreous inflammation. Options for the visual rehabilitation

include scleral fixation or scleral tunnel fixation of an intraocular lens or contact lens. Complete resolution of all signs of infection and inflammation for up to 3 months is mandatory before any further surgical procedure is done.

4. Conclusion

Madurella fungal endophthalmitis can be a complication of phacoemulsification, as reported in this case. *Madurella* prefers the anterior segment and tends to spare the retina and the optic nerve. Surgeons should pay careful attention to completely remove the capsular bag and the discrete areas behind the iris and the ciliary processes where the fungal hyphae may nest. *Madurella* infection response to systemic itraconazole and intravitreal voriconazole is satisfactory.

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Declaration of Interest

The authors report no conflict of interest.

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