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Case report

Bilateral endogenous *Trichoderma* endophthalmitis in an immunocompromised host

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ABSTRACT

Purpose: To report a case of bilateral endogenous endophthalmitis, caused by the *Trichoderma* species, in a severely immunocompromised patient.

Observations: A 39-year-old man with acute myeloid leukemia, in a relapsed state on high-dose chemotherapy, experienced profound neutropenia and immunosuppression. The patient reported two weeks of severe bilateral vision loss. The diagnosis of bilateral endogenous endophthalmitis was initially established based on the patient's history, immune status, clinical findings, and confirmed positive vitreous culture.

The patient was initially managed with vitreous tap, pars plana vitrectomy with silicone oil injection in the left eye, and vitreous tap and antibiotic injection of the right eye. Eventually, the right eye underwent pars plana vitrectomy as well. Cultures of the vitreous sample grew a filamentous fungus, identified as the *Trichoderma* species. His blood and urine culture tested negative. The patient was kept on systemic amphotericin B over 52 weeks, and his condition improved dramatically. Three months post phacoemulsification and silicone oil removal, best-corrected visual acuity values were 20/50 in both eyes.

Conclusion and Importance: This is the first reported case of bilateral endogenous endophthalmitis, caused by the *Trichoderma* species, in an immunocompromised patient. Early recognition and intervention were associated with good functional and anatomical outcomes.

1. Introduction

Endogenous endophthalmitis is a potentially devastating intraocular infection, in which pathogens reach the eye via the bloodstream. It is rare, accounting for only 2–15% of all cases of endophthalmitis.[1] Fungal infections lead to endogenous endophthalmitis more often than bacterial infections, with a ratio of 62:38. It has increased in recent decades as the number of chronically debilitated patients and the use of invasive procedures has increased.[1] Among the different fungal species, *Candida* is the most common organism causing fungal endogenous endophthalmitis.[2]

Trichoderma species are filamentous fungi responsible for localized and threatening invasive infections, causing up to 53% mortality in immunocompromised patients.[3]

Nine species have been reported as potential human pathogens: *Trichoderma atroviride*, *T. citrinoviride*, *T. harzianum*, *T. koningii*, *T. longibrachiatum*, *T. orientale*, *T. pseudoko-ningii*, *T. reesei*, and *T. viride*. The diseases attributed to these species include the following: endocarditis, invasive sinusitis, cutaneous infections, mediastinitis, peritonitis, pulmonary infections, liver infection, stomatitis, brain abscesses, infection of cardiac implantable electronic devices, and disseminated infections.[3] *T. longibrachiatum* is the most common species involved in *Trichoderma* infections.[4] Here, we report the rare case of endogenous *Trichoderma* endophthalmitis in an acute myeloid leukemia patient, who was severely immunocompromised on high dose chemotherapy.

2. Case report

A 39-year-old man, known to have acute myeloid leukemia, in a relapsed state, was admitted to the adult Hematology Oncology Department of King Fahad Medical City, Riyadh, Saudi Arabia for allogeneic hematopoietic stem cell transplantation (HSCT). The patient was treated with seven cycles of induction chemotherapy followed by two cycles of high-dose cytarabine (Ara-C) chemotherapy regimen.

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During hospitalization, the patient developed profound neutropenia (absolute neutrophil count, <100 cells/mm^3), associated with bilateral gradual severe vision loss. An attending oncologist assessed the patient, and a systemic septic work-up was repeated while systemic, empirical, broad-spectrum antibiotics (piperacillin sodium–tazobactam sodium) were initiated. Ophthalmology was consulted.

His eye assessment showed poor best-corrected visual acuity (BCVA) with light perception (LP) in both eyes. Intraocular pressure (IOP) values were 13 and 14 mmHg in his left and right eyes, respectively.

A slit lamp examination of both eyes revealed moderate conjunctival injection, clear cornea, and early lenticular cataract. Fibrin was seen in the anterior chamber of both eyes with 3+ cells, and 360-degree posterior synechia. Funduscopic examination showed no view of either retina, secondary to dense vitritis in both eyes.

Brightness scan (B scan) Ultrasound at presentation of the right and left eyes showed moderate-to-dense vitreous opacities with vitreal membrane formation. (Fig. 1).

A diagnosis of bilateral endogenous endophthalmitis was highly suspected, based on the patient's history, immune status, and clinical findings. On the same day, the right eye underwent diagnostic vitreous tap and intravitreal vancomycin hydrochloride, ceftazidime, and voriconazole injections; the left eye was treated with diagnostic and therapeutic pars plana vitrectomy with silicone oil injection and intravitreal antimicrobial agents were administered at the end of the procedure. One vitreous sample from each eye was sent for culture and sensitivity.

Ten days later, the right eye also underwent therapeutic vitrectomy with silicone oil injection and intravitreal antibiotics. One vitreous sample from each eye was sent for culture and sensitivity.

The culture of the vitreous specimens from both eyes was performed at the Mycology Unit of the Microbiology Lab at King Fahd Medical City, Riyadh, Saudi Arabia on Sabouraud dextrose agar that was incubated at 28 °C and yielded a filamentous fungus after eight days. It was identified as *Trichoderma* spp., based on microscopic characteristics of key features on the branching systems of the conidiophores, the phialide disposition, and the character of the phialospores.[5] Additionally, the serum and vitreous aspergillus galactomannan antigen indices were negative (0.13 and 0.11, respectively).

The fungus was found to be sensitive to voriconazole (minimum inhibitory concentration (MIC), 0.5 μg/mL), amphotericin B (MIC, 16 μg/mL) and caspofungin (MIC, 0.5 mg/mL).

Subsequently, intravenous liposomal amphotericin B was initiated by the infectious disease team as systemic anti-fungal monotherapy and continued over a 52-day period. The other body culture results remained negative and the primary source of the patient's infection remained unclear. The treatment was well tolerated, the patient completely recovered, and later underwent phacoemulsification with intraocular lens implantation, silicone oil and epiretinal membrane removal. His last ophthalmic evaluation showed quiet pseudophakic eyes with flat retina and BCVA 20/50 in both eyes (Figs. 2 and 3).

3. Discussion

Endogenous endophthalmitis is a sight-threatening condition with poor visual acuity outcome.[6] Despite recent advances in the therapy of infectious diseases, opportunistic mold-disseminated infections remain a major cause of morbidity and mortality in patients with hematological malignancies and transplants, making prompt diagnosis and treatment crucial.[2] Patients who are undergoing allogeneic HSCT or remission induction chemotherapy for acute myelogenous leukemia/myelodysplastic syndrome (AML/MDS) are at an especially high risk, with 20-fold higher rates of fungemia.[7]

Clinically, a lack of obvious eye symptoms or typical signs contributes to the high rate of endogenous fungal endophthalmitis misdiagnosis and missed diagnoses, as in this case. The patient did not complain, and his primary physician elicited no eye signs. In the literature, misdiagnosis at initial presentation has been reported in 16%–63% of cases,

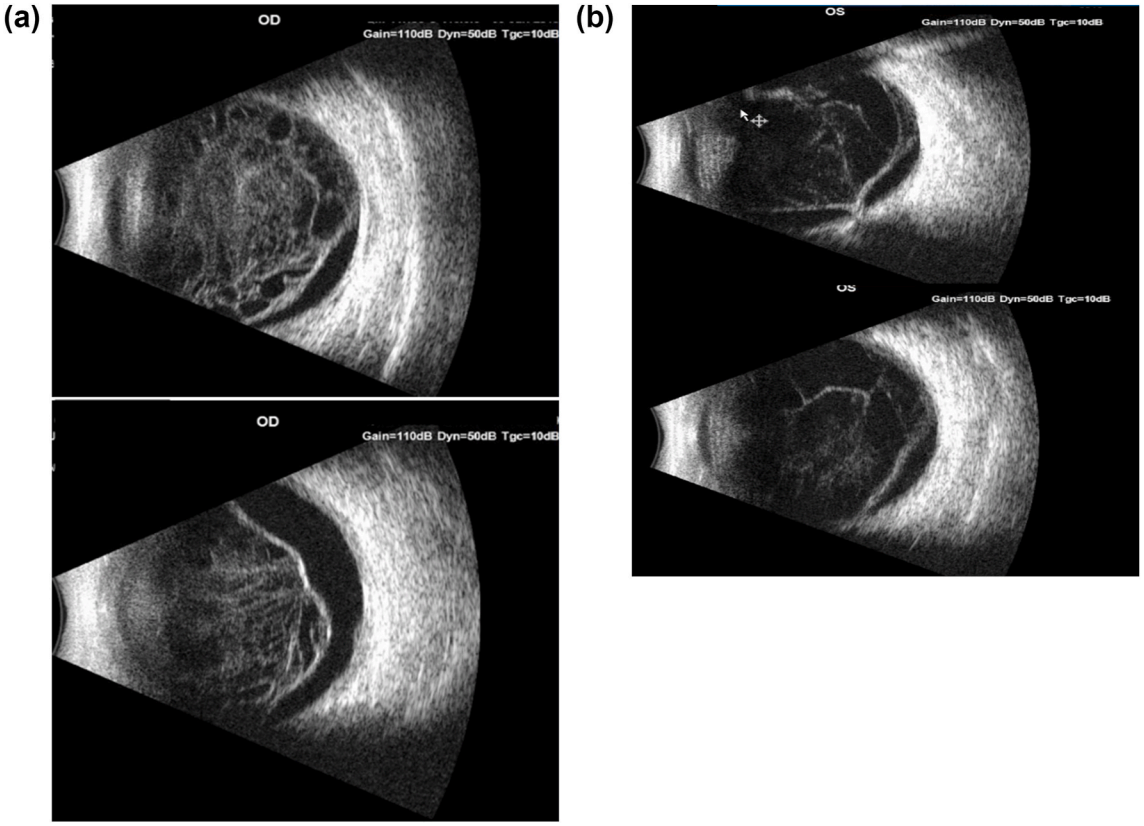

Fig. 1. Ultrasound at presentation of the right and left eyes showing moderate-to-dense vitreous opacities with vitreal membrane formation.

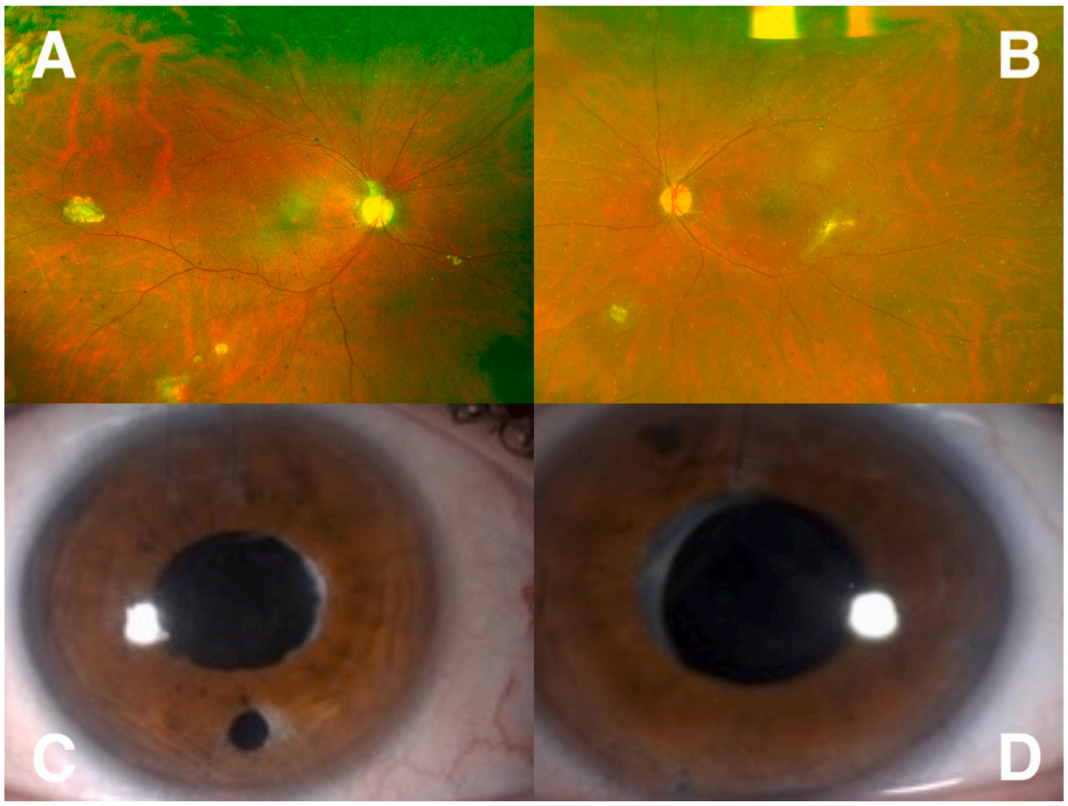

Fig. 2. Three months post silicone oil removal and phacoemulsification; A, B: Fundus photography showing flat retina with extramacular areas of chorioretinal scarring, corresponding to scarred chorioretinitis. C, D: An anterior segment photo of both eyes showing clear cornea, quiet anterior chambers, and pseudophakia with old peripheral iridotomies.

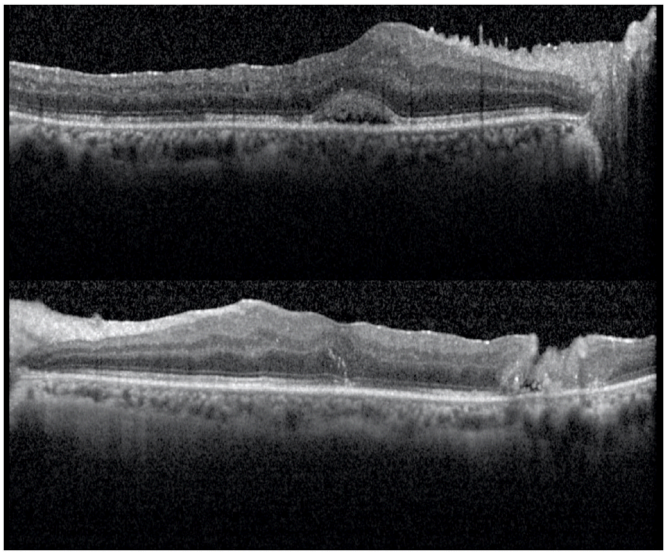

Fig. 3. Optical coherence tomography (OCT) showed bilateral flat retina with residual epi-retinal membrane. Right eye with small neurosensory retinal detachment and left eye with a temporal area of fibrosis.

leading to delays in prompt treatment and resulting in a worse prognosis.[1]

These infections are characterized by the presence of fine septate hyphae in tissue sections or specimens. There are obvious morphological similarities on direct examination between hyphae, which explains misdiagnosis between a *Trichoderma* infection and aspergillosis. Cultures of tissue sample are needed for a definitive diagnosis of a *Trichoderma* infection.[8]

In this case, diagnosis was based on the culture of a vitreous sample. Moreover, the negative result of the *Aspergillus* galactomannan assay, performed on the vitreous humor, made *Aspergillus* unlikely, as it has been reported useful test in the diagnosis of *Aspergillus* endophthalmitis with high sensitivity and specificity.[9] However, molecular techniques for species identification in the genus *Trichoderma*, have been demonstrated to be clinically useful.[10]

Furthermore, and unlike in our patient, *Aspergillus* endophthalmitis is generally associated with worse visual outcomes due to characteristic macular lesions, hemorrhaging, and retinal/choroidal ischemia.[11]

To the best of our knowledge, endophthalmitis, due to the *Trichoderma* species, in a patient who underwent allogeneic HSCT, has not been reported in the literature. Previously, *Trichoderma* was believed to be a nonpathogenic organism, but only recently, it has been the cause of invasive fungal infections in immunocompromised hosts.[4]

The effective treatment of endogenous fungal endophthalmitis rests on the combination of timely vitrectomy and systemic antifungal therapy, which would also help eradicate the primary site of the infection.[12] In this case, due to the aggressive nature and poor visual prognosis in fungal endophthalmitis, we decided to manage the patient with bilateral vitrectomies and silicone oil tamponade. Some studies have suggested that silicone oil has capabilities to prevent microbial growth,[13] and other reports have advocated the combination of vitrectomy, silicone oil, and intravitreal antibiotics for management of this condition,[14,15] allowing for prompt control of the infection with less complications like retinal detachments or hypotony.

In this case, a multidisciplinary team approach including hematology, oncology, infectious disease, and ophthalmology saved the life and sight of this severely ill patient.

In conclusion, fungal infections, due to the *Trichoderma* species, are of growing concern in immunocompromised individuals and are likely

to increase in the future, leading to significant morbidity and mortality. Medical professionals managing immunocompromised patients need to be vigilant to recognize early signs of fungal endophthalmitis, which will help improve the final outcome.

4. Patient consent

IRB approval from King Khaled Eye Specialist Hospital and written informed consent was obtained for this case report.

Conflict of interest

No conflict of interest exists.

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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

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

IRB approval was obtained (required for studies and series of 3 or more cases).

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).

Authorship

All listed authors meet the ICMJE criteria. We attest that all authors contributed significantly to the creation of this manuscript, each having fulfilled criteria as established by the ICMJE.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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