Fungal Endophthalmitis Secondary to Aspergillus terreus Exacerbated by Intravitreal Dexamethasone in a Patient With Sarcoidosis

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Abstract
Purpose: To report a case of Aspergillus terreus endophthalmitis associated with systemic immunosuppression and an intraocular steroid implant in a patient with sarcoidosis. Methods: A case report was evaluated and a literature review performed. Results: A patient with a history of pulmonary and ocular sarcoidosis presented with new-onset uveitis and was treated for presumed sarcoid flare with oral prednisone and an intravitreal dexamethasone implant before developing worsening vision. She was ultimately diagnosed with A terreus endophthalmitis. Despite both systemic and local antifungals, the visual acuity at the most recent follow-up was no light perception without pain or active inflammation. No definitive source of the fungal disease had been identified. Conclusions: Endophthalmitis resulting from A terreus is associated with poor outcomes. Given the ability of fungal endophthalmitis to mimic other causes of uveitis, one must maintain a high suspicion in patients with any degree of immunosuppression.

Keywords
Aspergillus terreus, endophthalmitis, sarcoidosis, uveitis

Introduction
Aspergillus terreus is a rare cause of fungal endophthalmitis. Outcomes are often poor as a result of a delayed diagnosis and the organism’s intrinsic resistance to available antifungal medications.1 Establishing the correct diagnosis is even more challenging when the signs and symptoms of infection can be mistakenly attributed to a concurrent systemic disease.

We report a case of A terreus endophthalmitis in a patient with a history of pulmonary and ocular sarcoidosis who was being treated for a presumed sarcoidosis uveitis flare with oral prednisone and an intravitreal dexamethasone implant. This case highlights the importance of maintaining a differential diagnosis and a high suspicion for infectious uveitis in the appropriate clinical context, as early diagnosis and treatment can be vision saving. In addition, we provide a review of all reported cases of A terreus endophthalmitis.

Case Report
A 74-year-old White woman with a medical history of obesity, hypertension, and congestive heart failure and a 40-year history of biopsy-proven sarcoidosis presented for evaluation of 8 months of blurry vision, flashes, and floaters in the right eye. Seven months before presentation, she was evaluated by an outside ophthalmologist for sudden vision loss, floaters, and photopsias in the right eye. The patient was diagnosed with panuveitis, presumably resulting from a sarcoidosis uveitis flare, and was treated with 60 mg oral prednisone and topical prednisolone, which led to initial improvement in her symptoms. She worsened again on a steroid taper, and 1 month before presentation, the outside ophthalmologist administered an intravitreal dexamethasone implant.

At the time of our initial evaluation, the patient said she felt her symptoms were much improved, yet persistent. She was taking oral methotrexate 25 mg weekly for sarcoid pulmonary disease and denied other recent systemic health changes on a thorough review of systems. The visual acuity (VA) was 20/40 OD and 20/25 OS. An anterior segment examination showed trace cell in the anterior chamber in the right eye. A dilated examination showed 1+ vitreous cell, trace haze, and a dexamethasone implant in the inferior vitreous. At this time, her findings were presumably consistent with sarcoid-related uveitis and she was instructed to return in 4 weeks after obtaining additional lab testing, including a comprehensive metabolic panel, a complete blood count, and evaluation for tuberculosis, syphilis, and toxoplasmosis, all of which were unremarkable.

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Four weeks later, the patient presented with gradually decreasing vision, with rapid deterioration within the most recent week. On examination, the VA in the right eye had diminished from 20/40 to hand motions. A dilated examination showed 2+ vitreous cells and large debris with central white clumping in the right eye (Figure 1A). A B-scan ultrasound of the right eye showed a dense, slightly mobile, large, oval-shaped clump of opacities in the posterior vitreous, measuring 11.0 mm × 15.5 mm × 15.0 mm (Figure 1B).

Given the vitreous clumping and increased suspicion for infectious or neoplastic etiology, a diagnostic and therapeutic 25-gauge pars plana vitrectomy (PPV) was performed in the right eye. A diluted vitreous specimen was sent for bacterial and fungal testing. Intraoperatively on scleral depression, a temporal raised white lesion was visualized near the pars plana. Intravitreal clindamycin (1.0 mg/0.1 mL) was administered.

After surgery, the patient was admitted to the medicine service at Cleveland Clinic, where she was evaluated by the infectious disease service. During this hospital admission, it was discovered that the patient had been diagnosed (at an outside hospital in another state) with esophageal candidiasis 2 months before presentation, which had been treated with 4 weeks of fluconazole followed by 4 weeks of voriconazole. Despite the previous extensive review of systems, she neglected to mention this diagnosis and the outside ophthalmology records that had been reviewed also did not mention the esophageal candidiasis. The patient’s methotrexate was stopped in the setting of presumed fungal infection, and she was started on oral voriconazole 200 mg daily.

The patient’s methotrexate was stopped in the setting of presumed fungal infection, and she was started on oral voriconazole 200 mg daily. However, she continued to have worsening pain and subjective vision loss with increased vitritis on examination. Over the following 2 weeks, she received 2 intravitreal injections of amphotericin B 5 mcg. She was also started on systemic IV micafungin 300 mg daily by the infectious disease service.

Despite receiving both systemic and intravitreal antifungal agents, the patient continued to have persistent pain and active intraocular inflammation with dense vitreous membrane formation, white retinal and preretinal lesions, and exudative retinal detachment (RD) (Figure 2A). She subsequently had a second diagnostic 25-gauge PPV. Only at this point was the source of the intraoperative cultures from the initial specimen finalized, revealing *A. terreus*, which is intrinsically resistant to amphotericin B. Antifungal susceptibility testing showed that the strain had minimum inhibitory concentration values of 2 μg/mL to amphotericin B, ≤0.06 μg/mL to micafungin, 0.25 μg/mL to voriconazole, 0.5 μg/mL to isavuconazole, and ≤0.06 μg/mL to combination micafungin–voriconazole. At the end of the second vitrectomy, she was treated with an injection of intravitreal voriconazole 0.1 mg. Two weeks later (1 month after the first vitrectomy and admission to the hospital), she was discharged from the hospital on IV micafungin 300 mg daily and oral isavuconazole 372 mg daily.

Despite 2 further injections of intravitreal voriconazole, the patient developed worsening VA to light perception (LP) and an open funnel RD (Figure 2B), for which she chose to undergo a third 25-gauge PPV and attempted RD repair, with injection of intravitreal voriconazole 0.1 mg. Cultures from this vitrectomy also yielded *A. terreus*. The IV micafungin and oral isavuconazole were discontinued, and the patient was started on oral voriconazole 200 mg daily.
During the immediate postoperative period, the patient was without pain; however, the retina remained detached and the VA decreased to no LP (NLP). She completed a 2.5-month course of oral voriconazole. At the most recent follow-up 4 months after the patient’s most recent surgery, she was without pain or active inflammation, although the VA remained at NLP. Her fellow eye remained free of disease, with 20/20 VA.

Conclusions

_A terreus_ is a ubiquitous mold found in soil, decaying vegetable matter, and house dust. It is a rare but known cause of fungal endophthalmitis.² Eyes with _Aspergillus_ endophthalmitis have poor outcomes because of the macular involvement, rapid progression, and increased antifungal therapy resistance.³ We report a case of _A terreus_ endophthalmitis associated with systemic immunosuppression. To our knowledge, this is the first reported case of _A terreus_ endophthalmitis associated with an intraocular steroid implant. The case also highlights the aggressive nature of this fungal species.

Our patient experienced 8 months of blurry vision that was managed by an outside ophthalmologist as a sarcoidosis uveitis flare with both systemic and local steroids. This led to 1 month of improved symptoms before our initial evaluation, at which time the patient had minimal inflammation on examination. However, she then experienced several weeks of worsening vision and 1 week of rapid vision loss, at which point the examination findings showed significant posterior segment inflammation suspicious for a fungal infection.

Given the timeframe of her symptoms, it is unlikely that the initial uveitis seen by the outside ophthalmologist 8 months earlier was caused by an _A terreus_ infection, although it is possible. It is more likely that the initial uveitis was a sarcoid uveitis flare followed by subsequent infectious endophthalmitis, secondary to endogenous spread and exacerbated by her immunosuppressed state and dexamethasone implant or secondary to the dexamethasone implant itself. Given that exogenous endophthalmitis typically follows a more rapid timeframe than 2 months, an endogenous source appears more likely, although a review of 91 eyes with culture-proven _Aspergillus_ endophthalmitis from both exogenous (89%) and endogenous (11%) sources reported an interval between the “inciting event” and the onset of symptoms of 1 to 75 days (mean 10.24 ± 17.8 days). The same review found that the range of symptom duration before presentation was 1 to 90 days (mean 13.61 ± 30.2 days), suggesting that the indolent nature of some _A terreus_ infections might contribute to a delayed diagnosis.⁴

Whether the fungal endophthalmitis was present at the time of our patient’s initial presentation to us is unknown. At the time of our initial evaluation, we presumed that her improving symptoms and minimal inflammation were secondary to a sarcoidosis uveitis flare that had been treated by the outside ophthalmologist. Regardless of whether the initial uveitis seen by the outside ophthalmologist was a sarcoidosis flare or the early presentation of fungal endophthalmitis, the patient presented to us in an immunosuppressed state (on methotrexate and with recent oral steroid use) with a persistently inflamed eye and an intravitreal dexamethasone implant, a setting that should always increase suspicion for an endogenous infectious process.

At the time of our initial examination, we were unaware of her concurrent esophageal fungal disease, which suggests possible ocular seeding. However, the esophageal candidiasis was caused by a presumably different fungal species, although culture results from the outside hospital were not available. The lungs or gastrointestinal tract are additional possible sites of the initial infection given her immunocompromised status and bronchiectasis, esophagitis, and gastritis identified on a systemic workup.

Immunosuppression is a well-known risk factor for endogenous fungal endophthalmitis.⁴⁻⁶ Our review of the literature identified 22 previously reported cases of _A terreus_ endophthalmitis from both endogenous and exogenous spread. Table 1 shows the immune status, risk factors, and suspected source of infection of the previously reported cases.¹,²,⁶⁻¹⁷ Of the 7 cases of endogenous _A terreus_ endophthalmitis, 2 were presumed to be caused by infected IV maintenance fluids or drugs in immunocompetent patients. Of the remaining cases, 3 patients were immunocompromised and 2 had chronic inflammation (bronchiectasis and gastroenteritis), which is known to induce immunosuppression via the induction of proinflammatory mediators and the accumulation of immune suppressor cells.

Our patient was receiving immunosuppressive therapy for sarcoidosis and also recently had an intravitreal dexamethasone implant placed. Corticosteroids, such as dexamethasone, not only reduce inflammation and thus delay the clinical presentation of fungal infection, they also further suppress the host’s immune response; thus, the fungus is able to replicate more freely and penetrate tissues more aggressively. Our patient also had bronchiectasis, esophagitis, and gastritis identified by a systemic workup, potentially leading to a further immunosuppressed state and an increased risk for endogenous endophthalmitis.

Previous reports have shown that early fungal endophthalmitis is misdiagnosed in up to 50% of cases, with a resulting delay in treatment.¹⁸ The most common posterior segment findings in ocular sarcoidosis is vitritis, and ocular sarcoidosis has been reported to resemble fungal endophthalmitis, with dense vitritis and fungal ball-like vitreous opacities.¹⁹,²⁰ This case highlights the importance of maintaining a high suspicion for infectious causes of ocular inflammation even when there is a history of noninfectious uveitis flares.

The prognosis of _A terreus_ endophthalmitis is poor, and there is no standardized treatment protocol. Of the 22 cases of _A terreus_ endophthalmitis that we identified, only 5 patients were reported to have a final VA better than 20/400, with 8 patients having a final VA of LP or worse (Table 1). As soon as the diagnosis is suspected, treatment should be initiated with both systemic and intravitreal antifungal agents. Although systemic and intravitreal amphotericin B has previously been the
<table>
<thead>
<tr>
<th>Study(^a) (Year)</th>
<th>Etiology</th>
<th>Associated Conditions/ Risk Factors</th>
<th>Identified Location of A terreus Infection</th>
<th>Therapeutic Intervention(s)</th>
<th>Visual Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puah(^6) (2018)</td>
<td>Endogenous</td>
<td>Bronchiectasis</td>
<td>+ Bronchial culture</td>
<td>Multiple IVI Vo; long-term PO Vo 200 mg bid; PPV</td>
<td>20/400</td>
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<td></td>
<td></td>
<td></td>
<td>+ Vitreous culture</td>
<td>PPV, IVI vanc, IVI AmB, IVI ceftazidime, and IVI dex; IVI AmB and dex on POD3 and POD9; PO Vo 200 mg bid × 3 mo</td>
<td>CF at 1 ft</td>
</tr>
<tr>
<td>Dogra(^7) (2018)</td>
<td>Endogenous</td>
<td>IV fluid infusion</td>
<td>+ Vitreous culture</td>
<td>PPV, IVI vanc, IVI AmB, IVI ceftazidime, and IVI dex; IVI AmB and dex on POD3 and POD9; PO Vo 200 mg bid × 3 mo</td>
<td>CF at 1 ft</td>
</tr>
<tr>
<td>Garg(^8) (2003)</td>
<td>s/p cataract surgery</td>
<td>—</td>
<td>+ Corneal scraping and AC cultures</td>
<td>Topical natamycin; oral azole (unspecified)</td>
<td>Phthisis bulbi</td>
</tr>
<tr>
<td>Mithal(^9) (2015)</td>
<td>s/p cataract surgery (8)</td>
<td>—</td>
<td>+ AC, vitreous, and intraocular lens cultures</td>
<td>• IVI AmB-Vo; PPV/IOL explant, IVI AmB-Vo; repeat PPV, IVI AmB-Vo</td>
<td>20/100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• PPV/IOL explant, IVI AmB-Vo; repeat PPV, PKP, IVI AmB-Vo</td>
<td>LP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• PPV/IOL explant, IVI AmB-Vo; repeat PPV, penetrating keratoplasty, IVI AmB-Vo</td>
<td>20/400</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• PPV/IOL explant; IVI AmB-Vo; repeat IVI AmB-Vo</td>
<td>CF at 2 ft</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• IVI AmB-Vo; PPV/IOL explant, IVI AmB-Vo</td>
<td>20/400</td>
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<td></td>
<td></td>
<td>• PPV/IOL explant, IVI AmB-Vo; repeat PPV, IVI AmB-Vo</td>
<td>20/60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• PPV/IOL explant, IVI AmB-Vo; repeat PPV, IVI AmB-Vo</td>
<td>LP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• PPV/IOL explant, IVI AmB-Vo; repeat PPV, PKP, IVI AmB-Vo</td>
<td>20/60</td>
</tr>
<tr>
<td>Bradley(^2) (2005)</td>
<td>Endogenous</td>
<td>Lung adenocarcinoma, emphysema on chemotherapy and oral steroids</td>
<td>+ Sputum culture</td>
<td>IVI ceftazidime, vanc, dex</td>
<td>NR (patient died)</td>
</tr>
<tr>
<td>Das(^10) (1993)</td>
<td>s/p cataract surgery</td>
<td>—</td>
<td>+ Vitreous culture</td>
<td>IVI AmB, PO ketoconazole 200 mg tid, topical natamycin</td>
<td>20/60</td>
</tr>
<tr>
<td>Gross(^12) (1992)</td>
<td>Endogenous</td>
<td>IV drug use</td>
<td>+ Vitreous culture</td>
<td>PPV, IVI AmB, subconjunctival AmB q2-3 days × 2 wk</td>
<td>CF</td>
</tr>
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(continued)
### Table 1. (continued)

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Etiology</th>
<th>Associated Conditions/ Risk Factors</th>
<th>Identified Location of <em>A. terreus</em> Infection</th>
<th>Therapeutic Intervention(s)</th>
<th>Visual Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moinfar(13) (2007)</td>
<td>s/p corneal laceration repair</td>
<td>—</td>
<td>+ Vitreous culture</td>
<td>PPV, IVI AmB, IVI Vo</td>
<td>Blindness, enucleation</td>
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<tr>
<td>Dave(14) (2011)</td>
<td>Unknown</td>
<td>Acute lymphoid leukemia on chemotherapy; indwelling femoral vein catheter</td>
<td>No systemic workup or ocular sample reported</td>
<td>IVI vanc, IVI ceftazidime, IVI AmB, 5% natamycin eyedrops, PO ketoconazole 200 mg bid</td>
<td>20/20</td>
</tr>
<tr>
<td>Chakrabarti(15) (2008)</td>
<td>s/p cataract surgery (2)</td>
<td>—</td>
<td>+ Ocular culture (not specified)</td>
<td>IVI AmB, PO itraconazole</td>
<td>Better than HM or CF (2)</td>
</tr>
<tr>
<td>Kramer(16) (2006)</td>
<td>Endogenous</td>
<td>Cystic fibrosis; s/p lung transplant on immunosuppressive therapy; thickened maxillary sinus mucosa</td>
<td>+ Vitreous culture</td>
<td>PPV, IVI cefoxitin, IVI vanc, IVI AmB; repeat IVI AmB, repeat IVI vanc, IVI Vo, IV Vo 200 mg bid × 4 wk followed by PO Vo</td>
<td>20/50</td>
</tr>
<tr>
<td>Wykoff(17) (2008)</td>
<td>s/p penetrating trauma s/p cataract surgery</td>
<td>—</td>
<td>+ Vitreous culture</td>
<td>PPV, IVI AmB, IVI Vo</td>
<td>NLP</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>PPV, IVI AmB, PO itraconazole</td>
<td>20/50</td>
</tr>
<tr>
<td>Panigrahi(1) (2014)</td>
<td>Endogenous</td>
<td>Recent gastroenteritis</td>
<td>+ Vitreous culture</td>
<td>PPV, IVI Vanc, IVI ceftazidime, and IVI Vo, repeat IVI Vo × 6, repeat PPV, PO V0 200 mg bid × 2 mo</td>
<td>NLP</td>
</tr>
<tr>
<td>Current</td>
<td>Endogenous</td>
<td>Immunosuppression for sarcoidosis; intravitreal dex implant; bronchiectasis; esophagitis; gastritis</td>
<td>+ Vitreous culture</td>
<td>PPV with IVI clindamycin; PO Vo and IV isavuconazole; IVI V0 × 2, IVI AmB × 2; intravenous micafungin 300 mg daily; repeat PPV with IVI Vo, repeat IVI Vo × 2; PO Vo</td>
<td>NLP</td>
</tr>
</tbody>
</table>

Abbreviations: *A. terreus*, *Aspergillus terreus*; AC, anterior chamber; AmB-Vo, amphotericin B and voriconazole; AmB, amphotericin B; bid, twice a day; CF, counting fingers; dex, dexamethasone; HM, hand motions; IOL, intraocular lens; IV, intravenous; IVI, intravitreal injection; LP, light perception; NLP, no light perception; NR, not reported; PKP, penetrating keratoplasty; PO, by mouth; POD, postoperative day; PPV, pars plana vitrectomy; q, every; s/p, status post; tid, 3 times a day; vanc, vancomycin; Vo, voriconazole.

\(a\)First author.
preferred treatment for *Aspergillus* endophthalmitis, *A terreus* shows resistance to amphotericin B in up to 98% of isolates, which was true in our case.1

Intravitreal voriconazole has been shown to be effective in case reports and is safe for the retina in doses up to 100 µg/mL.14,22 However, providers should note that the half-life of voriconazole in a vitrectomized eye is approximately 8 hours compared with more than 24 hours for amphotericin B, requiring more frequent injections.4

The most frequently recommended systemic antifungal therapy for *A terreus* endophthalmitis is voriconazole, although favorable outcomes have been reported with the use of oral ketoconazole and itraconazole. Regardless, as stated previously and shown in our case, the VA in most patients is worse than 20/400, with rare exceptions. In addition, all reports of *A terreus* endophthalmitis include multiple medications, and it is unclear which medications were effective. The duration of systemic antifungal therapy is variable but should be at least 1 month.23 In addition to medical management, early vitrectomy may lead to better outcomes by aiding in a diagnosis and removing fungal elements in the vitreous.24 Table 1 shows the attempted treatment regimens of previously reported cases of *A terreus*.

In conclusion, *A terreus* is a rare cause of fungal endophthalmitis, and it can pose significant diagnostic and management challenges. Given the ability of fungal endophthalmitis to mimic other causes of uveitis, one must maintain a high suspicion for fungal endophthalmitis in patients with any degree of immunosuppression or in those who do not respond to standard treatment with steroids or antibiotics. *A terreus* endophthalmitis demands a multidisciplinary treatment approach.

**Ethical Approval**

This case report was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected patient health information was performed in a US Health Insurance Portability and Accountability Act–complaint manner.

**Statement of Informed Consent**

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

**Declaration of Conflicting Interests**

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**References**


