Case report

**Aspergillus flavus Scleritis: successful treatment with voriconazole and caspofungin**

ALAN HOWELL, JOHN MIDTURI, MIGUEL SIERRA-HOFFMAN, JOHN CARPENTER, DOUGLAS HURLEY & RICHARD WINN

Department of Internal Medicine, Division of Infectious Disease, Scott & White Memorial Hospital and Clinic, Scott, Sherwood and Brindley Foundation, The Texas A&M University System Health Science Center, Temple, Texas, USA

Aspergillus scleritis is a potentially devastating ocular infection difficult to treat because of poor scleral vascularity. Most *Aspergillus* cases occur following ocular surgery, but others have been associated with trauma or intravenous drug use. No anti-fungal agents are consistently efficacious in the treatment of scleral fungal infections. We report a case of *Aspergillus* scleritis successfully treated with a combination of voriconazole and caspofungin, as well as a review of the literature concerning treatment of *Aspergillus* scleritis.

**Keywords** *Aspergillus* scleritis, voriconazole, caspofungin

**Background**

*Aspergillus* species are a leading cause of invasive mycoses, associated with high morbidity and mortality in immunosuppressed patients [1]. In immunocompetent individuals the fungus can co-exist in certain body cavities without causing an invasive disease; in others, it may cause severe allergic syndromes, i.e., allergic bronchopulmonary aspergillosis [2], and ocular infections associated with intravenous drug use [3].

**Case report**

A 54-year-old woman without significant past medical history presented complaining of a non-traumatic, painful, erythematous left eye for three weeks. The prominent conjunctival and scleral vessel injection along with scleral tenderness identified on examination were consistent with diffuse anterior scleritis. An extensive autoimmune evaluation was undertaken and empiric treatment with non-steroidal anti-inflammatory medications and later oral glucocorticoids was initiated. Evaluation for autoimmune etiology was negative and the patient showed an initial but transient improvement on high dose oral prednisone. While on immunosuppressant therapy, the patient developed a scleral nodule in the inferotemporal quadrant of her left eye. With this change in the clinical picture, a scleral biopsy was performed. The architecture of the superficial sclera appeared normal and a split-thickness trephination over the scleral nodule revealed extensive mucopurulent drainage. The mucopurulent drainage was subjected to Gram staining as well as being plated on blood agar for culture. Rare Gram-positive cocci were reported on examination of the Gram’s stain but no growth on culture media was observed.

Intravenous and topical moxifloxacin was begun and an evaluation for a systemic infectious etiology was performed including computed tomography (CT) evaluation of the orbits and sinuses, transesophageal echocardiography (TEE) and abdominal ultrasound. No evidence of other systemic infectious disease was identified. During this time, an additional scleral nodule developed medially, was biopsied and revealed purulent material. Aerobic, anaerobic, fungal and mycobacterial cultures were obtained and a biopsy specimen was submitted for pathologic evaluation. Dense fibrous connective tissue with aggregates of...
acute and chronic inflammatory cells was described on pathological evaluation. Rare fungal hyphal elements were present with GMS stain on histopathology and *Aspergillus flavus* was identified on fungal culture. Additional stains including Periodic Acid Schiff (PAS), Warthin-Starry, Acid Fast Bacilli stain (AFB), and Gram stain disclosed no organisms. After further questioning, the patient admitted to intravenous injection of cocaine into her right thigh three to four weeks prior to the onset of her symptoms.

Voriconazole was begun at a dose of 400 mg orally twice daily for six weeks without significant improvement. Oral monotherapy with voriconazole in addition to topical voriconazole was continued for an additional month. During this time, two additional abscesses developed, were drained, and cultures were again positive for *Aspergillus flavus*. Combination therapy with caspofungin (50 mg IV daily) and lipid-based amphotericin B (3 mg/kg/day) was begun. Unfortunately, after one week of therapy, toxicity from amphotericin B occurred with an increase in the patient’s creatinine up to 3.0 mg/dl. Amphotericin B was discontinued and oral voriconazole was restarted at 200 mg orally twice daily in combination with caspofungin. Over the next two weeks a decrease in pain was noted. Physical exam revealed a decrease in both erythema as well as abscess size. The patient had a peripherally inserted central catheter placed, and was discharged to continue therapy with caspofungin 50 mg intravenously daily and 200 mg voriconazole orally twice daily as an outpatient. She was monitored through the hospital’s home infusion service while on the intravenous therapy. Improvement continued, no drug toxicity developed, and therapy was discontinued after four months. Physical examination at that time demonstrated clearing of the involved conjunctiva and sclera, and only a small residual scar at the site of infection. She had no recurrence of her symptoms at twelve months.

**Discussion**

Scleritis is a destructive, severe ocular inflammatory process centered within the sclera and frequently causes destruction of the sclera. It can be caused by both infectious but more commonly autoimmune etiologies. Infectious causes include bacterial, viral, mycobacterial, protozoal, and as in our patient, fungal organisms. Of the autoimmune etiologies, rheumatoid arthritis is the most common; others include Wegener’s granulomatosis, polyarteritis nodosa, systemic lupus erythematosus, non-infectious granulomatous disease and inflammatory bowel disease [4,5].

Review of published cases of *Aspergillus* scleritis, defined as biopsy or culture proven cases, reveals two proposed pathophysiologic mechanisms: hematogenous dissemination including intravenous drug use (Table 1) [6,7] or direct inoculation of the eye by either external trauma or surgery. A history of ocular trauma (Table 2) [8,9], though mild and seemingly innocuous, can result in *Aspergillus* scleritis. Ophthalmologic surgery (Table 3) [5,10–14] is the most commonly reported mechanism of infection.

*Aspergillus* scleritis as a result of hematogenous dissemination (Table 1) resulted in cure for two of three patients. The case described by Jager [7] did not receive systemic therapy for *Aspergillus* and resulted in enucleation, compared to the other two cases that received systemic therapy, and were cured. The use of systemic antifungal therapy may be necessary to salvage the eye and avoid enucleation in hematogenous cases. Both cases of *Aspergillus* scleritis caused by direct trauma (Table 2) resolved after combination therapy with topical antifungal drugs and surgery.

In reviewing the literature, six different authors describe twelve cases of *Aspergillus* scleritis occurring as a result of surgery (Table 3). The time to presentation ranged from three days to greater than ten years postoperatively. Pain, erythema and visual disturbance

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<tr>
<th>Yr/Author [Ref.]</th>
<th>Presentation</th>
<th>Antifungal therapy</th>
<th>Surgical treatment</th>
<th>Duration of antifungal</th>
<th>Outcome</th>
<th>Species ID</th>
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<td>2005/Howell [this study]</td>
<td>Pain/erythema</td>
<td>Oral VRC/IV CAS</td>
<td>I&amp;D</td>
<td>4 months</td>
<td>Cure</td>
<td>A. flavus</td>
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IVDU, Intravenous drug use; I&D, Incision and drainage; AmB, Amphotericin B; FLC, fluconazole; VRC, voriconazole; CAS, Caspofungin; ID, identification by culture.
were the most common presentation. Three cases received antifungal monotherapy as their initial treatment. Two of these three patients ultimately underwent additional surgical intervention. The remaining nine cases received combination antifungal therapy. Four of these nine cases did not have corrective surgery as an additional part of treatment; one patient demonstrated cure while the remaining three patients lost the affected eye. In this subset, a common feature was early recognition, less than one week. Of the remaining five cases, the infection was cleared in three patients (but there was persistent visual loss), one patient underwent enucleation and no data was available regarding the final outcome in the last patient.

Rapid recognition and referral to a specialist is critical. Appropriate biopsy and cultures must be obtained for definitive diagnosis as delay can have significant and devastating consequences including enucleation. Autoimmune etiologies remain the most common cause of scleritis and, therefore, local steroids are frequently given as initial therapy, just as in our patient. If a patient fails to demonstrate marked persistent improvement, or if there is deterioration after adequate duration of therapy, a different diagnosis must be considered.

Treatment of infectious scleritis is complicated by the poor vascularity of the sclera [4,15,16]. The literature comments on the difficulty of treating scleral infections due to poor penetration of antibiotics in general [9,12–14]. Therefore, most of the knowledge on penetration of antifungal drugs is derived anecdotally. The sclera’s metabolic needs are met by arteries from the neighboring choroid and episclera [16]. Other factors which contribute to the efficacy of antifungal drugs in

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AmB, Amphotericin B; 5FC, flucytosine; FLC, fluconazole; ID, identification by culture.

Table 3  Aspergillus scleritis due to ophthalmic surgery

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<th>Yr/Author [Ref.]</th>
<th>Antifungal therapy</th>
<th>Surgical treatment*</th>
<th>Duration of antifungal</th>
<th>Outcome</th>
<th>Species ID</th>
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<tbody>
<tr>
<td>2003/Garg [13]</td>
<td>Topical natamycin/oral KTC or oral ITC</td>
<td>None</td>
<td>8 weeks</td>
<td>Cure</td>
<td>A. tereus</td>
</tr>
</tbody>
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[Ref]. References; ITC, itraconazole; KTC, ketoconazole; AmB, amphotericin B; CLT, clotrimazole; 5FC, flucytosine; VRC, voriconazole; Surgical treatment*: surgery performed after acquisition of Aspergillus infection from initial ophthalmologic surgery; ID, identification by culture.

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ophthalmic mycosis include: molecular mass of drug, concentration of the drug, route of administration, duration of contact, and lipid solubility [17]. There is a paucity of information in the literature regarding antifungal drug penetration of the sclera. Historically, the three classes of antifungal drugs having a clear and well-studied efficacy in the management of ophthalmic mycoses include: the polyenes, the azoles, and 5-FC [17]. They are used parenterally, orally, or topically. None, unfortunately, have been documented to be consistently efficacious in the treatment of scleral fungal infections [17]. The utility of topical drugs in the treatment of scleral infections, particularly those due to hematogenous dissemination is problematic. Amphotericin B remains the treatment of choice for life-threatening and severe ophthalmic mycoses [17]. Among the available antifungal agents, echinocandins are a new class of antifungals that inhibit 1,3-beta-D-glucan synthesis, a polysaccharide within the fungal cell wall [18]. Echinocandins are fungistatic against *Aspergillus* species [19], and to date there is no data concerning their use in scleral mycosis. Echinocandins do not penetrate the blood-brain barrier and cannot be recommended for cases involving the optic nerve or retina. The ability of echinocandins to diffuse through the sclera has not been quantitatively determined. Voriconazole, recently found to be effective against some forms of invasive aspergillosis [20], is a new extended spectrum triazole that inhibits the fungal P-450-dependent 14-alpha-demethylase enzyme in the sterol biosynthesis cascade inhibiting formation of the fungal cell membrane [21]. Although there is a paucity of published data regarding ability of voriconazole to penetrate the sclera, there is evidence that oral voriconazole can reach intraocular concentrations above the MIC90 (minimum inhibitory concentration) of 0.5 µg/mL for *A. fumigatus* [14]. *In vitro* susceptibilities of *Aspergillus* species reveals low minimum effective concentrations for caspofungin and minimum inhibitory concentrations for voriconazole, making both antifungals effective against *Aspergillus* [22]; however, at present, there is insufficient data correlating *in vitro* fungal susceptibility test results with *in vitro* outcome. Because of this, *in vitro* susceptibility data are difficult to interpret and are not used routinely in choosing antifungal drug therapy. Our patient did not have susceptibility testing performed for the *Aspergillus flaus* isolate.

A combination of both medical and surgical treatment is frequently required for optimal outcomes [11] and was beneficial in our patient. Duration of therapy in the published literature appears to require a minimum course of three months and more commonly as many as eight months to a year. Combination antifungal therapy remains a topic of intense debate about its benefits [23–26] and potential problems. Research on combination antifungal therapy is in the initial stages and currently is not recommended universally for treatment. It may be used for selected populations such as: invasive infections with poor prognosis, acute or fulminant refractory infections, or fungal infections involving the central nervous system [18]. *In vitro* studies of voriconazole combined with caspofungin report synergistic activity against *Aspergillus* species [20].

In our patient, four different treatment modalities were used: (1) oral voriconazole alone, (2) oral voriconazole plus topical voriconazole, (3) lipid-based amphotericin B plus caspofungin, and ultimately (4) oral voriconazole plus caspofungin parenterally. The final regimen was successful in cure. Possible explanations for this final success could represent the synergistic activity of combination antifungal therapy, or possibly the effectiveness of sequential therapy. This combination of oral voriconazole and parenteral caspofungin shortened the overall course of treatment to four months. Based upon this review optimal treatment for *Aspergillus* scleritis should include surgical debridement in combination with dual antifungal therapy. The successful outcome, short course and minimal side effect profile of this case warrants additional evaluation of combination therapy for *Aspergillus* scleritis.

References