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Successful management of *Aspergillus* scleritis by medical and surgical treatment

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Abstract

Background **Inflammatory scleral disease is frequently associated with autoimmune disorders and only occasionally caused directly by an infective agent. Fungal infections primarily involving the sclera are rare, and the outcome is generally poor. Here we report three patients with post-operative *Aspergillus* scleritis who were successfully managed by medical therapy and surgical intervention.**

Patients **Scleral infection with *Aspergillus* sp. was diagnosed 6 and 5 months after cataract extraction in a 76-year-old diabetic and an 82-year-old woman respectively, and in a 54-year-old man 3 months after trabeculectomy. Swabs and/or scrapings had not been conclusive and the diagnosis of *Aspergillus* infection was established in all cases only after scleral biopsy.**

Results **The infection was eliminated in all cases. This was achieved in one eye by treatment with oral itraconazole in combination with systemic and topical amphotericin B. The two patients with fungal scleritis after cataract extraction required in addition to the medical therapy (oral itraconazole, topical econazole and amphotericin B) scleral excisions and patch grafts to control infection.**

Conclusion **Fungal scleritis may remain undiagnosed for months. A scleral biopsy may be necessary to establish this diagnosis. Prolonged systemic antifungal therapy alone may not eradicate fungal infection. Surgical excision improves the outcome of fungal scleritis.**

Key words Amphotericin B, Antifungal, Econazole, Fungus, Imidazole, Itraconazole, Scleritis, Triazole

Inflammatory scleral disease is frequently associated with autoimmune disorders and is only occasionally caused directly by an infective agent.[1] Fungal infections primarily involving the sclera are extremely rare, but have been reported after trauma,[2] retinal detachment surgery,[3,4] treatment of pterygium,[5,6] cataract surgery,[7,8] and in association with systemic fungal infection.[9,10] The outcome is generally poor (Table 1). Here we report three patients with post-operative *Aspergillus* scleritis who were successfully managed by medical therapy and surgical interventions.

Case reports

Case 1

This 76-year-old diabetic woman underwent uncomplicated extracapsular cataract extraction and posterior chamber intraocular lens insertion via a corneoscleral section in her left eye. She received post-operative treatment with topical steroids and antibiotics. Uncorrected vision in this eye was 6/60, thought to be due to age-related maculopathy. One month post-operatively 'anterior uveitis' was noticed that settled with topical steroids. Three weeks later, in January 1994, the eye became painful with loss of vision down to correct light projection. An infiltrate at one of the stitches and a small hypopyon were recorded. These signs resolved on topical gentamicin and ceftazidime. Two months later, in March 1994, some of the sutures were removed and gentamicin 15 mg/ml and ceftazidime 50 mg/ml continued, since conjunctival hyperaemia was still present. Three weeks later a stitch abscess around one of the remaining loose sutures was diagnosed and swabs taken from this area and from beneath the adjacent conjunctiva. There was growth of *Aspergillus* on only one of several swabs. Contamination was suspected and the area reswabbed without any microbial growth. The antibiotics were discontinued and topical econazole instituted. After two further weeks without signs of improvement the patient was referred to Moorfields Eye Hospital.

Vision was 'counting fingers' at 1 m. Abnormal findings on ocular examination were limited to the anterior segment of the left eye. The conjunctiva was hyperaemic and the sclera at the upper part of the globe thickened. Therapy with topical and systemic ciprofloxacin was started and the econazole drops continued, but the scleritis persisted. A scleral biopsy was

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Proprietary interest: None

Table 1. *Published reports on fungal scleritis*

Author(s) and reference	Predisposing condition	Fungal isolate	Medical antifungal therapy	Surgical therapy	Outcome (visual acuity)
Köllner,[2] 1906	Trauma, piece of wood as foreign body	*Aspergillus* or *Trichophyton*			'Healed'
Chaillous,[9] 1912	Systemic sporotrichosis	*Sporotrichum*	Oral potassium iodide		'Much improved'
Podedworny and Suie,[7] 1964	Cataract extraction	*Paecilomyces* sp.	IV and topical amphotericin B	Excision	'Completely healed'
Lincoff *et al.*,[3] 1965	Diabetes mellitus; scleral buckling operation	Probably *M. mycosis*	IV amphotericin B	Implant removal	'Eye lost'
Milauskas *et al.*,[4] 1967	Diabetes mellitus; scleral buckling operation	'Yeast cells'; exact identification on morphological basis not possible			Enucleation
Stenson *et al.*,[10] 1982	IV drug use; systemic *Aspergillus* disease 5 years previously	*Aspergillus oryzae*	Topical natamycin and amphotericin B, oral flucytosine, IV amphotericin B	Biopsies	'Complete resolution'
Margo *et al.*,[5] 1988	Pterygium excision/ irradiation	*Aspergillus* sp.	Topical natamycin, topical miconazole, oral flucytosine	None	Enucleation
Reynolds and Alfonso,[20] 1991	Not reported	*Acremonium*	Topical natamycin	Not reported	Not reported
Carlson *et al.*,[8] 1992	Cataract surgery	*Aspergillus flavus*	Topical amphotericin B, oral ketoconazole and itraconazole	Biopsies	6/6
Moriarty *et al.*,[6] 1993	Pterygium excision/ irradiation	*Petriellidium boydii*	Topical natamycin, oral ketoconazole, IV amphotericin B	Debridement, lamellar and penetrating grafts	6/36
	Pterygium excision/ irradiation	*Petriellidium boydii*	Topical natamycin, IV amphotericin B	Lamellar grafts	Enucleation
	Pterygium excision/ irradiation	*Scedosporium inflatum*	Topical natamycin, oral fluconazole, IV amphotericin B	Debridement, lamellar grafts	6/24
	Pterygium excision/ irradiation	*Fusarium*	Topical natamycin, oral ketoconazole	Debridement (2×)	6/6

IV, intravenous.

taken that contained fungal elements consistent with *Aspergillus* sp. (Fig. 1). Oral itraconazole, 200 mg per day, was instituted and repeated injections of subconjunctival amphotericin B given. The scleral inflammation deteriorated slowly over the next 6 weeks and a necrotic area, measuring 3 × 4 mm, developed (Fig. 2). At this stage therapeutic surgery was planned.

An excision of the affected sclera and a deep lamellar dissection of the adjacent cornea was carried out (Fig. 3). The defect was covered with one corneal patch graft (Fig. 4) and antifungal therapy was continued as before. Over the next 4 weeks there was further expansion of the scleritis (Fig. 5). The patch graft was therefore removed. The necrotic borders were debrided and two donor corneas were required to fill the resulting large full-thickness defect. Systemic treatment with itraconazole was stopped since the patient had, on the third day after the intervention, developed a cerebral transient ischaemic attack. On 1 August 1994 the topical antifungal treatment was stopped. The eye remained quiet and the sutures were removed in December 1994 (Fig. 6). Astigmatism remained +12 in 170 and corrected vision (+5/−12×80) was 6/18.

Case 2

This otherwise healthy 82-year-old woman underwent uncomplicated extracapsular cataract extraction and posterior chamber intraocular lens insertion via a corneoscleral section in her left eye. She received standard post-operative treatment with topical steroids and antibiotics. At 4 weeks corrected visual acuity was 6/9 and the post-operative appearance was normal. Six weeks post-operatively she noticed ocular discomfort and the eye became progressively more painful with loss of vision down to correct light perception. A stitch abscess around the most nasal suture was diagnosed and swabs taken from this area. Topical treatment with methicillin and gentamicin forte was started. Oral flucloxacillin 500 mg and amoxicillin 500 mg were given at the same time four times a day and twice per day respectively. The culture showed growth of *Staphylococcus epidermidis* and the antibiotic treatment was subsequently changed to fucidic acid drops and oral fucidin 100 mg three times daily, later increased to 1 g per day. The subconjunctival abscess was drained and, as there was no improvement and signs of intraocular

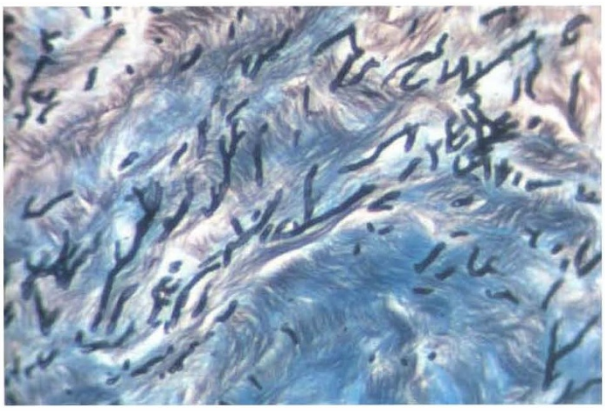

Fig. 1. *Septate fungal hyphae with dichotomous branching in the scleral biopsy specimen of case 1. Hyphae appear black against a green background when the specimen is stained with Grocott-Gomori methamine silver (×400).*

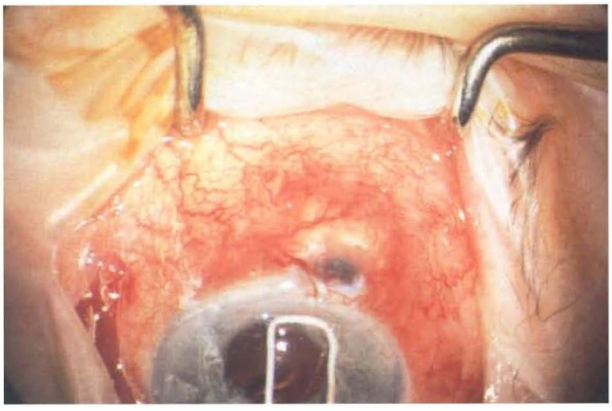

Fig. 2. *Case 1. The left eye 7 months after uneventful cataract extraction. The scleritis had deteriorated slowly over the preceding weeks despite systemic and topical antifungal treatment. A necrotic area is now visible and excision of the affected sclera is planned.*

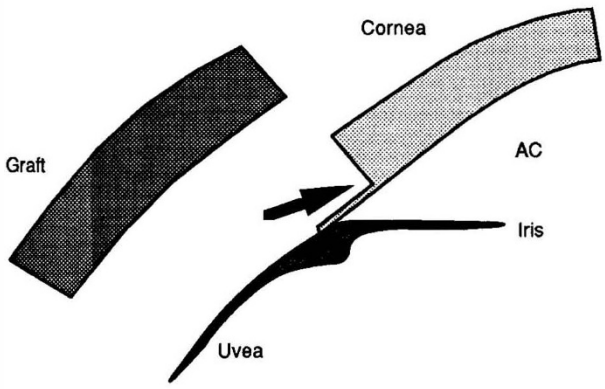

Fig. 3. *Case 1. Schematic drawing of the technique that was used to excise the necrotic tissue. Deep lamellar dissection (arrow) followed macroscopic clearance of the infected tissue at the limbus without entering the anterior chamber.*

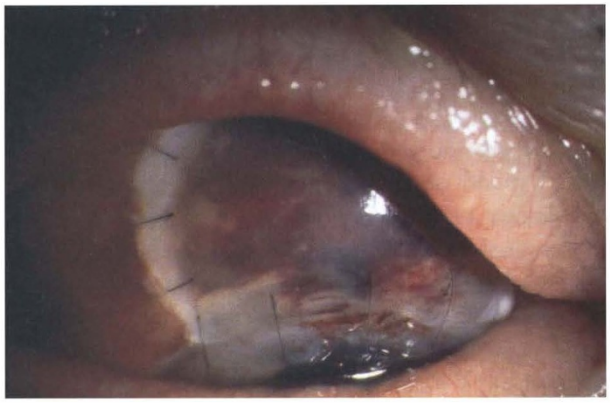

Fig. 4. *Case 1. The debridement resulted in a large sclero-corneal defect that was covered with a large corneal patch graft.*

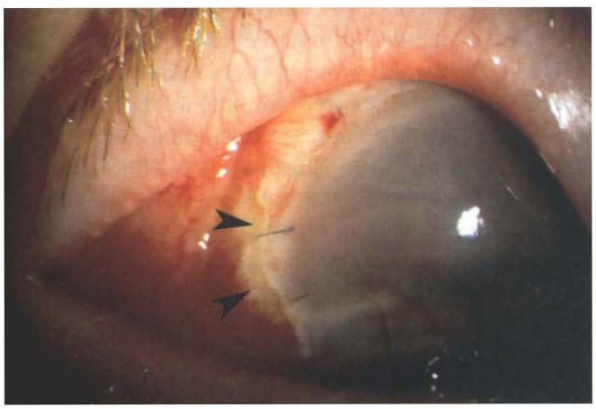

Fig. 5. *Case 1. Over the next 4 weeks there was further expansion of the scleritis. The graft was subsequently removed to allow debridement of the necrotic borders. Two large grafts were then sutured in to cover the defect.*

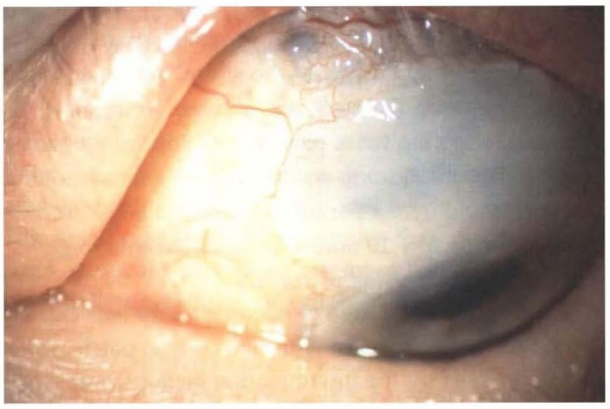

Fig. 6. *Case 1. The same eye 5 months later. The antifungal treatment had been stopped 4 months previously. Visual acuity is now 6/18.*

inflammation developed, an aqueous tap taken. Although no bacterial growth developed in the cultured aqueous, *Staphylococcus* endophthalmitis was suspected. On 14 January 1994, i.e. 1 week after the initial diagnosis of a 'suture abscess', the patient was referred to Moorfields Eye Hospital.

Visual acuity was 6/60 and on examination a hyperaemic and thickened conjunctiva was found. The corneal wound was slightly infiltrated with some sutures still *in situ*. There was a moderate to severe inflammation in the anterior chamber with cells and flare, but no hypopyon. Fundoscopy was difficult, but signs of a severe vitritis were absent. Aqueous and vitreous taps were taken, but no micro-organisms were grown. Intravitreal injections of amikacin 0.4 mg and vancomycin 1.0 mg were given and intravenous ciprofloxacin 200 mg twice a day together with oral steroids started. The topical treatment was changed to

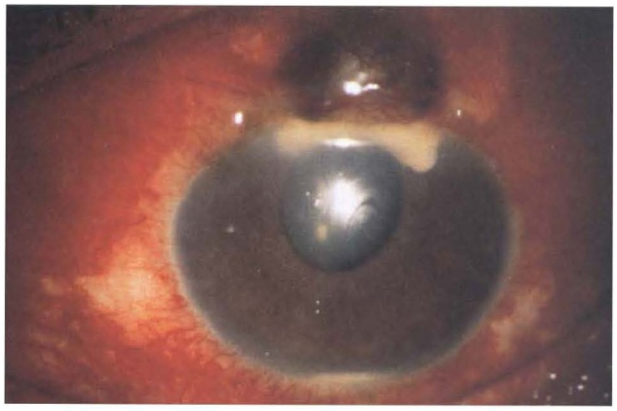

Fig. 7. *Case 3. The left eye of a 54-year-old black man who had undergone trabeculectomy 3 months previously. Note the oval stapyhloma at the trabeculectomy site and the white infiltrate surrounding this lesion and reaching into the limbal cornea.*

gentamicin 15 mg/ml, cefuroxime 50 mg/ml and prednisolone 0.3%. On this regime the inflammation began to subside and vision increased to 6/36.

By 1 month after the patient had left the hospital, on 25 February 1994, her eye had become painful again and on examination a mild scleritis in the upper part of the globe was diagnosed. Therapy with oral flurbiprofen, in addition to the above medication, was started. Three weeks later this localised scleritis was more prominent; the intraocular inflammation, however, had almost resolved and vision had increased to 6/18. Another 3 weeks later, on 6 April, the sclera became necrotic and a scleral biopsy was taken after the antibiotic treatment had been stopped for 48 h. The histological examination revealed fungal elements and *Aspergillus fumigatus* was later isolated from the half of the scleral specimen that had been cultured. Therapy was changed to oral itraconazole 100 mg twice per day and topical econazole 2 hourly. This medication was not effective in controlling the scleritis and over a period of 3 weeks a large necrotic area measuring 3 × 10 mm developed. At this stage therapeutic surgery was planned.

Excision of a large area of necrotic sclera was carried out and the defect covered with two corneal patch grafts.

Post-operatively the inflammation began to subside and 2 months later, on 23 June, itraconazole was reduced to 100 mg once a day. Visual acuity was then 6/18. One month later all medications were discontinued. When the patient was discharged in November 1994, the eye was quiet with 6/9 vision (+1.5/−2.0×120).

Case 3

A 54-year-old black man who had undergone trabeculectomy in his left eye 3 months previously was referred to Moorfields Eye Hospital because of persistent inflammation of this eye. When he was first seen on 9 February 1990, vision was light perception with projection. Examination showed an oval staphyloma at the trabeculectomy site, measuring 5 × 4 mm, and a white infiltrate surrounding this lesion and reaching into the limbal cornea (Fig. 7). The overlying conjunctiva and episclera were intensely inflamed, and there were aqueous cells and a small hypopyon, but no vitritis. These findings and the fact that previous intensive and prolonged treatment with topical antibiotics and steroids had not cleared the inflammation prompted us to suspect fungal scleritis.

A surgical exploration of the trabeculectomy site with scleral and uveal biopsies was undertaken. The bacteriological studies were negative, but cultures on Sabouraud's medium showed fungal growth and subsequently *Aspergillus* sp. was identified. Histological examination revealed fungal elements in the scleral specimens that were consistent with *Aspergillus*. In addition to the intravitreal injection of 5 μg of amphotericin B during the surgical exploration, a course of subconjunctival injections (750 μg per injection) and topical amphotericin was instituted. On this regime there was increased intraocular inflammation with development of a dense cyclitic membrane across the anterior lens surface. One week after the first intervention diagnostic anterior chamber and vitreous taps were therefore taken and intravitreal injections of amikacin 0.4 mg and vancomycin 1.0 mg carried out. There was no growth of micro-organisms in these samples and steroids were started topically and orally. Fungal sensitivities showed minimal inhibitory concentrations of 0.25 mg/l to the imidazoles (itraconazole, econazole, clotrimazole), a concentration of 0.5 mg/l to amphotericin and resistance to flucytosine. These results are shown in Table 2 for comparison with those of the other two cases (the methodology of antifungal sensitivity testing has been described elsewhere[11]). Oral itraconazole (100 mg twice per day) and topical clotrimazole 1% were started. On this regime the inflammation began to subside.

On 19 March 1990, a cataract extraction via corneal section and an anterior vitrectomy were carried out. Biopsies of the anterior capsule and adherent iris were taken for histological and bacteriological investigation and both were positive for *Aspergillus*. The antifungal

Table 2. *Activity of antifungal drugs against* Aspergillus fumigatus *strains isolated from scleritis cases*

	Minimum inhibitory concentration (mg/l) for *Aspergillus fumigatus* isolates[a]							
Case no.	Amphotericin B	Clotrimazole	Miconazole	Econazole	Ketoconazole	Intraconazole	Fluconazole	Nystatin
1	2.0	<0.12	1.0	<0.12	1.0	<0.03	>64	Not done
2	0.5	0.5	1.0	<0.25	2.0	<0.25	Not done	Not done
3	0.5	<0.25	2.0	0.25	1.0	<0.25	Not done	8.0

[a]For methodology see Griffiths *et al.*[11]

sensitivities on the *Aspergillus* isolated at this time were identical to those from the previous culture. After cataract extraction a retrocorneal membrane adjacent to the corneal section developed over a 2 week period and the pupil became almost completely secluded with the development of a thick cyclitic membrane. Progression of fungus infection was assumed and an intravitreal injection of amphotericin 5 μg together with amphotericin 750 μg subconjunctivally over the staphyloma was carried out on 9 April. A course of 23 daily injections of subconjunctival amphotericin starting on 18 April followed. The oral steroids were tailed off during this period and the intraocular inflammation almost completely resolved. By 23 May the intraocular inflammation had completely resolved. To provide a view of the posterior segment, the cyclitic membrane was removed surgically on 23 May and iris, vitreous and scleral biopsies were taken. No *Aspergillus* was cultured from the multiple biopsies that were taken. Histological examination of the divided specimens, however, showed the presence of fungal hyphae in all iris and scleral specimens. Therapy with oral itraconazole 200 mg twice a day was continued for another month together with topical steroids and the eye remained quiet with light perception afterwards.

Discussion

These case reports demonstrate the problems that may be encountered in the management of fungal scleritis. These include the difficulty of diagnosing mycotic infections, the choice of antifungal therapy, the difficulty of eliminating mycotic scleritis by medical therapy alone, and determining the technique and timing of surgical measures.

Scleritis is most frequently an aseptic, immune-mediated inflammation that can occasionally be initiated by surgical trauma.[1,12,13] *Infectious* scleritis after surgery should be suspected when there is no history of autoimmune disease and when the disease characteristics are atypical of immune-mediated scleral inflammation. Signs that were indicative of an infection in the reported cases include suture abscess, hypopyon, endophthalmitis and scleral necrosis without episcleral non-perfusion. Negative microbiology findings from swabs or scrapings are – as in fungal keratitis[14] – a frequent finding and do not exclude an infection, since the organisms may be present only in the deep stroma. The diagnosis of *Aspergillus* infection was established in all three cases only after scleral biopsy. We recommend, therefore, as with bacterial keratitis,[15] that in cases of progressive scleritis when infection is suspected, scleral tissue should be taken and divided for histopathological diagnosis and further microbiological investigations. The presence of mycotic elements on histological examination alone, without fungal growth in the cultured tissue, however, does not allow conclusions on their viability. Fungal elements may persist in the sclera after successful medical treatment, as shown by case 3.

The management of patients with scleromycosis remains difficult despite the availability of new antifungal agents. There are no clear guidelines for the selection and administration of antifungal antibiotics since scleromycosis is extremely rare and *in vitro* sensitivity data are of only limited value.[16] Topical and systemic antibiotic therapy is recommended for infectious scleritis. Until recently, amphotericin B was the drug of choice for systemic *Aspergillus* infection.[16] More recently itraconazole has become an alternative to amphotericin B for this indication.[17] Successful management solely by medical therapy was reported by Carlson *et al.*[8] in one patient with *Aspergillus* scleritis following cataract surgery. These authors attributed the successful outcome to the use of oral itraconazole. Although itraconazole may have an enhanced efficacy and cause fewer problems with toxicity in comparison with amphotericin B,[17] reliable control of mycotic scleritis by medical therapy alone is not the rule. In our cases 1 and 2 scleral inflammation was progressive and the formation of a necrotic area was observed while the patients were on oral itraconazole (200 mg/day) and intensive topical antifungal medication.

Surgical methods are important means of controlling fungal scleritis. They should be considered in cases unresponsive to medical treatment. It has to be borne in mind, however, that massive inflammatory reactions may occur after initiation of medical therapy (as in case 3). These may represent an immunological response to fungal cell death rather than actual disease progression ('Herxheimer type' of reaction).[18,19] Surgical interventions may consist of conjunctival resection with cryotherapy to the immediate surrounding sclera or lamellar or full-thickness procedures to excise the involved sclera with subsequent graft, or both.[20,21] Surgical excision with subsequent grafting has the advantage over cryotherapy in that tissue for diagnosis is provided and the treated area is more clearly defined. The efficacy of the different surgical procedures in the management of fungal scleritis still needs to be clarified. This small case series demonstrates that, in selected cases, surgical intervention improves the outcome of this potentially devastating disorder.

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