Differences in clinical ocular outcomes between exogenous and endogenous endophthalmitis caused by *Sporothrix*: a systematic review of published literature

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ABSTRACT

Background Sporotrichosis is an implantation mycosis caused by *Sporothrix* species prevalent worldwide, which occasionally can also result in intraocular infection presenting as an exogenous or endogenous infection (disseminated sporotrichosis). Knowledge in its clinical recognition and management is limited.

Aims To systematically review and analyse data from published literature with a view to comparing clinical outcomes between exogenous and endogenous endophthalmitis caused by *Sporothrix*.

Methods Case reports of intraocular sporotrichosis, published from 1960 to 2016, were retrieved from MEDLINE, Embase, Cochrane, LILACS and SciELO databases. The entire data set was divided into two patient groups: (1) exogenous endophthalmitis and (2) endogenous endophthalmitis. Primary outcomes were differences in ocular findings and clinical ocular outcomes between the two groups.

Results From 16 publications retrieved, a total of 8 eyes of 8 patients with exogenous endophthalmitis and 13 eyes of 10 patients with endogenous endophthalmitis were identified. Compared with exogenous endophthalmitis, endogenous endophthalmitis was more common in patients infected with HIV (p=0.001) and those from hyperendemic areas (p=0.036). Anterior uveitis (p=0.015) and posterior uveitis (p=0.04) were more common in the exogenous and endogenous endophthalmitis groups, respectively. The majority of patients with endogenous endophthalmitis had partial or full clinical resolution of ocular lesions with systemic amphotericin B alone or in combination with an oral antifungal, whereas patients with exogenous endophthalmitis had poor outcomes with irreversible vision loss, enucleation and evisceration.

Conclusions Anterior uveitis is more common in exogenous endophthalmitis with worse overall outcomes and complications, compared with endogenous endophthalmitis where posterior uveitis is the most common clinical manifestation, especially in patients infected with HIV and those from hyperendemic areas. *Sporothrix* infection should be included in the differential diagnosis for ocular inflammation, regardless of the presence or absence of autoimmune comorbidities and whether the patient resides in an endemic area or not. Ophthalmologists should consider intravitreal and systemic antifungal therapy for exogenous and endogenous endophthalmitis caused by *Sporothrix*.

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INTRODUCTION

Sporotrichosis is an implantation or inoculation mycosis caused by several *Sporothrix* species complex,[1 2] which occasionally can also result in intraocular infection, including endophthalmitis, retinal granuloma, granulomatous necrotising retinochoroiditis and granulomatous uveitis.[3–6] Ocular involvement can present as two distinct clinical patterns, exogenous and endogenous fungal endophthalmitis, depending on whether infection is isolated or disseminated. Exogenous infection occurs following inoculant trauma of deep eye structures with vegetable matter, whereas in endogenous infection, ocular involvement occurs by haematogenous spread of cutaneous or disseminated sporotrichosis.[7] These different clinical patterns of ocular sporotrichosis imply differences in clinical outcomes and response to therapy. In recent years, little attention has been focused on ocular manifestations of *Sporothrix* infection, given its relative rarity and lack of pathognomonic clinical features, although a literature review shows that ocular manifestations of *Sporothrix* infection might not be as uncommon as originally thought.[3–6] Predisposing risk factors, ocular manifestations and clinical outcomes that differentiate between exogenous and endogenous *Sporothrix* infection are yet to be elucidated. Thus, clinical recognition and the ability to distinguish between the different clinical patterns of disease are essential to monitor the sequelae of inflammatory ocular lesions.

The aim of this study was to systematically review and analyse data from published literature with a view to comparing clinical outcomes between exogenous and endogenous endophthalmitis caused by *Sporothrix*.

METHODS

This systematic review was conducted using the Preferred Reporting Items for a Systematic Review and Meta-analysis (PRISMA) statement as guideline.[8]

Search strategy

Case reports and case series of intraocular sporotrichosis, published from January 1960 to August 2016, were retrieved from literature searches using MEDLINE, Embase, Cochrane, LILACS and SciELO databases. No language restrictions were applied in those searches. The following keywords

were used: 'ocular sporotrichosis', '*Sporothrix schenckii*', '*Sporothrix brasiliensis*', 'cat transmitted sporotrichosis', 'endophthalmitis', 'exogenous endophthalmitis', 'endogenous endophthalmitis', 'chorioretinitis', 'uveitis', 'scleritis', 'retinitis', 'keratitis' and 'intraocular sporotrichosis'. We also reviewed the bibliography lists from selected reports. We used individual patient data from these case reports to create an entire data set for subsequent analysis, which was divided into two groups: patients in whom ocular involvement presented as an isolated disease, without any cutaneous lesions and not disseminated (defined as 'exogenous endophthalmitis'), and patients in whom ocular involvement was accompanied by cutaneous lesions or disseminated with joint and bone involvement or associated with widespread multiorgan dissemination (defined as 'endogenous endophthalmitis'). Ocular involvement was defined as injury to deep eye structures, including scleritis, keratitis, corneal perforation, iridocyclitis, iris nodule formation, necrotising granulomatous chorioretinitis, granulomatous uveitis, optic neuritis and vitritis.[7]

Inclusion criteria

Case reports were included in this systematic review if they met the following inclusion criteria: (1) discussion of a clinical syndrome consistent with either exogenous or endogenous endophthalmitis; (2) cases diagnosed on the basis of histologic analysis or positive culture, with recovery of isolates of *Sporothrix* species from tissue or clinical samples and (3) formal ophthalmological examination documenting ocular infection and inflammation. Reports lacking clinical details or only describing injuries in ocular adnexa were excluded.

Data collection

Data collected included demographic characteristics, comorbidities, systemic immunosuppression including HIV status, and risk factors associated with intraocular sporotrichosis. Data collected on ocular manifestations included eye involvement, laterality, symptom duration, anatomical location of intraocular inflammation, ophthalmological examinations (visual acuity, intraocular pressure and anterior chamber cell score), diagnostic investigations (histologic examination and microbiological investigations), treatment and clinical ocular outcomes. Ocular findings were assessed by an ophthalmologist and grouped into five categories according to the anatomical location of intraocular inflammation (ie, anterior uveitis, intermediate uveitis, posterior uveitis, panuveitis and optic neuritis), as determined by the Standardization of Uveitis Nomenclature Working Group[9] (table 1). In addition, information on clinical presentation in patients with endogenous endophthalmitis (disseminated sporotrichosis) was also gathered.

Table 1 Anatomical location of intraocular inflammation[9]

Type	Primary site of inflammation
Anterior uveitis	Anterior chamber, including keratitis, scleritis, iritis and iridocyclitis
Intermediate uveitis	Vitritis
Posterior uveitis	Retina or choroid, including choroiditis, retinochoroiditis, necrotising (and non-necrotising) retinitis, retinal vasculitis/periphlebitis, serous retinal detachment or papillitis
Panuveitis	Anterior chamber, vitreous, and retina or choroid
Optic neuropathy	Papillitis, optic neuritis or neuroretinitis

Statistical analysis

Differences in demographic characteristics, ocular and laboratory findings and clinical ocular outcomes between exogenous and endogenous endophthalmitis were examined using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables, with a level of significance set at $p<0.05$. For statistical purposes, Snellen visual acuity values were converted to logMAR visual acuity scores. All analyses were performed using SPSS V.22.0.

RESULTS

A total of 19 patients with intraocular sporotrichosis caused by *Sporothrix schenckii* and *Sporothrix brasiliensis* were identified from 17 case reports, of which 2 case reports were excluded due to lack of clinical details and the inability to obtain a copy of the reports. In addition, to include all cases of intraocular sporotrichosis, a case of keratitis caused by the non-pathogenic *S. pallida* was also included and analysed together with the cases caused by *S. schenckii* and *S. brasiliensis*. Thus, only 21 eyes of 18 patients were included for data extraction and analysis: 8 eyes of 8 patients with exogenous endophthalmitis and 13 eyes of 10 patients with endogenous endophthalmitis.[3–6 10–21] No additional case reports were identified from the bibliography list of selected case reports (figure 1).

Demographic characteristics

The mean (±SD) age of the patients (40.8±20 years vs 32.1±14 years, $p=0.314$) and the proportion of male patients (87.5% vs 90%, $p=1.0$) were similar in both exogenous and endogenous endophthalmitis groups. Eight (80%) of 10 endogenous endophthalmitis cases were from Brazil, a country with known areas of hyperendemicity ($p=0.001$) (table 2). Ten patients were from the USA.

The most common extraocular lesions in patients from the endogenous endophthalmitis group included cutaneous lesions, followed by osteoarticular involvement. Documented lesions were grouped as follows: disseminated (n=8, including cutaneous (n=1), cutaneous and osteoarticular (n=3), mucocutaneous and osteoarticular (n=2), widespread multiorgan dissemination (n=2, including cutaneous, osteoarticular and pulmonary)), lymphocutaneous involvement (n=1) and endocardial involvement (n=1).

Ocular and systemic risk factors predisposing to exogenous and endogenous endophthalmitis

There were no significant differences in the number of patients with selected baseline comorbidities, predisposing risk factors and immunocompromised status between the two groups, except for the number of patients with HIV infection, which was significantly greater in the endogenous endophthalmitis group ($p=0.036$) (table 2). In those patients with HIV infection, the median $CD4^+$ T-cell lymphocyte count was 168 cells/µL (range, 25–560 cells/µL); viral load measurements were not available. Viral suppression (<50 cells/µL) was observed in two patients only (table 2).

Ocular findings

There were no significant differences in bilateral involvement, duration of ocular manifestations and ophthalmological examination findings between the two groups. Anterior uveitis was a more common manifestation in the exogenous endophthalmitis group ($p=0.015$), whereas posterior uveitis was more common in the endogenous endophthalmitis group ($p=0.04$) (table 3).

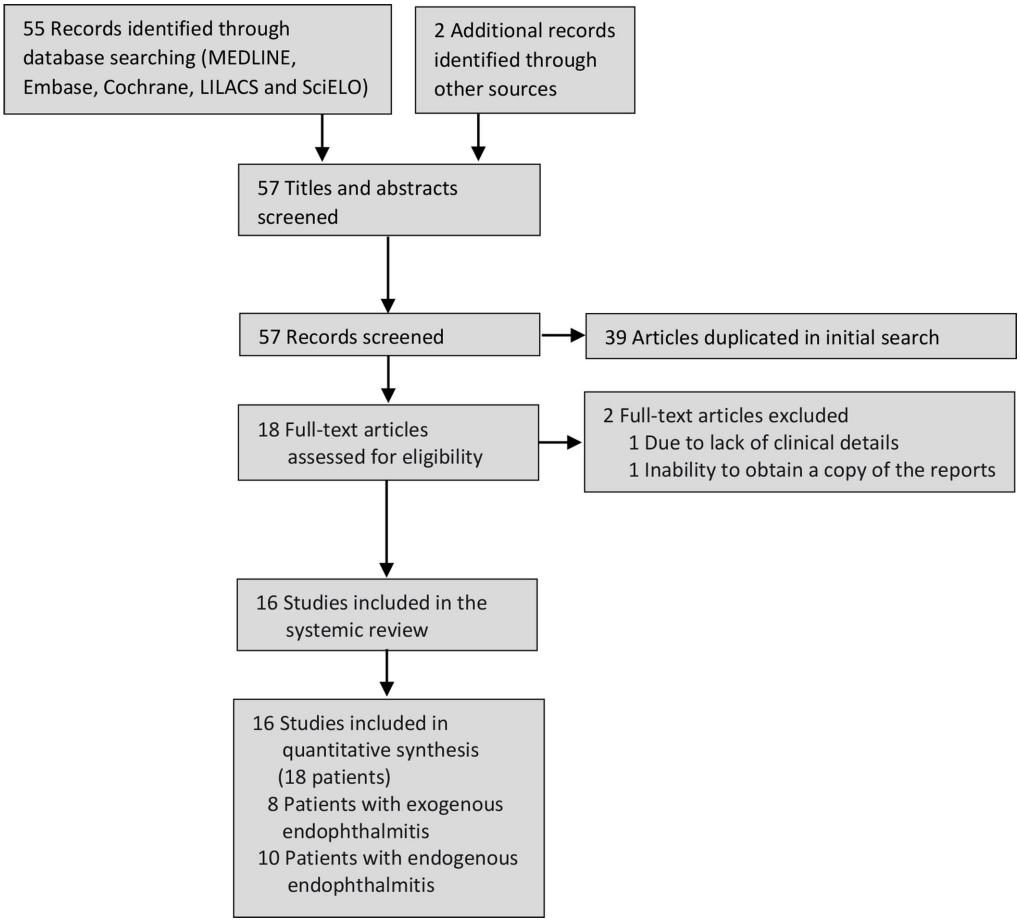

Figure 1 Flow diagram of study selection.

Histopathology and microbiology findings

Culture of ocular specimens, including vitreous samples, aqueous fluid and corneal and scleral scrapings, was the main investigation used in the diagnosis of exogenous endophthalmitis (p=0.031). Histological examination of ocular biopsy samples and Gram staining of vitreous aspirates established the diagnosis of exogenous endophthalmitis in a total of two patients. In 2 of 10 patients with endogenous endophthalmitis, initial aqueous or vitreous paracentesis culture results were negative, whereas a diagnosis of endogenous endophthalmitis was obtained from only two aqueous paracentesis samples. Aqueous or vitreous paracentesis was not performed in the remaining six cases of endogenous endophthalmitis. A diagnosis of endogenous endophthalmitis was established from culture (p=0.036) and histological examination (p=0.036) of skin biopsy samples. Although the majority of cases were caused by *S. schenckii*, compared with *S. brasiliensis* and *S. pallida*, there were no significant differences in causative fungi species between the two groups (table 4).

Treatment strategies

The following treatments were administered to the eight eyes with exogenous endophthalmitis: systemic amphotericin B (n=1), intravitreal and subconjunctival amphotericin B (n=1), topical and intravitreal amphotericin B (n=1), intraocular steroids (n=2), topical voriconazole (n=1), and systemic or topical amphotericin B in combination with an oral antifungal or potassium iodide (n=2). For patients in the endogenous endophthalmitis group, initial treatment consisted of amphotericin B alone or in combination with an oral antifungal, in cases of ocular infection accompanied by either cutaneous disseminated infection or widespread multiorgan dissemination. Of the 13 eyes with endogenous endophthalmitis, 4 were treated with systemic amphotericin B, 1 with systemic and intravitreal amphotericin B, 1 with systemic amphotericin B in combination with vitrectomy, 5 with systemic amphotericin B in combination with an oral antifungal and 1 with intravitreal amphotericin B in combination with oral fluconazole and oral potassium iodide (table 5).

Clinical ocular outcomes

Clinical ocular outcomes were similar in both groups. Although the majority of patients with endogenous endophthalmitis who were treated with systemic amphotericin B alone or in combination with an oral antifungal had partial or full clinical resolution of ocular lesions, there were no significant differences in clinical resolution of ocular lesions between the two groups (37.5% vs 53.8%, p=0.367). In the group of patients with exogenous endophthalmitis, ocular outcomes were particularly poor with irreversible vision loss: two eyes initially treated with intraocular steroids and one eye with topical amphotericin B and nystatin were enucleated, and one eye was eviscerated after discontinuing amphotericin B, all because of uncontrolled infection/inflammation following spontaneous corneal perforation in two of these eyes; one eye underwent keratoplasty after treatment with voriconazole (table 5) and one eye became phthisical following scleral perforation, despite therapy with intravitreal and subconjunctival amphotericin B, for which enucleation was

Table 2 Demographic and health characteristics at diagnosis of 18 patients with exogenous and endogenous endophthalmitis

Characteristics	Exogenous endophthalmitis (n=8 patients)	Endogenous endophthalmitis (n=10 patients)	p Value
Mean age±SD, years (IQR)	40.8±20 (13–75)	32.1±14 (12–56)	0.314*
Sex, n (%)			
Male	7 (87.5)	9 (90)	1.0
Female	1 (12.5)	1 (10)	
Place of residence, n (%)			
Hyperendemic†	0 (0.0)	8 (80)	0.001‡
Non-hyperendemic	8 (100)	2 (20)	
Immunocompromised status, n (%)			
HIV infected	0 (0.0)	5 (50)	0.036‡
ART, uncontrolled viral load	0 (0.0)	4 (40)	0.092
Median $CD4^+$ count, cells/µL (IQR)§	–	168 (25–560)	
Comorbidity, n (%)			
Cardiovascular	0 (0.0)	1 (10)	1.0
Diabetes mellitus	2 (25)	1 (10)	0.559
Alcoholism	0 (0.0)	1 (10)	1.0
Risk factors, n (%)			
Vegetative trauma	2 (25)	2 (20)	1.0
Contact with cats with sporotrichosis	0 (0.0)	1 (10)	1.0

*Mann-Whitney U test (non-parametric test).
†Hyperendemic: Brazil, an area known to have a high rate of sporotrichosis where contact with cats has been identified as a risk factor for transmission.
‡p<0.05; Fisher's exact test.
§Median $CD4^+$ count was obtained from four patients.
ART, antiretroviral therapy.

Table 3 Comparison of baseline eye characteristics in patients with exogenous and endogenous endophthalmitis

Baseline eye characteristics	Exogenous endophthalmitis (n=8 eyes)	Endogenous endophthalmitis (n=13 eyes)	p Value
Affected eye, n (%)			
OD	6 (75)	5 (38.5)	>0.10
OS	2 (25)	8 (61.5)	
Laterality, n (%)			
Unilateral disease	8 (100)	7 (70)	>0.10
Bilateral disease	0 (0.0)	3 (30)	
Initial ocular examination			
>1+ cells at first examination, n (%)	2 (25)	2 (15.4)	>0.10
IOP>21 (mm Hg), n (%)	3 (37.5)	2 (15.4)	>0.10
Visual acuity, logMAR, mean* (IQR)	0.6 (0–0.54)	0.67 (0–1)	0.867†
Mean disease duration at diagnosis, days; mean	123.6	76.5	0.558†
Ocular manifestation, n (%)‡			
Anterior uveitis	6 (75)	2 (16.7)	0.015§
Posterior uveitis	2 (25)	9 (75)	0.04§
Panuveitis	0 (0.0)	1 (8.3)	>0.10

*Data on visual acuity were available for 9 of 21 eyes included in the study.
†Mann-Whitney U test (non-parametric test).
‡Data on ocular manifestations were available for 8 and 12 eyes with exogenous and endogenous endophthalmitis, respectively.
§p<0.05; Fisher's exact test.
IOP, intraocular pressure; OD, right eye; OS, left eye.

Table 4 Histopathology and microbiology results for patients with exogenous and endogenous endophthalmitis

Investigation result	Exogenous endophthalmitis (n=8 patients)	Endogenous endophthalmitis (n=10 patients)	p Value
Positive specimen on culture, n (%)			
Culture of ocular specimens	6 (75.0)	2 (20.0)	0.031§
Vitreous samples	3 (37.5)	0 (0.0)	
Aqueous culture	1 (12.5)	2 (20)	
Scleral scraping	1 (12.5)	0 (0.0)	
Corneal scraping	1 (12.5)	0 (0.0)	
Skin clinical sample			
Skin biopsy	0 (0.0)	4 (40)	0.092
Lymph node	0 (0.0)	5 (50)	0.036§
Histological examination, n (%)			
Skin biopsy	0 (0.0)	5 (50)	0.036§
Ocular biopsy	1 (12.5)	0 (0.0)	0.444
Other microbiology investigations, n (%)			
Gram stain of the vitreous aspirate	1 (12.5)	0 (0.0)	0.444
Pathogen, n (%)			
Sporothrix schenckii	7 (87.5)	7 (70)	0.588
S. brasiliensis	0 (0.0)	3 (30)	0.216
S. pallida	1 (12.5)	0 (0.0)	0.444

§p<0.05; Fisher's exact test.

declined by the patient. In the group of patients with endogenous endophthalmitis, 3 of 12 eyes treated with systemic amphotericin B had irreversible vision loss: one eye was enucleated after treatment with systemic and intravitreal amphotericin B and one eye was enucleated without previous treatment with antifungals, both due to uncontrolled infection/inflammation; one patient treated with vitrectomy and systemic amphotericin B was lost to follow-up (table 5). No eyes developed glaucoma, cataract, retinal detachment or other complications in either groups. In 7 of 10 patients with endogenous endophthalmitis, cutaneous disseminated lesions and/or osteoarticular involvement responded well to treatment with systemic amphotericin B alone or in combination with an oral antifungal. In addition, in one patient in whom the eye was enucleated without antifungal treatment, the skin and articular lesions were successfully treated with oral itraconazole.

DISCUSSION

There is a paucity of information in the published literature about ocular manifestations in sporotrichosis because endophthalmitis caused by *Sporothrix* is exceedingly rare.[3–6 10–21] To our knowledge, this is the first study to systematically review and analyse data from existing literature on ocular manifestations in sporotrichosis, to examine the differences in clinical outcomes between exogenous and endogenous endophthalmitis caused by *Sporothrix* species, although with a large heterogeneity in data quality and a limited number of patients with sporotrichosis with ocular involvement. In this systematic review, anterior uveitis was found to be more common in exogenous endophthalmitis, and posterior uveitis in endogenous endophthalmitis. This finding is likely to indicate intraocular sporotrichosis, assuming that these represent distinct ocular patterns.

In this study, there were no differences in demographic characteristics and predisposing risk factors between the two groups;

Table 5 Treatment and clinical ocular outcomes in patients with exogenous and endogenous endophthalmitis

	Exogenous endophthalmitis (n=8 eyes)	Endogenous endophthalmitis (n=13 eyes)	p Value*
Treatment, n (%)†			
Systemic AmB	1 (12.5)	4 (30.8)	0.344
Intravitreal AmB+subconjunctival injection AmB	1 (12.5)	0 (0.0)	0.133
Topical AmB+intravitreal AmB	1 (12.5)	0 (0.0)	0.381
Systemic AmB+intravitreal AmB	0 (0.0)	1 (7.7)	0.619
Systemic AmB+vitrectomy	0 (0.0)	1 (7.7)	0.619
Intraocular steroids	2 (25)	0 (0.0)	0.133
Topical voriconazole	1 (12.5)	0 (0.0)	0.381
Combination therapy			
Systemic AmB+oral ITR	0 (0.0)	3 (23.1)	0.215
Systemic AmB+oral TRB	0 (0.0)	2 (15.4)	0.371
Intravitreal AmB+oral FCZ+oral SSKI	0 (0.0)	1 (7.7)	0.619
Systemic AmB+subconjunctival injection AmB+oral SSKI	1 (12.5)	0 (0.0)	0.381
Topical AmB+topical nystatin	1 (12.5)	0 (0.0)	0.381
Clinical ocular outcomes, n (%)‡			
Clinical resolution	2 (37.5)	7 (53.8)	0.367
Blindness	0 (0.0)	3 (23.1)	0.215
Enucleation	3 (37.5)	2 (15.4)	0.262
Evisceration	1 (12.5)	0 (0.0)	0.381
Penetrating keratoplasty	1 (12.5)	0 (0.0)	0.381

*Fisher's exact test.
†One eye of a patient with endogenous endophthalmitis was enucleated without previous treatment.
‡One patient with endogenous endophthalmitis was lost to follow-up.
AmB, amphotericin B; FCZ, fluconazole; ITR, itraconazole; SSKI, saturated solution of potassium iodide; TRB, terbinafine.

however, of note, all patients with exogenous endophthalmitis were from the USA and almost all patients with endogenous endophthalmitis were from hyperendemic areas in Brazil, known to have a high rate of sporotrichosis through contact with cats. These findings are consistent with previous studies that reported the majority of cases of disseminated and disseminated cutaneous sporotrichosis occurring in the USA and Brazil.[22] This 'geographical' difference may be partly explained by the increasing emergence of sporotrichosis in Brazil, especially cases of disseminated disease in immunocompromised hosts. Therefore, exogenous endophthalmitis caused by *Sporothrix* seems to be mainly restricted to American populations, and endogenous endophthalmitis to Brazil.

There are very few case reports on the ocular manifestations of *Sporothrix* infection in patients with HIV. In this study, endogenous endophthalmitis was predominantly found in HIV-infected hosts compared with exogenous endophthalmitis. This can be explained by the haematogenous spread of the fungal infection following initial inoculation in cutaneous, osteoarticular or disseminated disease. These findings are consistent with studies of sporotrichosis in patients infected with HIV, which found that disseminated and cutaneous manifestations were the most common clinical presentations in these patients.[22] Thus, results in this present study indicate a significant difference between the two clinical patterns of intraocular sporotrichosis, suggesting that HIV infection may predispose to an increased risk for disease progression to endogenous endophthalmitis in patients with disseminated sporotrichosis (cutaneous and osteoarticular).

In this study, it was not possible to determine the importance and role, if any, of ophthalmological examination in differentiating between exogenous and endogenous endophthalmitis. This lack of positive finding may be attributable to the small number of cases in each group.

It is unclear why anterior uveitis would be more common in exogenous endophthalmitis, and posterior uveitis in endogenous endophthalmitis caused by *Sporothrix*. One possible explanation is that exogenous endophthalmitis occurs when *Sporothrix* fungus is introduced into the eye following surface trauma penetrating the eyeball into the anterior segment, via the cornea or anterior sclera, thus resulting in inflammation localised to the anterior segment; but rarely in immunocompromised hosts, the *Sporothrix* infection may also spread into the posterior segment due to uncontrolled infection/inflammation following spontaneous perforation of the cornea and anterior sclera caused by retinochoroiditis (posterior uveitis), which would be consistent with a longer duration of symptoms, as in the case of a patient in the exogenous endophthalmitis group here. In contrast, in endogenous endophthalmitis caused by *Sporothrix*, it is possible that posterior uveitis is simply an indicator of prolonged, untreated disseminated infection that occurs when the fungal infection invades the posterior segment via the bloodstream (haematogenous dissemination), thus resulting in inflammation localised to the choroid that may invade through the retina or vitreous or cause a reactive inflammatory infiltrate in the structures abutting the choroid; this occurs most commonly in immunocompromised individuals, mainly those with HIV/AIDS. Rarely, in endogenous endophthalmitis, anterior uveitis might be a consequence of contiguous dissemination of posterior uveitis since, in the present study, one patient with endogenous endophthalmitis and HIV infection developed granulomatous uveitis (anterior uveitis). Another possible explanation is that anterior and posterior uveitis in patients with exogenous and endogenous endophthalmitis, respectively, resulted from prolonged chronic fungal infection since we found that patients with exogenous and endogenous endophthalmitis were diagnosed within 123.6 and 76.5 days of symptom onset, respectively (table 3). Thus, clinicians should bear in mind a possible diagnosis of exogenous and endogenous endophthalmitis caused by *Sporothrix* when assessing cases presenting with ocular inflammation, that is, ocular sporotrichosis should be in the differential diagnosis for ocular inflammation, regardless of whether the patient resides in hyperendemic areas or not. Similarly, in those patients not adequately responding to ocular anti-inflammatory therapy, *Sporothrix* infection should be considered, along with referral to a uveitis specialist.

It is difficult to distinguish exogenous from endogenous endophthalmitis based solely on clinical presentation. Findings from this study strongly suggest that exogenous endophthalmitis can be diagnosed using culture from ocular specimens since *S. schenckii* was preferentially isolated from vitreous samples, although aqueous fluid aspirates and scleral and corneal scrapings are rarely used to establish the presence of *S. schenckii* and *S. pallida*. In addition, in the absence of a positive culture from an ocular sample, early diagnosis of endogenous endophthalmitis was possible using histopathological examination of skin biopsy samples, which identified the causative micro-organism, that is, *S. schenckii* or *S. brasiliensis*. Therefore, these results highlight the importance of seeking microbiological, as well as histopathological, evidence in diagnosing the cause of ocular infection/inflammation before committing a patient to antifungal therapy.

To date, there are no clinical trials or published guidance on treatment for intraocular sporotrichosis. From published case reports, treatment with either systemic and/or intravitreal amphotericin B alone or in combination with antifungal agents remains the mainstay treatment for exogenous and endogenous endophthalmitis caused by *Sporothrix*, respectively, although both treatment options are associated with limited outcomes, but this may be due to the small number of published cases. Since only two eyes with exogenous endophthalmitis and seven with endogenous endophthalmitis were successfully treated, with irreversible vision loss and loss of the involved eye in the remaining patients, it was not possible to demonstrate a significant difference in clinical ocular outcomes between both groups. It is possible that those patients with a delayed diagnosis had irreversible vision loss and loss of the involved eye since we found that patients with exogenous and endogenous endophthalmitis were diagnosed within 123.6 and 76.5 days of symptom onset, respectively (table 3). This indicates a prompt and correct diagnosis is likely to improve clinical ocular outcomes in patients with exogenous and endogenous endophthalmitis. Another possible explanation for poor treatment outcomes in some eyes with exogenous endophthalmitis is the use of intraocular steroids, topical voriconazole or subconjunctival amphotericin B. Appropriate therapy for fungal endophthalmitis consists of intravitreal antifungal agents with consideration for systemic antifungals. In the present study, topical antifungals that exhibit poor penetration of the cornea and sclera were used, and treatment with intraocular steroids most certainly would have allowed the fungal infection to progress as endophthalmitis does not respond to steroid therapy. Treatment outcomes were also poor in eyes with endogenous endophthalmitis treated with systemic amphotericin B, probably due to the lack of intravitreal antifungal agents that exhibit better corneal and scleral penetration to treat intraocular fungal infections. Therefore, since topical, subconjunctival and oral agents show poor eye penetration, ophthalmologists should consider intravitreal as well as systemic antifungal therapy in cases of endophthalmitis caused by *Sporothrix* (both exogenous or endogenous). Thus, clinical diagnosis and treatment can be a challenge to ophthalmologists, as much remains to be learnt about intraocular sporotrichosis.

The main limitations of this study are the small sample size due to only a few cases published on intraocular sporotrichosis. Furthermore, the study findings are relevant to Brazil and the USA, which reported all cases of exogenous and endogenous endophthalmitis included in the study. Therefore, conclusions from the study may not be generalisable and must be interpreted with due caution.

CONCLUSIONS

These findings suggest that anterior uveitis is more common in exogenous endophthalmitis and may result in worse overall ocular outcomes and complications, compared with endogenous endophthalmitis where posterior uveitis is the most common clinical manifestation, especially in those with HIV infection and those residing in areas of hyperendemicity. Thus, *Sporothrix* infection should be included in the differential diagnosis for ocular inflammation, regardless of the presence or absence of autoimmune comorbidities and whether the patient resides in an endemic area or not. Ophthalmologists should also consider intravitreal and systemic antifungal therapy in cases of exogenous or endogenous endophthalmitis caused by *Sporothrix*.

Correction notice This article has been corrected since it published Online First. In the 'Demographic characteristics' section, the number 48 has been changed to 40.8 in the sentence "The mean (±SD) age of the patients (40.8±20 years vs 32.1±14 years, p=0.314) …".

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