DOI 10.5935/0034-7280.20200067

Fungal keratitis management in a referral cornea center in Brazil

Manejo de ceratites fúngicas em centro de referência no Brasil

Fernanda Machado Bezerra[1] https://orcid.org/0000-0002-4655-2594
Ana Luisa Höfling-Lima[1] https://orcid.org/0000-0003-0338-3951
Lauro Augusto de Oliveira[1] https://orcid.org/0000-0002-7384-9342

ABSTRACT

Purpose: To report etiological diagnosis, predisposing risk factors, therapeutic strategies and visual outcome of patients treated at the Department of Ophthalmology of Federal University of São Paulo. **Methods:** This is a retrospective, descriptive, and observational study from medical and laboratory records of the Department of Ophthalmology of Federal University of São Paulo, including all patients with culture proven fungal keratitis in 5 years, from October 2012 through October 2017. **Results:** There were 2260 fungi microbiologic test requests. Of these, 140 samples had positive cultures for fungi and sixty-six patients were followed at our clinic. Forty-five patients (68.2%) were men, and the mean age was 48.06 (±17.39) years. Fusarium spp. was the most frequently isolated fungus (32 cases; 48.5%), followed by Candida parapsilosis (12 cases; 18.2%). Thirty-four patients (51.5%) underwent intracameral injection of amphotericin B (5 µg per 0.1 ml). In 11 patients (32.3%), infection was eradicated after intracameral amphotericin B associated to topical antifungal treatment and, in 23 patients (67.7%), therapeutic keratoplasty was needed. No complication related to intracameral amphotericin B injection was observed in this series. Forty-three patients (65.1%) ended up with therapeutic keratoplasty. Three patients (4.5%) evolved to evisceration or enucleation. At the last follow-up visit, 53 patients (80.3%) had visual acuity worse than 20/200. **Conclusion:** Despite current antifungals drugs and distinct administration strategies, fungal keratitis remains challenging. Delayed antifungal therapy may explain poor clinical outcomes. Intracameral amphotericin B associated to topical antifungal treatment seems to be a safe and helpful alternative for non-responsive fungal keratitis. But it is important to formulate other treatment strategies, hence to improve patients' outcomes, since most patients ended-up with significant visual impairment even after current treatment.

Keywords: Antifungal agents; Fungi; Eye infections, fungal; Corneal transplantation; Keratitis

RESUMO

Objetivo: Descrever diagnósticos etiológicos, fatores de risco, estratégias terapêuticas e resultados visuais de pacientes com ceratite fúngica tratados no Departamento de Oftalmologia da Universidade Federal de São Paulo. **Métodos:** Trata-se de um estudo retrospectivo, descritivo e observacional, a partir da análise de prontuários médicos e laboratoriais do Departamento de Oftalmologia da Universidade Federal de São Paulo, incluindo todos os pacientes com ceratite fúngica comprovada por cultura no período de outubro de 2012 a outubro de 2017. Resultados: Foram realizadas 2260 solicitações de testes microbiológicos. Destas, 140 amostras apresentaram culturas positivas para fungos, e 66 pacientes foram acompanhados em nosso serviço. Quarenta e cinco pacientes (68,2%) eram do sexo masculino, e a média de idade foi de 48,06 (± 17,39) anos. Fusarium spp. foi o fungo mais freqüentemente isolado (32 casos; 48,5%), seguido por Candida parapsilosis (12 casos; 18,2%). Trinta e quatro pacientes (51,5%) foram submetidos à injeção intracameral de anfotericina B (5 µg por 0,1 ml). Destes, 11 pacientes (32,3%) tiveram a infecção erradicada. Nos outros 23 pacientes (67,7%), o transplante terapêutico foi necessário. Nenhuma complicação relacionada à injeção intracameral de anfotericina B foi observada neste estudo. No total, 43 pacientes (65,1%) evoluíram para transplante terapêutico, e 3 pacientes (4,5%) foram submetidos à evisceração ou enucleação. Cinquenta e três pacientes (80,3%) apresentaram acuidade visual final pior que 20/200. Conclusões: Apesar dos diversos medicamentos antifúngicos atuais e vias de administração, o tratamento das ceratites fúngicas permanece desafiador. O atraso no início do tratamento adequado pode justificar o desfecho clínico desfavorável de grande parte dos pacientes. A injeção intracameral de anfotericina B mostrou-se uma alternativa terapêutica segura para ceratites fúngicas refratárias. Mas outras estratégias de tratamento devem ser formuladas, visando melhorar os resultados visuais dos pacientes.

Descritores: Antifúngicos; Fungos; Infecções oculares fúngicas; Transplante de córnea; Ceratite

[1]Cornea and External Disease Sector, Department of Ophthalmology and Visual Sciences, Universidade Federal de São Paulo, Sao Paulo, Brazil.

Project authorized under number 89081118.7.0000.5505 on the Research Ethics Committee of Federal University of Sao Paulo.

The authors declare no conflict of interest

Received for publication 28/3/2020 - Accepted for publication 19/8/2020.

Introduction

Fungal infections are an important cause of ocular morbidity. The prevalence of these infections has increased since the end of 19th century, probably due to frequent use of corticosteroids and topical antibiotics, which facilitate the penetration of these pathogens and alter the ocular surface creating a less competitive environment for microorganisms, respectively.[1] They are typically more prevalent in rural regions with warmer and more humid climates, and their incidence is variable.[1,2]

Pathogens prevalence depends on the geographic region. In general, the most frequently isolated agents are filamentous fungi, which are responsible for 50% to 88.4% of cases, with Fusarium spp. and Aspergillus spp. being the most prevalent.[3-7] Among yeast infections, Candida spp. is the most representative genus, and Candida albicans is the most frequently isolated species. These infections are commonly related to chronic ocular-surface disorders, as well as to systemic diseases such as diabetes and immunosuppression.[3,5]

The first-line treatment is topical antifungals such as natamycin and amphotericin B— associated or not with oral antifungals. Natamycin is a polyene antifungal, and it is considered the most effective medication against filamentous fungi (e.g., Fusarium and Aspergillus). However, it presents low corneal penetration due to its high molecular weight, being recommended as a monotherapy mainly for superficial fungal keratitis.[9] Amphotericin B is a macrolide polyene with broad-spectrum antifungal action, mainly against Candida and Aspergillus; being recommended to treat severe ocular fungal infections such as deep keratitis and endophthalmitis.[8,9] Another class of antifungal agents comprises the azole derivatives, including imidazoles (miconazole, econazole, and ketoconazole) and triazoles (fluconazole, itraconazole, voriconazole, and posaconazole). This drug class's spectrum of action and bioavailability are quite variable. Fluconazole and itraconazole are most effective against Candida spp., whereas ketoconazole is most effective against filamentous fungi. These drugs are often administered orally as adjuvants to treat deep fungal keratitis.[9] Miconazole presents good efficacy and safety when subconjunctivally administered to treat Candida, Fusarium, and Aspergillus infections.[10,11] Among the azoles, voriconazole is an interesting alternative for fungal-infection treatment due to its low toxicity, good spectrum against filamentous and yeast fungi, and to its several routes of administration (topical, subconjunctival, intracameral, intravitreal, oral, and venous).[9,12,13] However, its high cost limits its use, especially in underdeveloped countries. Recently, echinocandins (e.g., caspofungin and micafungin) have emerged as therapeutic alternatives for yeast infections, mainly for versions of Candida spp. that are resistant to fluconazole. Echinocandins are administered intravenously to treat severe systemic infections. They have also been shown to be efficacious in animal studies when topically administered in the treatment of Candida keratitis.[8,9]

On the horizon, researchers are trying to develop new molecules, drugs formulations and delivery systems (liposomal formulations, polymeric micelles, nanoparticles). Alternative therapeutic strategies such as photochemical collagen cross-linking (PACK-CXL) have also been reported for mycotic keratitis treatment. [14]

Conventional treatment with topical and oral antifungals is usually effective in early stages of such infections. However, despite treatment, 12 to 38% of severe fungal keratitis require therapeutic corneal transplantation.[15] Intrastromal and intracameral injections of amphotericin B have been used as an alternative to conventional treatment in deep fungal keratitis to postpone or prevent therapeutic keratoplasty. Corneal transplantation is effective at controlling the infection, but therapeutic keratoplasty—especially if performed on large ulcers or very inflamed eyes—presents inferior results when compared to optic keratoplasty after healing.[16]

Our service is a referral and tertiary cornea center. Most of our fungal keratitis patients are severe cases that often require alternative treatments such as intracameral amphotericin B injection. In this study, we analyzed fungal keratitis cases that were diagnosed and followed at the Department of Ophthalmology and Visual Sciences at -Federal University of São Paulo within 5 years. We report the etiological fungal profile, predisposing risk factors, therapeutic strategies and visual outcome of patients treated in our service.

Methods

This is a five years retrospective, descriptive, and observational study regularly approved by the Research Ethics Committee of the Federal University of São Paulo under approval number 89081118.7.0000.5505. We included all patients who were diagnosed with culture-proven fungal keratitis, from October 2012 through October 2017. Data were collected from medical and laboratory records. Follow-up loss and incomplete medical records were the exclusion criteria.

Fungal keratitis diagnoses were based on clinical signs (satellite lesions, feathery border, elevated areas, rough texture), with laboratory confirmation through gram stains or culture (Sabouraud / BHI agar) from corneal scraping or biopsy, such as previously described.[17,18] For all cases, empirical topical antibiotic treatment was given while waiting for the microbiological results. Once confirmed, tailored topical antifungal therapy was initiated hourly and tapered according to patient`s responses. The criteria for choosing the antifungal agent was made not only based on the etiology but also based on clinical severity. Topical 5% natamycin was the first choice in superficial cases (less than 1/3 of corneal stroma) and topical 0.15% amphotericin B in deeper corneal infiltrates. Oral antifungal was prescribed in cases with deep involvement (more than 1/3 of corneal stroma) and were administered after liver function evaluation. The criteria to proceed with intracameral amphotericin B administration were clinical-treatment refractoriness and/or anterior-chamber involvement. We defined as nonresponsive those patients who did not show clinical improvement (i.e., a smaller ulcer or corneal infiltration) after 14 days of antifungal eye drops (amphotericin B or natamycin) with or without oral antifungal treatment (fluconazole or ketoconazole).

Patients with impending corneal perforation, perforation, athalamia, and scleral involvement were unable to performe intracameral amphotericin B and were submitted to therapeutic keratoplasty. Intracameral injections were performed under locoregional anesthesia and with ideal asepsis and antisepsis conditions. After aspiration of 0.1 ml of aqueous humor, 0.1 ml of amphotericin B (50 μg/ml) was injected into the anterior chamber.

The main outcome measures were necessity of therapeutic keratoplasty, recurrence rate, and final visual acuity. We defined recurrence after therapeutic keratoplasty as the presence of new corneal infiltration and/or hypopyon.

Results

We identified 2260 fungi microbiologic test requests from October 2012 through October 2017. Of these, 140 samples had positive cultures for fungi, 66 of which had this diagnosis confirmed and were followed at our service. Forty-five patients (68.2%) were men, and the mean age was 48.06 (±17.39) years. The main risk factors were ocular trauma (27.3%), previous surgery (24.2%), topical steroids use (15.1%) and soft contact lens wear (10.6%) (Table 1). Filamentous fungi were the most prevalent (50 cases; 75.8%), Fusarium spp. was the most frequently isolated genus (32 cases; 48.5%), and Fusarium solani was the most frequent species identified (28 cases; 42.5%), followed by Candida parapsilosis (12 cases; 18.2%) (Table 2).

Sixty-four patients were treated with 0.15% amphotericin B eye drops and only 2 patients were treated with topical 5% natamycin. The criteria for choosing the antifungal agent was made based on the etiology and based on clinical severity. Patients treated with topical natamycin presented less severe and more superficial infiltrates. Both ended-up with fungal eradication without needing adjuvant intracameral amphotericin B. On average, eye drops were used for 2 months. Thirty-four patients (51.5%) underwent intracameral amphotericin B. In 11 patients (32.3%), infection was eradicated after intracameral amphotericin B injection associated to topical treatment and, in 23 patients (67.7%), therapeutic keratoplasty was needed. Intracameral amphotericin B was usually performed every 48-72 hours associated to topical treatment and the mean number of injections per patient was 3.6. None adverse effect related to intracameral amphotericin B was observed in this series. Forty-three (65.1%) out of 66 patients required therapeutic keratoplasty. Of these, 23 patients had undergone intracameral injection of amphotericin B and 20 patients had not. Filamentous fungus was the main cause for intracameral amphotericin B injection (91%) and corneal therapeutic transplantation (86%).

Infection recurrence after keratoplasty was suspected in 12 cases (27.9%). In all cases, cultures were positive for filamentous fungi. Recurrence suspicion defined additional intracameral amphotericin B therapy. Three patients (4.5%) evolved to evisceration or enucleation, one due to endophthalmitis and two after corneal perforation and uveal prolapse. The mean follow-up period was 17.14 months.

Regarding visual acuity at the last follow-up visit, 5 patients (7.6%) achieved 20/40 or better, 8 patients (12.1%) were between 20/40 and 20/200, and 53 patients (80.3%) ended up with visual acuity worse than 20/200 (Table 3).

Table 1
Baseline patient characteristics

Characteristic	n (%)
Male	45 (68.2)
Age	
< 18 yr	02 (3)
18-40 yr	23 (34.8)
40-65 yr	30 (45.4)
> 65 yr	11 (16.7)
Duration of symptoms before visit (days)	
< 15	25 (37.9)
15-30	18 (27.3)
> 30	23 (34.8)
Risk factors	
Ocular trauma	18 (27.3)
Previous surgery	16 (24.2)
Topical steroids	10 (15.1)
Soft contact lens wear	07 (10.6)

Table 2
Prevalence and etiologic agents

Etiologic agents	n(%)
Filamentous	50 (75.8)
Fusarium sp.	32 (48.5)
Fusarium solani	28 (42.5)
Fusarium non-solani	4 (6)
Aspergillus spp.	6 (9.1)
Others	12 (18.2)
Yeasts	16 (24.2)
Candida parapsilosis	12 (18.2)
Candida albicans	4 (6)
Total	66

Discussion

Geography influences both the prevalence of fungal keratitis and its etiological agents. This condition is endemic in warm regions such as India.[8] Worldwide epidemiologic studies reported that filamentous fungi have a particularly high prevalence and that the condition has predominant male involvement.[3,6,19-22] In accordance to that, our series also demonstrated higher prevalence

Table 3
Surgical treatments, infection recurrence, visual outcomes for filamentous fungi and yeast fungi

	Filamentous fungi (n=50)	Yeast fungi (n=16)	Total
Intracameral Amphotericin B (%)	31	03	34 (51.5)
Corneal transplant (%)	37	06	43 (65.1)
Recurrence after keratoplasty (%)	12	--	12 (27.9)
Evisceration/Enucleation (%)	01	02	03 (4.5)
Final Visual Acuity (%)			
VA < 20/200	38	15	53 (80.3)
VA 20/40 a 20/200	07	01	08 (12.1)
VA > 20/40	05	--	05 (7.6)

of fungal keratitis in male patients.

Fungal keratitis treatment is a challenge. Changes in the ocular surface facilitate microorganism penetration, which leads to deep corneal involvement, intense inflammation, and necrosis. When microorganisms reach the deep stroma and pass Descemet's membrane leading to anterior-chamber or sclera involvement, eradication becomes more difficult.[8] The high incidence of this infection in rural patients (particularly those of low socioeconomic level), as well as the prevalence of late diagnoses and empirical treatments without antifungal coverage, may result in worse prognoses and higher risk of complications such as descemetocele, perforation, endophthalmitis, and blindness.[23]

Some eye centers use topical natamycin as first-line drug to treat all cases of fungal keratitis. In our department, however, natamycin is the first choice only in superficial keratitis caused by filamentous fungi. In order to prevent or reduce therapeutic keratoplasty rates, we use other routes of antifungal administration (e.g., intrastromal, intracameral and subconjunctival) to increase drug's bioavailability, as proposed in previous studies.[24] Some researchers have shown intrastromal and intracameral amphotericin B use to be effective and safe, with good response and good infection-eradication rates.[16,23,25,26] Sharma et al.[27], otherwise, evaluated 45 patients divided into 3 groups (topical treatment, topical treatment plus intracameral amphotericin B injection, and topical treatment plus intracameral amphotericin B injection with hypopyon removal) and reported no statistical differences among the groups regarding healing time, treatment success, or final visual acuity. Although the sample size is insufficient and more clinical trials are needed to conclude this. In our opinion, these alternative routes should be used in cases of low adherence and/or refractoriness, as shown in our treatment flow chart below (Figure 1).

Despite all therapeutic options, severe cases continue to be difficult to treat due to toxicity, low penetration, and antifungal resistance. According to literature, 12% to 38% of fungal keratitis cases require corneal transplantation, even after adequate treatment.[15,16,19] In our study, 43 patients (65.1%) underwent therapeutic keratoplasty. Besides that, most patients ended-up with significant visual impairment even after infection eradication, and final visual acuity was less related to the causal agent and more related to lesion's severity/depth, with better outcomes in superficial cases. We speculate that this high rate might be due to the fact that our service is a referral-based one and mainly provides tertiary care for late-stage cases. Only 37.9% of our patients had symptoms for less than 15 days before their first visit (Table 1). This may justify the severity of our cases, explain the high usage of topical amphotericin B, and poor visual acuity prognosis.

According to the previously mentioned criteria (i.e., patients who were refractory to clinical treatment or who had anterior chamber involvement), 34 patients were treated with topical and intracameral amphotericin B injection. No complication related to this procedure was observed. Eleven patients (32.3%) had infection eradicated. Our results do not allow us to assure that intracameral amphotericin B injection reduces the need for therapeutic keratoplasty. However, adjuvant therapy with intracameral amphotericin B aims not only to eradicate the infection but also to prevent or to postpone therapeutic keratoplasty until more favorable conditions are achieved.

Other important findings in our series were the replacement of Candida albicans by Candida parapsilosis as more prevalent among yeasts in the last decade[3] and the higher prevalence of filamentous fungi (75.8%) in patients who underwent intracameral injections and therapeutic keratoplasty. Twelve of 43 patients (27.9%) who underwent corneal transplantation experienced infection recurrence after keratoplasty. This rate is similar to others recurrence rate reported in literature (7.4% to 50%).[14,19,22] In all recurrence cases, cultures were also positive for filamentous fungi, which confirms these pathogens' refractoriness to treatment and poor clinical outcomes, especially Fusarium solani, as described in previous studies.[28,29]

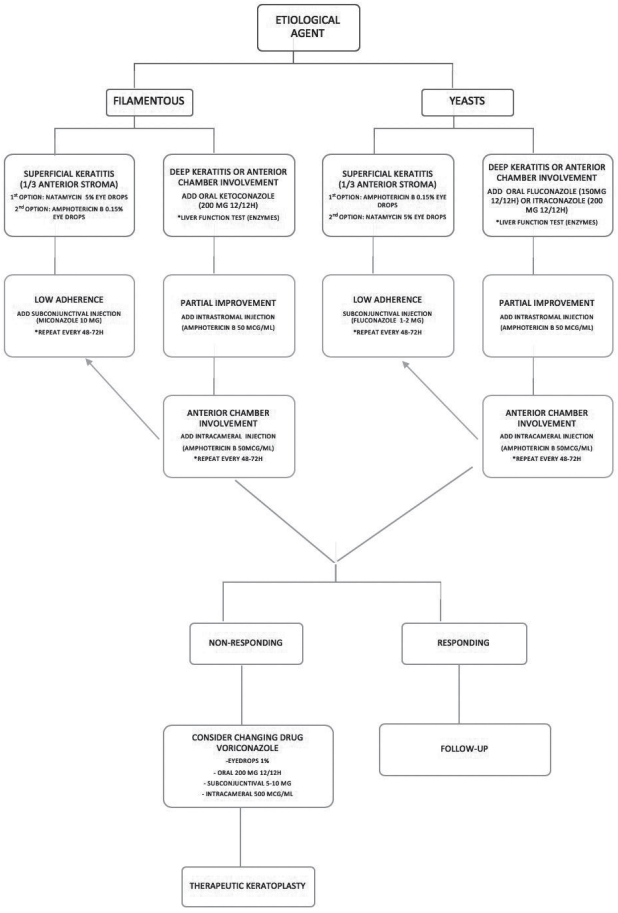

Figure 1. Flow chart for fungal keratitis treatment
Adapted from: 9. Müller GG, Kara-José N, de Castro RS. Antifungals in eye infections: drugs and routes of administration. Rev Bras Oftalmol. 2013;72(2):132–41.[9]

Dursun et al.[30] showed that, in 9 of 10 cases of Fusarium spp. keratitis with intraocular involvement, infection did not respond to combined therapy with oral antifungal (fluconazole or ketoconazole), topical natamycin, and (when necessary) intravitreal injection of amphotericin B. This suggests that early diagnosis is critical to clinical treatment.[30]

Conclusions

Despite current antifungal drugs and distinct administration strategies, fungal keratitis remains challenging. Delayed antifungal therapy may explain poor clinical outcomes.

Regardless of this retrospective study limitations, intracameral amphotericin B (5 µg per 0.1 ml) associated with topical antifungal treatment seems to be a safe and helpful alternative for non-responsive fungal keratitis, as it cured keratitis and avoi-

ded therapeutic transplantation in one-third of cases. Even so, multicenter and randomized clinical trials are required to clarify the benefits of intracameral amphotericin B in fungal keratitis treatment.

At last, most patients ended-up with significant visual impairment even after current treatment. So, continuous search for alternative treatment strategies, hence to improve our patients' outcomes is necessary.

References

1. Keay LJ, Gower EW, Iovieno A, Oechsler RA, Alfonso EC, Matoba A, et al. Clinical and microbiological characteristics of fungal keratitis in the United States, 2001-2007: a multicenter study. Ophthalmology. 2011;118(5):920–6.
2. Oliveira LA, Takata TT, Shiguematsu AI, Melo Júnior LA, Gompertz OF, Sousa LB, et al. Effect of topical 0.5% povidone-iodine compared to 5% natamycin in fungal keratitis caused by Fusarium solani in a rabbit model: a pilot study. Arq Bras Oftalmol. 2008;71(6):860–4.
3. Höfling-Lima AL, Forseto A, Duprat JP, Andrade A, Souza LB, Godoy P, et al. Estudo laboratorial das micoses oculares e fatores associados às ceratites. Arq Bras Oftalmol. 2005;68(1):21–7.
4. Agrawal V, Biswas J, Madhavan HN, Mangat G, Reddy MK, Saini JS, et al. Current perspectives in infectious keratitis. Indian J Ophthalmol. 1994;42(4):171–92.
5. Tanure MA, Cohen EJ, Sudesh S, Rapuano CJ, Laibson PR. Spectrum of fungal keratitis at Wills Eye Hospital, Philadelphia, Pennsylvania. Cornea. 2000;19(3):307–12.
6. Jastaneiah SS, Al-Rajhi AA, Abbott D. Ocular mycosis at a referral center in Saudi Arabia: A 20-year study. Saudi J Ophthalmol. 2011;25(3):231–8.
7. Rizvi Y, Agarwal PM, Mishra PP, Dokania A. Microbiological pattern and epidemiologic trends of fungal keratitis in north India. J. Evid. Based Med. Healthc. 2016;3(48):2445–50.
8. Ansari Z, Miller D, Galor A. Current thoughts in fungal keratitis: diagnosis and treatment. Curr Fungal Infect Rep. 2013;7(3):209–18.
9. Müller GG, Kara-José N, de Castro RS. Antifungals in eye infections: drugs and routes of administration. Rev Bras Oftalmol. 2013;72(2):132–41.
10. Alfonso EC, Galor A, Miller D. Fungal keratitis. In: Krachmer JH, Mannis MJ, Holland EJ, editors. Cornea: fundamentals, diagnosis and manage- ment. 3rd ed. New York: Mosby Elsevier; 2011.
11. Foster CS. Miconazole therapy for keratomycosis. Am J Ophthalmol. 1981;91(5):622–9.
12. Prakash G, Sharma N, Goel M, Titiyal JS, Vajpayee RB. Evaluation of intrastromal injection of voriconazole as a therapeutic adjunctive for the management of deep recalcitrant fungal keratitis. Am J Ophthalmol. 2008;146(1):56–9.
13. Hariprasad SM, Mieler WF, Lin TK, Sponsel WE, Graybill JR. Voriconazole in the treatment of fungal eye infections: a review of current literature. Br J Ophthalmol. 2008;92(7):871–8.
14. Garg P, Roy A, Roy S. Update on fungal keratitis. Curr Opin Ophthalmol. 2016;27(4):333–9.
15. Barut Selver O, Egrilmez S, Palamar M, Arici M, Hilmioglu Polat S, Yagci A. Therapeutic corneal transplant for fungal keratitis refractory to medical therapy. Exp Clin Transplant. 2015;13(4):355–9.
16. Shao Y, Yu Y, Pei CG, Tan YH, Zhou Q, Yi JL, et al. Therapeutic efficacy of intracameral amphotericin B injection for 60 patients with keratomycosis. Int J Ophthalmol. 2010;3(3):257–60.
17. Leck A. Taking a corneal scrape and making a diagnosis. Community Eye Health. 2009;22(71):42–3.
18. Lee P, Green WR. Corneal biopsy. Indications, techniques, and a report of a series of 87 cases. Ophthalmology. 1990;97(6):718–21.
19. Ximenes KF, Vasconcelos KF, Monte FQ. Epidemiology of fungal keratitis treated with penetrating keratoplasty by means of histopathologic findings. Rev Bras Oftalmol. 2016;75(3):195-204.
20. Gopinathan U, Garg P, Fernandes M, Sharma S, Athmanathan S, Rao GN. The epidemiological features and laboratory results of fungal keratitis: a 10-year review at a referral eye care center in South India. Cornea. 2002;21(6):555–9.
21. Punia RS, Kundu R, Chander J, Arya SK, Handa U, Mohan H. Spectrum of fungal keratitis: clinicopathologic study of 44 cases. Int J Ophthalmol. 2014 Feb;7(1):114–7.
22. Xie L, Dong X, Shi W. Treatment of fungal keratitis by penetrating keratoplasty. Br J Ophthalmol. 2001;85(9):1070–4.
23. Hu J, Zhang J, Li Y, Han X, Zheng W, Yang J, et al. A combination of intrastromal and intracameral injections of amphotericin B in the treatment of severe fungal keratitis. J Ophthalmol. 2016;2016:3436415.
24. Wu J, Zhang WS, Zhao J, Zhou HY. Review of clinical and basic approaches of fungal keratitis. Int J Ophthalmol. 2016;9(11):1676–83.
25. Yoon KC, Jeong IY, Im SK, Chae HJ, Yang SY. Therapeutic effect of intracameral amphotericin B injection in the treatment of fungal keratitis. Cornea. 2007;26(7):814–8.
26. Yilmaz S, Ture M, Maden A. Efficacy of intracameral amphotericin B injection in the management of refractory keratomycosis and endophthalmitis. Cornea. 2007;26(4):398–402.
27. Sharma N, Sankaran P, Agarwal T, Arora T, Chawla B, Titiyal JS, et al. Evaluation of intracameral amphotericin B in the management of fungal keratitis: randomized controlled trial. Ocul Immunol Inflamm. 2016;24(5):493–7.
28. Walther G, Stasch S, Kaerger K, Hamprecht A, Roth M, Cornely OA, et al. Fusarium Keratitis in Germany. J Clin Microbiol. 2017;55(10):2983–95.
29. Oechsler RA, Feilmeier MR, Miller D, Shi W, Hofling-Lima AL, Alfonso EC. Fusarium keratitis: genotyping, in vitro susceptibility and clinical outcomes. Cornea. 2013;32(5):667–73.
30. Dursun D, Fernandez V, Miller D, Alfonso EC. Advanced fusarium keratitis progressing to endophthalmitis. Cornea. 2003;22(4):300–3.

Corresponding author:
Fernanda Bezerra.
Department of Ophthalmology and Visual Sciences, Paulista School of Medicine, Universidade Federal de São Paulo, Sao Paulo, SP, Brazil.
Rua Botucatu, 822, Zip Code 04023-062, São Paulo, SP, Brazil.
E-mail: fernandamb1901@gmail.com
Phone: +5511948552455