

CASE REPORT

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Favorable outcome of *Lasiodiplodia theobromae* keratomycosis : a clinical case and systematic review

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Abstract

Background Keratitis caused by *Lasiodiplodia theobromae* is rare and typically associated with a poor prognosis. Current literature lacks sufficient evidence on effective management of patients with this condition.

Case presentation A 74-year-old former agricultural worker presented with a red right eye, discomfort, and decreased visual acuity, progressing over three days without treatment. Examination revealed type 2 diabetes and a non-perforating, spiculated corneal abscess with a hypopyon in the right eye. Initial treatment included a triple antibiotic therapy and supportive care. Direct mycological examination identified numerous septate mycelial filaments. Antifungal treatment with natamycin and voriconazole, both topically and orally, was initiated. Cultures confirmed *Lasiodiplodia theobromae*. The patient showed significant improvement. Treatment continued for eight weeks, with a final visual acuity of 20/50 due to a stromal scar.

Conclusion An extensive literature review conducted in November 2023, using databases such as PubMed and Google Scholar with the keywords “*lasiodiplodia*” and “keratitis” yielded no previous cases of this specific condition being managed solely with the combined use of natamycin and voriconazole. This antifungal combination is commonly included in most management protocols for fungal keratitis. Factors such as the use of corticosteroids and delayed diagnosis were noted to adversely affect the prognosis. This case and this systematic review underscores the potential for non-surgical management options in severe fungal keratitis.

Keywords Fungal keratitis, *Lasiodiplodia theobromae*, Keratomycosis

Background

Fungal keratitis, in general, are rare infections with a poor prognosis, particularly affecting developing areas and tropical regions [1]. Due to their unusual nature, adequate treatment is generally only initiated after a certain delay, which contributes to the poor outcomes often encountered. These are mainly filamentous fungi in tropical climates, foremost among which is *Fusarium* and *Aspergillus* [2].

Lasiodiplodia theobromae is a black fungus, often found in tropical regions, where it contributes to the rot of bananas, sugar cane, cocoa and other plants. It was first

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described as a cause of fungal keratitis by Puttanna in 1967 in India [3].

Since then, only 68 observations of ocular infections by this germ have been recorded in the literature, with mostly unfortunate outcomes. We present a case of *Lasiodiplodia theobromae* keratitis with a favorable outcome under medical treatment with a combination of natamycin and voriconazole.

Case presentation

A 74-year-old man presented to the Department of Ophthalmology, University Hospital of Martinique, Fort de France, France (French West Indies) with a red right eye, sensation of “discomfort,” no significant pain, associated with decreased visual acuity and progressing for 3 days without any initiated treatment. There was no history of trauma or foreign bodies, but the patient, a former agricultural worker living in a rural area, often worked in a banana plantation and had several animals. He had no known medical history, had not received medical follow-up and appeared to be in good general health. During his hospitalization, examinations revealed previously unknown type 2 diabetes. No other abnormalities were found in the general clinical examination.

The examination revealed a visual acuity of “counting fingers” at one meter on the right, unimprovable, and 20/25 Parinaud 2 on the left eye with correction. In the anterior segment, a large (5 mm diameter), non-perforating, spiculated corneal abscess with epithelial haze and a barely visible millimetric hypopyon in the anterior chamber were noted on the right. On the left eye, there was only a cortico-nuclear cataract (Fig. 1). The ocular pressure was measured at 15mmHg on the left with a pachymetry of 517 μm , and 13mmHg on the right. The fundus was inaccessible on the right eye; B-scan ultrasound revealed no signs of posterior segment involvement.

We began local antibiotic treatment immediately after collecting corneal scrapings. The patient was given an antibiotic triple therapy with gentamicin, piperacillin, and vancomycin eye drops. Additionally, we administered atropine and moisturizers, along with paracetamol for pain management. The corneal scraping was performed under oxybuprocaine anesthesia. This procedure took place in a sterile room using a microscope. Following the scraping, cultures were promptly initiated by a biologist. The next day, a direct mycological examination showed numerous septate and branched mycelial filaments. These filaments, which were turoid with intercalary chlamyospores, were visible with May Grunwald Giemsa staining (Fig. 2). Based on these findings, we prescribed antifungal treatment. This included 5% natamycin eye drops, voriconazole eye drops, and an oral dose of voriconazole at 400 mg/day. In addition to antifungals, we used a bi-antibiotic therapy (ciprofloxacin and tobramycin eye drops). We continued antibiotic treatment until bacteriological samples returned negative results.

The culture allowed the isolation of a filamentous fungus, grey, with abundant aerial mycelium, without fruiting bodies. Identification of *Lasiodiplodia theobromae* was made by mass spectroscopy. Those microbiological analysis were performed by the Mycology Department at CHU Fort de France. The strains were also sent to the CNRMA at the Institut Pasteur (Paris, France) for diagnostic confirmation by molecular biology.

The clinical picture improved favorably, allowing discharge from the hospital on the thirteenth day under natamycin eye drops and voriconazole eye drops and orally. The patient’s condition improved favorably, and the treatment was maintained at full dose for 8 weeks, with a gradual decrease leading to a complete cessation of treatment around the third month. At the end of the treatment, the patient achieved a visual acuity of 20/50

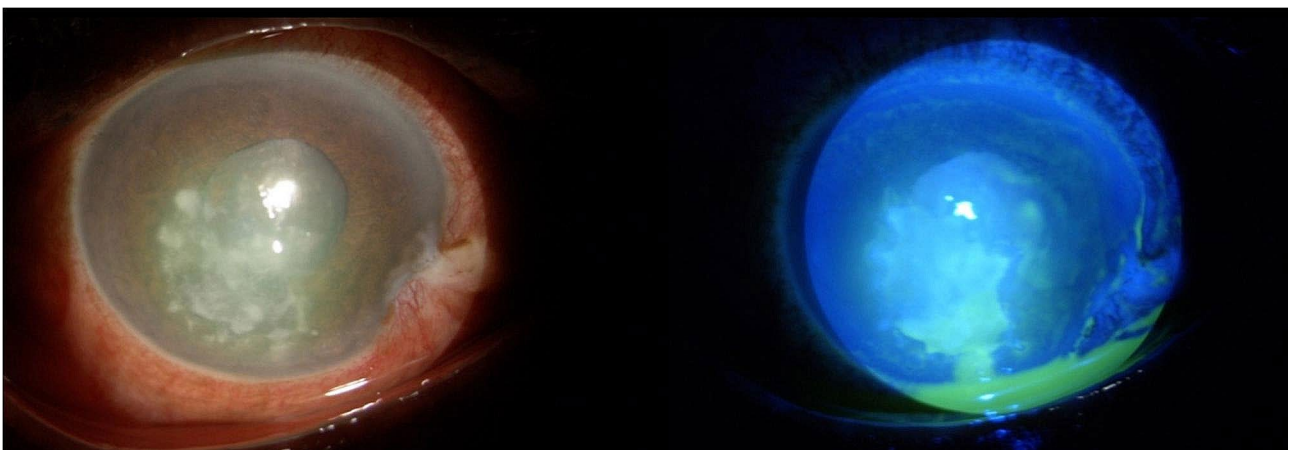


Fig. 1 Clinical photography of the first examination

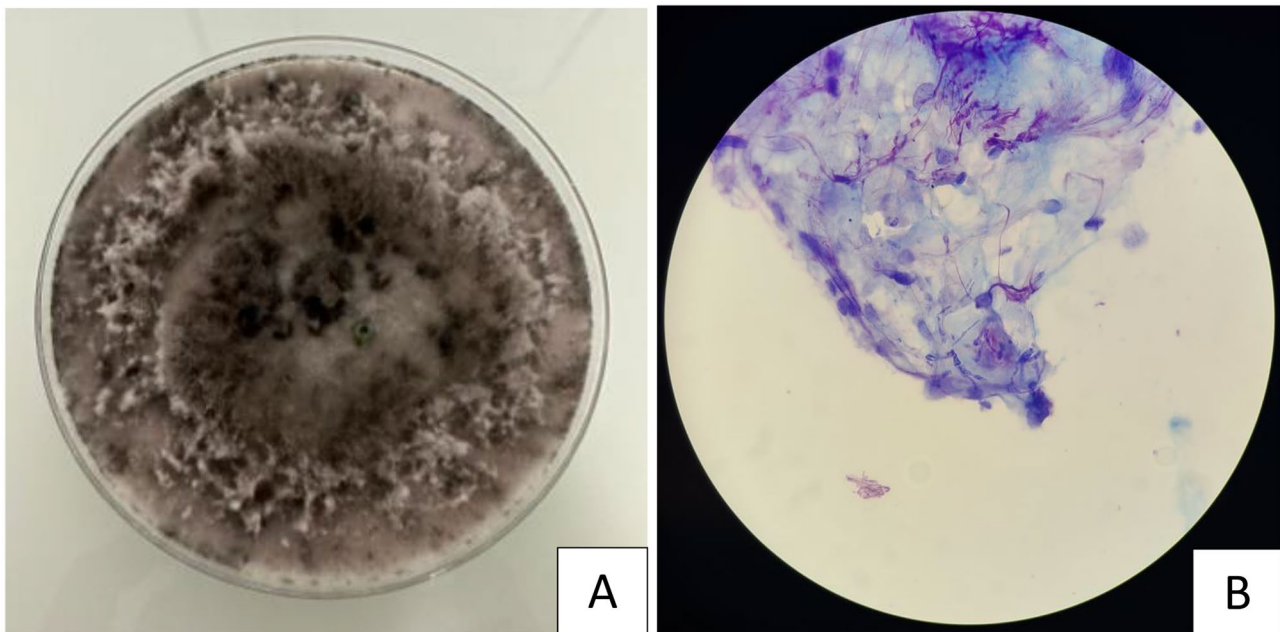


Fig. 2 Photography of *Lasiodiplodia Theobromae* petri dish (A) and of direct examination of MGG-stained scrapings (B)

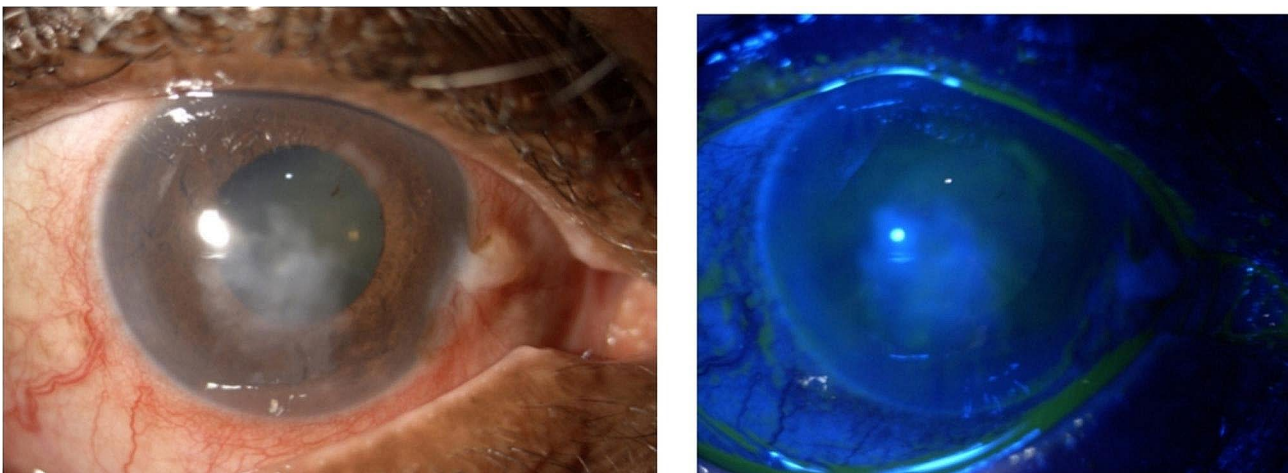


Fig. 3 Clinical photography at M3

due to the presence of a stromal scar in the visual axis (Fig. 3).

Discussion

While fungal keratitis is estimated at 1.5 million cases per year globally [3], *Lasiodiplodia theobromae* keratitis remains understudied. An extensive literature review in November 2023, utilizing databases such as PubMed and Google Scholar with the keywords “*lasiodiplodia*” and “*keratitis*”, revealed no previous instances of *Lasiodiplodia theobromae* keratitis being managed with only this specific antifungal regimen.

The analysis of the literature was complicated by several factors. Firstly, there are few experimental studies

in this field, but mostly descriptive studies, mainly case reports, which limits the scientific conclusions. Moreover, some fungi can be saprophytic in the flora of the eyelids and conjunctiva, particularly in individuals working outdoors in conditions of high heat and humidity. It is also sometimes difficult to identify the fungal strain, and some misclassifications may occur. This underscores the importance of collaborating with competent microbiological analysis services in centers treating serious ocular infectious pathologies.

Only 68 ocular infection cases are described in the literature, including one in French Guiana [4] and one in Martinique [5], comprising 65 keratitis cases and 3 endophthalmitis cases (Table 1). This contrasts with over 5000

Table 1 Previous *Lasiodiplodia theobromae* ocular infection cases

First author	Country	Year	Type of infection	Treatment	Outcome	Number of patient
Puttanna and al. [3]	India	1967	Keratitis	Medical x2	Perforated x2	2
Laverde and al. [21]	Colombia	1973	Keratitis	Cauterization	« Healed after 20 days »	1
Valenton and al. [22]	Philippines	1975	Keratitis	Medical	LP	1
Rebell and al. [9]	USA (Florida)	1976	Keratitis	Medical x3 PKP x1	VA : 20/30+, 20/25, 20/20, 20/50	4
Liesegang and al. [24]	USA (Florida)	1980	Keratitis	Not available	Not available	5
Dutta and al. [25]	India	1981	Keratitis	Not available	Not available	1
Slomovic and al. [26]	USA (Florida)	1985	Endophthalmitis	-	Enucleation	1
Thomas and al. [27]	India	1991	Keratitis	PKP	Graft clear	1
Gonnawardena and al. [36]	Sri Lanka	1994	Keratitis	Not available	Not available	1
Rosa and al. [28]	Floride	1994	Keratitis	Not available	Not available	2
Dunlop and al. [29]	Bangladesh	1994	Keratitis	Not available	Not available	2
Hagan and al. [30]	Ghana	1995	Keratitis	Not available	Not available	6
Borderie and al. [4]	Guyane française	1997	Endophthalmitis	-	Enucleation	1
Srinivasan and al. [31]	India	1997	Keratitis	Not available	Not available	5
Garg and al. [32]	India	2000	Keratitis	Not available	Not available	3
Gopinathan and al. [33]	India	2002	Keratitis	Not available	Not available	7
Donnio and al. [5]	Martinique	2006	Endophthalmitis	-	Enucleation	1
Thew and al. [34]	Australia	2008	Keratitis	Not available	Not available	2
Saha and al. [10]	India	2012	Keratitis	PKP	Graft failed after 3 months	1
Prajna and al. [35]	India	2013	Keratitis	Not available	Not available	4
Samudio M and al. [1]	Paraguay	2014	Keratitis	PKP	Not available	1
Lekhanont and al. [15]	Thaïlande - Cambodge	2015	Keratitis	Médical (1) PKP (1)	VA 20/200 (1) Counting finger (1)	2
Stephen Tak-lun Li and al. [13]	Hong Kong	2016	Keratitis	PKP	VA 06/30	1
Prajna and al. [19]	India	2016	Keratitis	Not available	Not available	2
Priscila Dallé da Rosa and al. [14]	Brésil	2018	Keratitis	PKP	Hand movements	1
Tangmonkongvoragul and al. [37]	Thaïlande	2021	Keratitis	PKP	Not available	6
Hamerski and al. [11]	USA (North Carolina)	2023	Keratitis	PKP	VA 20/40	1
Konwar and al.[12]	India	2024	Keratitis	Medical (3)	Counting finger (3)	3

LP : Light perception

PKP : Penetrated keratoplasty

references for *Fusarium keratitis* and more than 4000 for *Aspergillus keratitis* [6].

The geographic distribution of these infections mirrors of other fungal germs, being rare in Western countries and more frequent in hot and humid climates (Fig. 4) [3]. In addition, there is a diversity of genera and species of molds that can be involved in ocular infections given the significant fungal biodiversity in tropical countries [7]. This partly explain why it's complicated to have validated therapeutic protocols. Also, most reported cases lack information on patient management and outcomes. Only 30 patient's management details are known, without always specifying the antifungals used, and among them, the final outcomes of 19 patients are known (Table 1).

Excluding endophthalmitis cases, which all resulted in evisceration, 11 out of 27 patients required a corneal transplant. 9 out of 19 recovered with a visual acuity (VA) less than 20/40. 7 out of 19 recovered with a visual acuity

(VA) more than 20/40, and 3 patients lost their eyeball (Table 1). These keratitis cases have a terrible prognosis, comparable to the worst series in the literature for fungal keratitis [8].

Regarding risk factors, we discussed the geographical distribution favoring hot and humid climates. In published observations, keratitis primarily occurs in traumatized eyes with a context of contamination by soil or plants [9–12]. Additionally, diagnostic delays of several months are sometimes evident [11]. There are also notions of prescribing topical corticosteroids by primary care providers [9, 11–15]. It is concerning that topical corticosteroids are sometimes prescribed without the benefit of a thorough slit-lamp examination, a practice that may lead to severe consequences. This highlights the importance of proper training and preventive measures for healthcare providers.

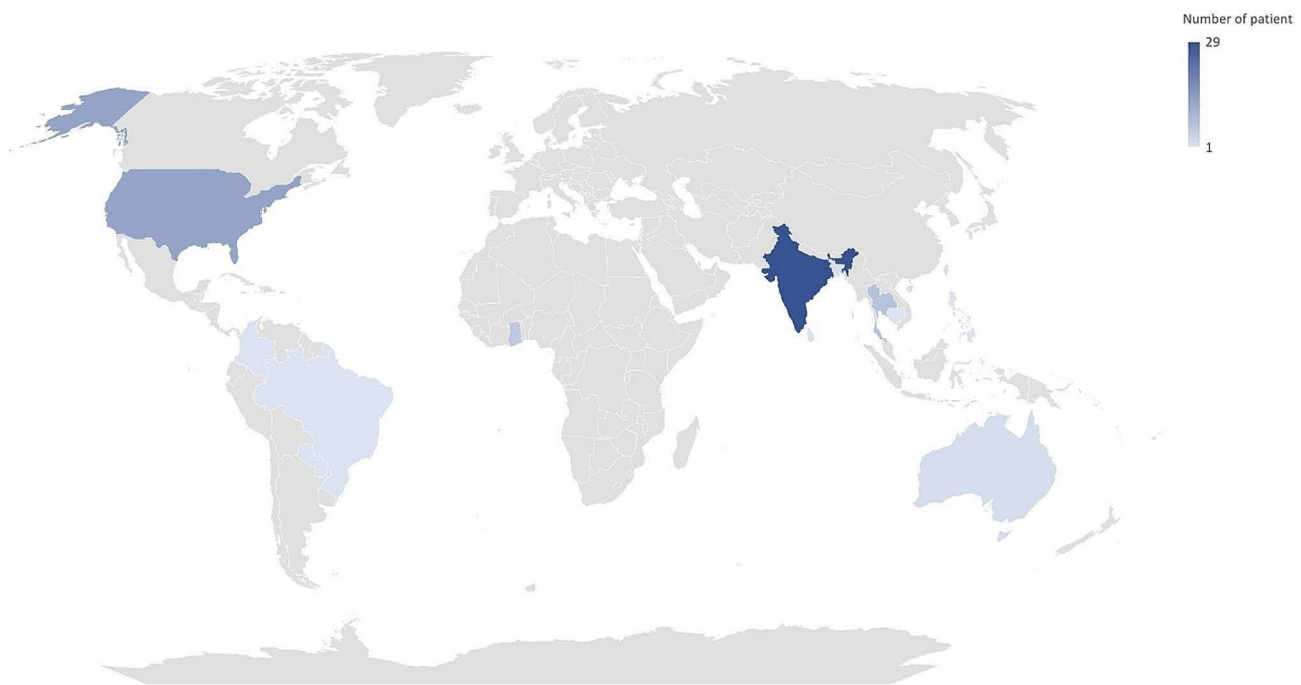


Fig. 4 Map showing reported cases of *L. theobromae* ocular infections

Table 2 Reports of in vitro sensitivity of *Lasiodiplodia theobromae* when involved in keratitis

First author	Sensibility	Resist	Outcome
Rebell and al. [9]	Amphotéricin B		AV : 20/30+, 20/25, 20/20, 20/50
Saha and al. [10]	Amphotéricin B Voriconazole	Itraconazole Fluconazole	PKP rejected at 3 months
Priscila Dallé da Rosa and al. [14]	Amphotéricin B Voriconazole	Itraconazole Fluconazole	Hand movements
Konwar and al.[12]	Amphotéricin B Voriconazole	Itraconazole Fluconazole Posaconazole	Counting finger (3)

Given the rarity of these infections, there is little information on the in vitro sensitivity of this germ. But in these papers the germ was sensitive to amphotericin B and voriconazole but resistant to other azoles (Table 2). It should be noted that, for our case, the sensitivity profile could not be carried out neither in our laboratory nor at the CNRMA of the Pasteur Institute due to the absence of fruiting bodies of the fungus (it is a fungus which does not fruit on the usual culture media) [16].

Details of the medical treatments initiated are available for 13 patients for whom outcome data are available (Table 3). The results in these observations are very disappointing: the success of medical treatment alone was only found in 7 patients [9, 12, 15]. It is observed that all patients who received corticosteroid treatment had to undergo a corneal transplant or lost their eyeball [5, 9, 11, 13]. No treatment combination seems satisfactory. Even

though all patients who received amphotericin B and natamycin without prior corticosteroids did not require surgery, they also had a very short care delay of less than 72 h [9]. A recent study by Konwar et al. documents a series of cases successfully treated with Voriconazole monotherapy, notably without the prior administration of corticosteroids. However, the precise duration between the onset of symptoms and the initiation of treatment was not disclosed [12]. Overall it is observed that patients with delayed care more often resorted to transplantation [11, 14].

So, to our knowledge, this was the first favorable evolution of keratitis with a germ known for poor prognosis with the combination of natamycin and voriconazole, a combination found in most management protocols for fungal keratitis in the literature [17, 18, 23]. All this during rapid management without diagnostic wandering, and no previous administration of corticosteroid. The combination of Natamycin and Voriconazole could be considered a possible treatment for *Lasiodiplodia theobromae* keratitis as it has proven effective in the management of other fungal keratitis [19]. However, more robust studies are needed to support this hypothesis, but they are improbable due to the rarity of the infection.

In this analysis, we omitted a case report of *Lasiodiplodia pseudotheobromae* keratitis, a closely related organism, which had shown significant evolutionary adaptation when treated with a combination of natamycin and voriconazole, initiated one week following the

Table 3 13 patients for whom detailed treatment and final outcome data are available

First author	Year	Steroid	TBT	Treatment	Evolution
Rebell and al. [9]	1976	NO	1 day	Amphotéricin B + Natamycin	20/30+
		NO	3 day	Neomycin, bacitracin polymyxin	20/25
		NO	3 day	Amphotéricin B + Natamycin	20/20
		YES	2 weeks	Natamycine	PKP 20/50
Donnio and al. [5]	2006	YES	« Many days »	Ciprofloxacin, gentamycin, rifamycin Fosfocin and ofloxacin	Enucleation
Saha and al. [10]	2012	NO	1 week	Voriconazole + Ketoconazole	Graft failed after 3 months
Lekhanont and al. [15]	2015	NO	1 week	Amphotéricin B + Natamycin and after Amphotéricin B + Voriconazole	20/200
		NO	« Many weeks »	Amphotéricin B + Voriconazole	PKP and CF
Stephen Tak-lun Li and al. [13]	2016	YES	4 days	Amphotéricin B + Natamycin + Voriconazole	PKP and 06/30
Priscila Dallé da Rosa and al. [14]	2018	YES	2 months	Amphotéricin B + Itraconazole and after Amphotéricin B + Natamycin + Voriconazole after PKP	PKP and SHM
Hamerski and al. [11]	2023	YES	2 months	Amphotéricin B + Natamycin + Kétoconazole	PKP and 20/40
Konwar and al. [12]	2024	NO	-	Voriconazole	Counting finger
		NO	-	Voriconazole	Counting finger
		NO	-	Voriconazole	Counting finger

TBT : Time before treatment

SHM : See hand movements

onset of symptoms without prior exposure to corticosteroid therapy [20].

Conclusion

In summary, although no universally accepted treatment protocol for *Lasiodiplodia theobromae* keratitis exists due to generally poor outcomes and limited in vitro sensitivity data, our case report is one of the few demonstrating a favorable outcome of this infection. We have also conducted the most comprehensive synthesis of all published cases of keratitis caused by this organism. Critically, it seems that the rapid initiation of antifungal therapy—in the absence of prior corticosteroid use—significantly contributed to a favorable outcome. This underscores the importance of early diagnosis and prompt treatment initiation.

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Author contributions

AL : first author, substantial contributions to the conception or design of the work, the acquisition, analysis, and interpretation of data for the work; conception of the work, data acquisition, bibliography analysis, clinical case writing and revisions. Drafting the work or revising it critically for important intellectual content and final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. ND : substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; microbiological data acquisition and analysis. Drafting the work or revising it critically for important intellectual content and final approval of the version to be published. MB : substantial contributions to the

conception or design of the work, the acquisition, analysis, and interpretation of data for the work and revising it critically for important intellectual content and final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. KO : substantial contributions to the conception or design of the work, the acquisition, analysis, and interpretation of data for the work and revising it critically for important intellectual content and final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. HM : substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; help for work design, work supervision. Drafting the work and revising it critically for important intellectual content and final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient. Each author approved the final version of the manuscript and all concur with the submission.

Competing interests

The authors declare that they have no competing interests.

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