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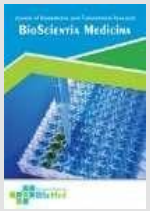

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Successful Management of Culture-Negative Fungal Keratitis with Epithelial Keratectomy and Intracameral Fluconazole Injection: A Case Report

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A B S T R A C T

Background: Fungal keratitis is a major cause of corneal blindness in tropical regions. Microbiological culture often yields negative results in up to 40% of clinically suspected cases, creating diagnostic and therapeutic challenges. This report describes successful management of culture-negative suspected fungal keratitis using epithelial keratectomy combined with intracameral fluconazole injection. **Case presentation:** A 58-year-old male presented with progressive visual loss in the left eye following mud exposure and irrigation with river water. Examination revealed a 3×3 mm paracentral corneal ulcer with stromal infiltration exceeding one-third depth, satellite lesions, and 1.5 mm hypopyon. Gram stain, potassium hydroxide preparation, and culture were all negative. Based on clinical suspicion of fungal etiology, the patient underwent epithelial keratectomy with intracameral fluconazole injection, supplemented by intensive topical and systemic antifungal therapy. Progressive improvement was observed, with complete hypopyon resolution by day 26 and visual acuity improving from 1/300 to 6/30 over four months. **Conclusion:** This case demonstrates that timely invasive antifungal intervention guided by clinical judgment can achieve favorable outcomes in culture-negative suspected fungal keratitis. The preservation of useful vision without corneal transplantation is particularly significant in resource-limited settings, underscoring the critical role of clinical decision-making when laboratory confirmation is unavailable.

1. Introduction

Fungal keratitis constitutes a major yet often underappreciated cause of corneal morbidity and blindness, particularly in tropical and subtropical regions where environmental, climatic, and socioeconomic conditions favor both fungal proliferation and exposure to corneal inoculation.[1,2] In endemic tropical areas of Asia, Africa, and Latin America, fungal organisms account for 5 to 40 percent of all infectious keratitis cases, with substantially higher proportions in agricultural populations with direct soil and plant exposure.[3,4] The warm temperature and high humidity of tropical climates provide ideal conditions for fungal growth and sporulation, while agricultural occupations associated with soil and plant exposure substantially increase the risk of ocular inoculation. Unlike bacterial keratitis, which typically presents with rapid onset and acute symptoms, fungal keratitis frequently exhibits a more indolent clinical course with gradual progression and relatively muted anterior segment inflammation, contributing to diagnostic delays and therapeutic difficulties.[5] The condition represents a significant public health burden in developing nations where it

remains an important yet often preventable cause of visual impairment and blindness.[6,7]

Several major fungal pathogens cause keratitis in tropical regions. Aspergillus species, particularly Aspergillus flavus and Aspergillus fumigatus, account for approximately 20–40 percent of fungal keratitis cases in tropical Asia.[4,5] Fusarium species, representing an increasingly important cause of severe keratitis with poor prognosis, account for 10–20 percent of cases in tropical regions. Candida species, while typically causing disease in immunocompromised patients, can cause keratitis in diabetic or systemically ill patients. Dematiaceous fungi, including Madurella and Phialophora species, cause indolent infections with gradual progression. Each fungal organism has distinct antifungal susceptibility patterns and clinical characteristics that guide optimal treatment selection.[5,6]

The diagnosis of fungal keratitis relies on a combination of clinical suspicion and microbiological confirmation, yet both components present substantial challenges in practical clinical settings.[8,9] Direct microscopy using potassium hydroxide wet mount preparation remains the most commonly employed diagnostic method due to its simplicity, low cost, and rapid turnaround time. However, the diagnostic sensitivity of this technique is disappointingly limited, ranging from 33 to 90 percent depending on multiple factors including fungal burden in the specimen, organism type, specimen processing technique, and observer expertise. Many reported cases with negative initial KOH preparations subsequently confirmed by culture represent failures of this screening method.[5] Fungal culture on appropriate media remains the gold standard for organism isolation and definitive identification, enabling species-level diagnosis and guiding antifungal susceptibility testing. However, culture methodology requires appropriate media selection. The most commonly employed medium is Sabouraud dextrose agar, which favors fungal growth through low pH and dextrose enrichment. Blood agar, particularly enriched blood agar, supports the growth of organisms requiring additional nutritional factors. Brain-heart infusion medium provides the most comprehensive nutrient profile and supports the growth of fastidious organisms. Even with appropriate media, culture frequently yields negative results due to several factors. Inadequate specimen quality or volume from corneal scrapings contributes to false-negative results in up to 15 percent of cases. Overgrowth of contaminating bacteria, particularly when specimens contain environmental organisms from trauma, can suppress or obscure fungal growth. Suboptimal environmental conditions for incubation, including improper temperature maintenance or inadequate humidity, compromise fungal viability.[1,3] Time to fungal culture positivity is notoriously protracted. While bacterial organisms typically show visible growth on culture media within 24 hours, fungal organisms frequently require 48 to 72 hours or even longer to produce sufficient colony growth for identification. This substantial diagnostic delay often forces clinicians to make treatment decisions and initiate therapy before culture results become available. This diagnostic lag creates a major clinical dilemma where treatment decisions must be made based on clinical suspicion rather than definitive laboratory confirmation. Antifungal susceptibility testing is rarely performed on fungal isolates from keratitis cases, limiting knowledge about organism-specific resistance patterns and optimal drug selection for severe infections.[9]

Indonesia presents a particularly challenging epidemiological context for fungal keratitis management. As a tropical island nation with high agricultural populations and a warm, humid climate throughout the year, Indonesia provides ideal environmental conditions for fungal proliferation and corneal exposure. The Indonesian population includes substantial rural and remote communities with very limited access to tertiary eye care services. Patients in rural areas typically must travel considerable distances to reach university hospital ophthalmology departments where specialist expertise and diagnostic capabilities are concentrated. This geographic

disparity results in delayed initial presentations and extended periods of disease progression before patients can access appropriate diagnostic and therapeutic resources. Additionally, self-medication practices are widespread throughout Indonesian society, with easy access to topical antibiotics and corticosteroids without prescription or medical supervision. Patients with presumed infectious keratitis frequently treat themselves with whatever ophthalmic medications are available from local pharmacies, often obtaining inappropriate medications that may exacerbate fungal disease or mask critical clinical signs.[3] The combination of high environmental risk, limited diagnostic resources, geographic barriers to care, and prevalent self-medication practices makes fungal keratitis a particularly significant and challenging clinical problem in Indonesia. Furthermore, knowledge of fungal keratitis among primary health center physicians in Indonesia remains limited, with many not recognizing fungal disease as a diagnostic consideration, instead attributing symptoms to bacterial infection and treating with inappropriate antibacterial agents. Lack of laboratory expertise and diagnostic fungal culture capability at primary health centers compounds diagnostic challenges.

This case report documents the clinical course, diagnostic challenges, and therapeutic approach in a patient with culture-negative suspected fungal keratitis from rural Indonesia. The case illustrates practical clinical decision-making when definitive microbiological confirmation is unavailable and demonstrates that appropriate empiric treatment guided by clinical morphological assessment can achieve favorable outcomes.[8,25] The experiences and insights from this case may provide valuable guidance to clinicians managing similar presentations in resource-limited tropical settings.

2. Case Presentation

Table 1 presents the demographic and clinical characteristics of the patient at initial presentation. A comprehensive summary of baseline parameters is provided to contextualize the severity of this case. A 58-year-old male agricultural laborer from a rural village in Bali presented to the Department of Ophthalmology at our university hospital with a chief complaint of progressive visual loss in the left eye spanning a duration of four weeks prior to his presentation. He provided a detailed history of a specific traumatic event that had occurred approximately four weeks before seeking medical care. During routine work in his rice paddy field, his left eye sustained direct contact with mud-laden vegetation and water. The eye was struck forcefully with vegetation containing soil and organic matter. Immediately following this traumatic event, the patient attempted first aid by irrigating his eye with available water, which unfortunately, was contaminated river water rather than a clean or sterile solution, thereby potentially introducing environmental pathogens into the corneal wound.

Despite the trauma, the patient did not seek immediate medical attention at that time, attempting instead to manage the injury with home care. However, over the subsequent weeks, he noted progressive deterioration in visual function, accompanied by increasing ocular discomfort, foreign body sensation, and photophobia. After approximately four weeks of progressive symptoms and functional decline, he was referred by a local primary health center to our tertiary ophthalmology department for specialist evaluation and management. The patient had no significant past ocular or systemic medical history. He was not diabetic and had no history of immunosuppression. He reported no prior episodes of ocular infection or inflammation. His general health was otherwise good with no evidence of systemic disease.

Table 1. Demographic and clinical characteristics of the patient at initial presentation.

Parameter	Finding
Age/Gender	58 years / Male
Occupation	Agricultural laborer (rice paddy farmer)
Location	Rural village, Bali, Indonesia
Chief complaint	Progressive visual loss, left eye, 4 weeks
Trauma history	Mud/vegetation contact; irrigated with river water
VA (Left eye)	1/300 (counting fingers 1 m)
VA (Right eye)	6/6 (normal)
IOP	16 mmHg (both eyes, normal)
Ulcer size	3 × 3 mm, paracentral
Stromal depth	> 1/3 corneal thickness
Satellite lesions	Present (multiple)
Hypopyon	1.5 mm
KOH preparation	Negative
Gram stain	Negative
Culture (SDA/BA/BHI)	Negative (7-day incubation)
Systemic history	No diabetes, no immunosuppression

VA = visual acuity; IOP = intraocular pressure; KOH = potassium hydroxide; SDA = Sabouraud dextrose agar; BA = blood agar; BHI = brain-heart infusion.

A comprehensive ophthalmological examination was performed by a senior ophthalmologist at our tertiary center, as summarized in Table 1 and illustrated in Figure 1A–B. Distance visual acuity in the affected left eye was markedly reduced to counting fingers at one meter distance (recorded as 1/300 in standard notation), representing substantial visual disability. The right eye was unaffected, with normal corrected visual acuity of 6/6. Intraocular pressure measured by applanation tonometry was normal at 16 millimeters of mercury in both eyes. Slit-lamp biomicroscopy using a slit-lamp examination under magnification revealed findings consistent with infectious keratitis. A paracentral corneal ulcer measuring approximately 3 millimeters by 3 millimeters was identified. The ulcer demonstrated elevated, infiltrated borders with surrounding stromal haze and opacity. Importantly, the depth of stromal involvement was substantial, with infiltration extending to greater than one-third of the total corneal thickness, indicating significant stromal penetration (Figure 1B). Multiple satellite lesions were visible in the cornea surrounding the main ulcer, a characteristic finding suggestive of fungal rather than bacterial keratitis. Fluorescein staining was performed to assess epithelial loss and highlight the ulcer margins. The fluorescein pattern demonstrated irregular, feathered ulcer edges with active epithelial disruption. The characteristic feathering pattern with serpiginous borders and satellite lesions appearing as separate infiltrates around the main ulcer were morphological features highly suggestive of fungal rather than typical bacterial keratitis. The anterior chamber contained a visible inflammatory reaction with fibrin strands, and a 1.5 millimeter hypopyon (layering of white cells) was evident at the inferior anterior chamber. This hypopyon indicated substantial anterior chamber inflammation secondary to the corneal infection. Gonioscopy was not performed. Posterior segment examination by indirect ophthalmoscopy through the dilated pupil was unremarkable with normal optic nerve appearance and intact retinal vasculature, demonstrating no involvement of structures posterior to the lens.

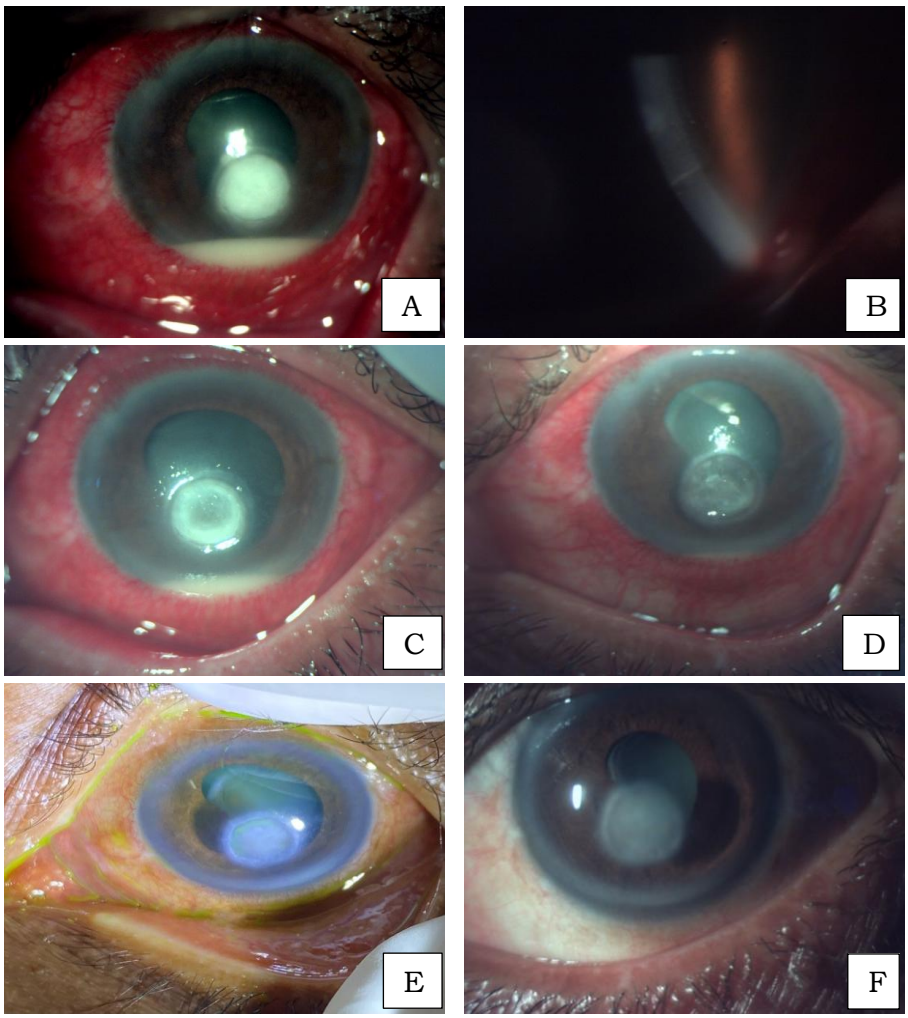

Figure 1. Serial Clinical Photographs Documenting Treatment Response. (A) Initial presentation: paracentral corneal ulcer (3×3 mm) with infiltrated borders, satellite lesions, and 1.5 mm hypopyon under diffuse illumination. (B) Slit-lamp examination at initial presentation demonstrated stromal infiltration depth exceeding one-third corneal thickness. (C) Day 8 post-keratectomy: reduction in infiltrate density and hypopyon height (~1.0 mm), with continued conjunctival injection. (D) Day 21: marked improvement with hypopyon resolution and progressive epithelial healing. (E) Two months: fluorescein staining showing near-complete epithelial closure with residual corneal opacity. (F) Four months: stable corneal leucoma with clear anterior chamber and quiet eye, final VA 6/18.

Microbiological investigations were initiated to determine the etiological agent. Corneal scrapings were carefully obtained from the infiltrated borders of the ulcer using a sterile Kimura platinum spatula under topical anesthesia with proparacaine. Gram staining was performed on the scraped material, which revealed neither gram-positive nor gram-negative bacteria, indicating negative bacterial cultures would be expected. Potassium hydroxide wet mount preparation of the corneal scraping material was also performed using a standard technique, yielding negative results with no fungal elements identified. Cultures were obtained on multiple media to optimize the chances of organism recovery.

Sabouraud dextrose agar plates were inoculated and incubated. Blood agar plates were also inoculated. Brain-heart infusion medium was employed as the most comprehensive nutrient medium. All culture media were incubated at 37 degrees Celsius in appropriate atmospheric conditions with monitoring for fungal growth over an extended seven-day observation period. Despite appropriate sampling technique, appropriate media selection, and adequate incubation time, all microbiological studies yielded negative results. Gram stain was negative for bacteria. Fungal culture on Sabouraud dextrose agar, blood agar, and brain-heart infusion medium all remained negative after seven days of incubation. The negative culture results were surprising given the clinical presentation, and may have reflected inadequate sampling, suboptimal culture conditions, organism characteristics limiting growth on available media, or fastidious organism requirements not provided by the media employed. Despite these negative microbiological results, the clinical presentation was nonetheless highly suggestive of fungal keratitis based on multiple factors. The history of environmental contamination with soil and river water provided epidemiological support for fungal etiology. The characteristic morphological appearance with feathering ulcer borders, satellite lesions, and deep stromal infiltration were findings strongly suggestive of fungal rather than bacterial disease. The failure of the patient to respond clinically to the antibacterial therapy that had been provided at the primary health center further supported fungal etiology.

Given the strong clinical suspicion of fungal keratitis, a multimodal treatment strategy was initiated as detailed in Table 2. Given the strong clinical suspicion of fungal keratitis despite negative microbiological studies, a decision was made to proceed with invasive therapeutic intervention. As outlined in Table 2, the patient underwent epithelial keratectomy (mechanical removal of the corneal epithelium) under topical anesthesia on Day 3, when the initial topical antifungal regimen failed to produce clinical improvement. Topical proparacaine 0.5 percent eye drops were instilled for anesthesia. The entire corneal epithelium overlying the ulcer and surrounding area was carefully mechanically removed using a sterile Kimura spatula, creating a denuded stromal surface. This mechanical epithelial removal served multiple purposes: removal of infected epithelial tissue and surface organisms, elimination of the corneal epithelial diffusion barrier to enhance drug penetration, and direct exposure of infected stromal tissue to therapeutic agents. Following epithelial removal, intracameral fluconazole injection was performed. Fluconazole 5 milligrams dissolved in 0.1 milliliters of preservative-free formulation was slowly injected into the anterior chamber using a 27-gauge needle with strict aseptic surgical technique to minimize contamination risk.[8,10] Following intracameral injection, intensive topical antifungal therapy was immediately initiated. Natamycin 5 percent suspension was instilled four times daily at four-hour intervals. Miconazole 1 percent eye drops were also instilled four times daily. These topical antifungals provided local drug delivery to the corneal surface and infected stromal tissue. Systemic antifungal therapy was initiated concurrently. Fluconazole was prescribed at a dose of 200 milligrams twice daily (400 milligrams total daily) administered orally, providing systemic antifungal coverage and achieving therapeutic levels in ocular tissues. The antifungal agent choice was based on the spectrum of activity against common tropical fungal keratitis pathogens and theoretical good corneal penetration. Topical antibiotic eye drops (ofloxacin 0.3 percent) were continued four times daily to prevent secondary bacterial infection of the denuded corneal surface. Topical lubricating drops were prescribed to be used frequently to promote corneal healing and maintain surface moisture. The patient was instructed to avoid all activities or substances that might irritate the cornea and to maintain careful ocular hygiene throughout the treatment period.

Table 2. Treatment regimen and clinical response timeline.

Time point	Treatment/Intervention	Clinical finding	Visual acuity
Day 0	Natamycin 5% + Moxifloxacin 0.5% QID; Fluconazole 200mg PO BID	3×3mm ulcer, 1.5mm hypopyon, satellite lesions	1/300
Day 3	Epithelial keratectomy + Intracameral fluconazole 5mg/0.1mL; Miconazole 1% QID added	No improvement on topical Rx alone; proceeded to intervention	HM
Day 8	Continued intensive topical + systemic Rx	Hypopyon ≤1.0mm, infiltrate density reduced (Figure 1C)	CF 1m
Day 14	Continued; oral fluconazole maintained	Active re-epithelialization, hypopyon barely visible	3/60
Day 21	Tapering topical Rx frequency	Hypopyon resolved, epithelial healing (Figure 1D)	6/60
Day 26	Oral fluconazole discontinued	Complete epithelial healing, stromal scar forming	6/45
2 Months	Topical lubricants; monitoring	Stable scar, clear AC (Figure 1E)	6/30
3 Months	Observation	Quiet eye, stable corneal leucoma	6/18
4 Months	Observation	Stable scar, no recurrence (Figure 1F)	6/18

QID = four times daily; BID = twice daily; PO = per oral; HM = hand movements; CF = counting fingers; AC = anterior chamber. Visual acuity progression is also illustrated in Figure 2.

Clinical follow-up assessments were performed to monitor treatment response. At postoperative day 7, slit-lamp examination revealed progressive clinical improvement. The hypopyon had decreased in height to approximately 1 millimeter, and the degree of stromal infiltration at the ulcer margins appeared reduced. By postoperative day 14, further improvement was evident. Fluorescein staining revealed that the epithelial defect size had substantially decreased compared to initial presentation, with clear evidence of active epithelial re-epithelialization across the corneal surface. The hypopyon had further decreased and was barely visible. By postoperative day 26, complete resolution of the hypopyon was documented. The corneal ulcer had achieved complete healing of the epithelial defect. However, as expected with substantial stromal disease, stromal opacity and scarring remained at the site of previous ulceration, creating a permanent stromal scar that would limit final visual acuity. No signs of recurrent or progressive disease were evident. Over the ensuing four months of follow-up, visual acuity gradually improved as the patient adapted to the refractive change induced by the corneal scar and inflammation resolved. Final corrected visual acuity stabilized at 6/30 (equivalent to 20/100), representing substantial functional improvement compared to the initial counting fingers vision at presentation. Anterior segment examination at final four-month follow-up demonstrated a well-healed corneal scar with stable appearance, clear anterior chamber, and no signs of infectious recurrence or clinical deterioration. The clinical timeline and visual acuity progression are graphically represented in Figure 2.

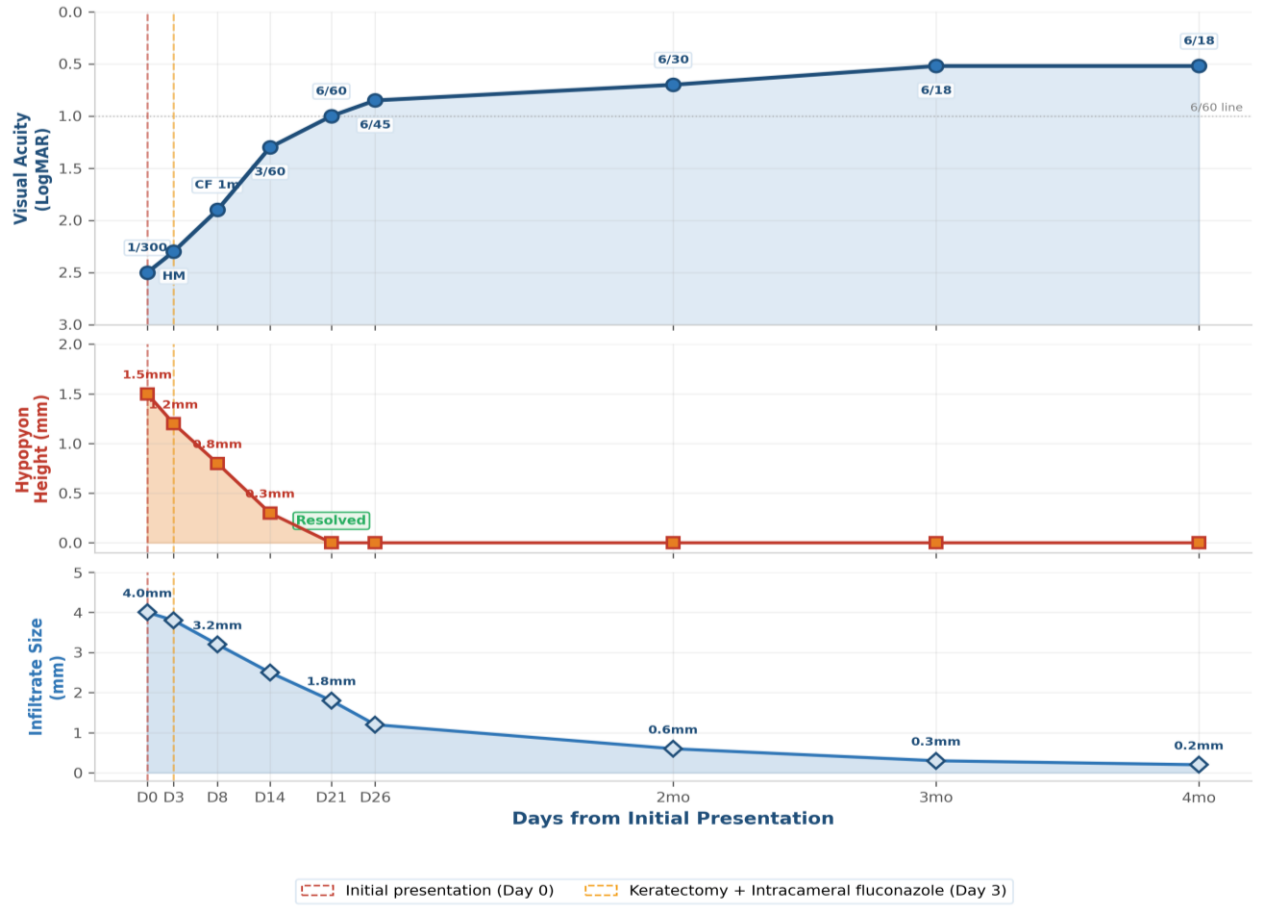

Figure 2. Clinical timeline: Treatment response and visual outcome. Three-panel graph showing: (Top) visual acuity improvement from LogMAR 2.5 (1/300) to 0.52 (6/18) over 4 months; (Middle) hypopyon height reduction from 1.5 mm to complete resolution by Day 21; (Bottom) corneal infiltrate size reduction from 4.0 mm to 0.2 mm residual scar. Red dashed line marks initial presentation (Day 0); gold dashed line marks epithelial keratectomy with intracameral fluconazole injection (Day 3). Data derived from serial clinical examinations as presented in Table 2.

Throughout the treatment period and follow-up, the patient tolerated all therapeutic interventions remarkably well without the development of significant adverse effects or complications from the intracameral injection. No evidence of intracameral injection-related complications such as endothelial cell damage, posterior synechiae, or permanent anterior chamber inflammation was observed. No infectious recurrence occurred during the follow-up period. The anterior chamber remained clear and non-inflamed. Posterior segment examination by indirect ophthalmoscopy remained unremarkable with normal optic disc appearance and intact retinal vasculature. The case represents a successful outcome of aggressive antifungal therapy in a patient with culture-negative suspected fungal keratitis in a resource-limited setting, with good clinical response and preservation of useful vision.

3. Discussion

This case presentation illustrates the substantial diagnostic and therapeutic challenges encountered in managing suspected fungal keratitis when microbiological confirmation through conventional

methods is unavailable or negative.[1,2] The clinical presentation in this patient was highly suggestive of fungal etiology based on multiple factors: epidemiological risk factors from agricultural exposure to soil and water, distinctive morphological characteristics of the corneal ulcer including feathered borders and satellite lesions, characteristic stromal infiltration pattern, and documented failure of response to initial antibacterial therapy. Yet definitive microbiological confirmation through standard culture methods could not be established, creating diagnostic uncertainty and forcing clinicians to make therapeutic decisions based on clinical impression rather than definitive laboratory confirmation. The successful clinical outcome achieved through timely and aggressive empiric antifungal intervention demonstrates that appropriate clinical judgment combined with treatment of the most likely diagnosis based on morphological assessment can result in favorable functional and anatomical outcomes even in the absence of definitive laboratory confirmation. This successful outcome validates the clinical approach of treating culture-negative suspected fungal keratitis when the clinical presentation is highly suggestive of fungal disease.[7-9]

Diagnostic accuracy in fungal keratitis is significantly complicated by the relatively poor sensitivity and specificity of standard diagnostic methods available in most clinical settings, particularly in resource-limited tropical regions.[5,10] Direct microscopy using potassium hydroxide preparation, while rapid and inexpensive, detects fungi in only 33 to 90 percent of fungal keratitis cases depending on organism type, specimen quality, fungal load, and examiner expertise.[3] Fungal culture, despite being the gold standard for definitive diagnosis and organism identification, is limited by slow growth kinetics requiring 48 to 72 hours or longer for visible growth, a requirement for specialized growth media, and susceptibility to suppression by contaminating bacteria.[11-13] In this particular case, the combination of culture-negative results with a highly characteristic clinical presentation of fungal keratitis appropriately led to empiric treatment of presumed fungal disease. This clinical approach, while not ideal from a microbiological standpoint, represents appropriate clinical decision-making when diagnostic methods fail and the disease appears to threaten vision.

In vivo confocal microscopy (IVCM) represents an emerging diagnostic technology with significant potential for improving fungal keratitis diagnosis, offering real-time high-magnification visualization of corneal cellular architecture and causative microorganisms at cellular resolution.[14-16] IVCM provides optical sections of corneal tissue at cellular resolution, allowing detailed assessment of morphology and identification of organisms based on characteristic appearance. Published studies demonstrate diagnostic sensitivity of 66 to 85 percent for detecting fungal organisms in cases of fungal keratitis, with good specificity for differentiating fungal from bacterial infections based on characteristic organism morphology and hyphal patterns. In vivo confocal microscopy offers the advantage of non-invasive assessment without requiring additional corneal sampling, providing rapid results within minutes, and enabling therapeutic monitoring during treatment. However, IVCM remains limited by high equipment cost exceeding $100,000 USD, significant maintenance requirements and ongoing expenses, lack of availability in most resource-limited settings, and substantial operator-dependent variability in image acquisition and interpretation. Expertise in image interpretation and fungal morphology recognition requires considerable training and clinical experience, not widely available. In most ophthalmology departments in developing nations including Indonesia, in vivo confocal microscopy remains unavailable due to cost and infrastructure constraints, limiting its practical clinical utility for most practitioners in resource-limited settings.[17]

Polymerase chain reaction-based molecular diagnostics have demonstrated considerable promise for rapid identification of fungal pathogens and assessment of antifungal susceptibility in cases of suspected fungal keratitis.[18] PCR employs

amplification of fungal DNA or ribosomal RNA to detect organisms present in clinical specimens, theoretically providing detection sensitivity approaching 100 percent with high specificity. PCR can provide results within hours compared to days or weeks required for traditional culture, and offers improved sensitivity for fastidious organisms or organisms with slow growth kinetics. Quantitative PCR may enable assessment of organism burden and treatment response monitoring. However, PCR-based diagnostics remain primarily research tools at present, not integrated into routine clinical practice, and are not widely available in resource-limited settings. Implementation of PCR requires access to molecular biology laboratory infrastructure including thermal cyclers and specialized equipment, trained molecular biology personnel, and significant financial investment. In Indonesia and most developing nations, PCR-based diagnosis is not accessible to most practicing ophthalmologists and remains unsuitable for routine clinical decision-making in most settings. Future development of simplified, less expensive point-of-care PCR methods might improve accessibility, but such tools are not yet available for clinical use.[18]

Anterior segment optical coherence tomography (AS-OCT) has emerged as a useful imaging tool for evaluation of corneal architecture and disease progression in infectious keratitis.[13] AS-OCT provides non-invasive cross-sectional imaging of corneal anatomy and enables precise measurement of ulcer depth, assessment of stromal involvement extent, and documentation of architectural changes during healing and scarring. While AS-OCT can substantially aid clinical assessment and longitudinal documentation of disease progression, it does not provide pathogenic organism identification and cannot reliably differentiate fungal from bacterial keratitis based on imaging characteristics alone. AS-OCT may prove helpful for monitoring treatment response and documenting morphological changes during corneal healing, but remains unavailable in many resource-limited settings and should not be considered a replacement for clinical examination and microbiological investigation when diagnostic methods are available. AS-OCT may become increasingly important for documenting treatment response and guiding duration of therapy in future fungal keratitis management protocols.

Epithelial keratectomy, defined as mechanical removal of the corneal epithelium using manual techniques with spatulas, successfully addresses multiple therapeutic objectives in fungal keratitis management.[15] First, epithelial keratectomy accomplishes mechanical removal of infected epithelial tissue, necrotic material, and surface organisms residing within or on the corneal epithelium, reducing the microbial load and removing infected tissue. Second, mechanical epithelial removal eliminates the corneal epithelial barrier, which normally represents a significant diffusion barrier to topical medications, substantially enhancing penetration of topically applied antifungal agents into the underlying stromal tissue. This enhanced drug penetration is particularly important for fungi residing in deep stromal tissue. Third, epithelial keratectomy exposes the underlying stromal tissue to direct contact with antifungal therapeutic agents applied topically, maximizing local drug concentration at the site of infection. The corneal epithelium functions as a highly selective permeable barrier that restricts the passage of many medications, and its removal dramatically improves drug penetration and corneal bioavailability. This approach has been previously reported in fungal keratitis management with variable results depending on disease severity, fungal organism type, and concurrently employed therapeutic agents. As performed in this patient (Table 2, Day 3), epithelial keratectomy is a simple procedure that requires no special equipment and is accessible in all resource-limited settings where basic ophthalmic instruments are available. The dramatic clinical improvement observed after the intervention (Figure 1C–D, Figure 2) supports its role as a key therapeutic component.

Intracameral antifungal injection represents a potentially aggressive but sometimes justified

therapeutic approach for advanced fungal keratitis with substantial stromal involvement and significant anterior chamber inflammation.[19] While intracameral injection of medications carries inherent risks, including endothelial cell toxicity with potential permanent corneal decompensation, permanent corneal and lens opacification, exacerbation of intraocular inflammation, and other serious complications, this approach may be appropriately employed in carefully selected cases with impending corneal perforation or very deep stromal involvement where conventional topical pharmacological therapy is likely to be insufficient to prevent irreversible vision loss. The intracameral route achieves exceptionally high intraocular concentrations of antifungal medications that substantially exceed levels achievable by topical application alone, and these high concentrations may penetrate infected stromal tissue more effectively than topical agents alone. Fluconazole, the antifungal agent employed in this patient, possesses relatively good penetration into corneal tissue and aqueous humor due to its lipophilic chemical properties and moderate molecular weight, making it suitable for intraocular use with an acceptable safety profile.[20-22] Published case reports and small case series describe the successful use of intracameral amphotericin B, voriconazole, and fluconazole in cases of fungal keratitis with severe stromal involvement. Optimal dosing strategies for intracameral antifungal agents remain inadequately defined in the literature due to the relative rarity of this severe disease and limited case experience. Long-term safety and complication rates of intracameral antifungal injections remain incompletely characterized.[14,21] In our patient, the absence of intracameral injection-related complications is encouraging and consistent with prior reports of acceptable safety profiles when appropriate dosing is employed.

Table 3 provides a comparative analysis of our case with previously reported cases involving intracameral antifungal therapy for severe fungal keratitis, contextualizing our findings within the broader literature.

Table 3. Comparison with selected published cases of intracameral antifungal therapy for severe fungal keratitis.

Study	Agent	Organism	Intervention	Final VA	Outcome
Yilmaz et al. (2007)	Ampho B IC	Mixed fungi	IC amphotericin B + topical	Variable	Resolved in 60% of cases
Gounder & Thool (2022)	Voriconazole IC	Aspergillus	IC voriconazole + topical natamycin	6/36	Healed without keratoplasty
Holland & Lee (2015)	Voriconazole	Paecilomyces	Medical Rx with topical + systemic voriconazole	6/12	Complete resolution
Prajna et al. (2010)	Natamycin	Mixed (RCT)	Natamycin 5% vs voriconazole 1% topical	Variable	Natamycin superior for Fusarium
Present case	Fluconazole IC	Culture-neg (suspected fungal)	Keratectomy + IC fluconazole + topical + systemic	6/18	Complete healing, no keratoplasty

Notes: IC = intracameral; Ampho B = amphotericin B; VA = visual acuity; RCT = randomized controlled trial; Rx = treatment. References: Yilmaz et al.[14], Gounder & Thool[21], Holland & Lee[25], Prajna et al.[10].

As demonstrated in Table 3, the present case achieved a favorable visual outcome (6/18) comparable to or better than several published reports, despite the additional challenge of culture-negative diagnosis.[10,14,21] The combination approach of epithelial keratectomy with intracameral fluconazole injection, supplemented by intensive topical and systemic antifungal therapy, appears to have synergistic benefit. The visual acuity trajectory shown in Figure 2 demonstrates sustained improvement over the four-month follow-up period, with the most rapid gains occurring in the first three weeks following intervention.

This case report is limited by several factors inherent to single-case documentation. The diagnosis of fungal keratitis remains presumptive and based on clinical suspicion rather than definitive microbiological confirmation through organism isolation and identification. The absence of in vivo confocal microscopy or molecular diagnostics, such as polymerase chain reaction, precluded definitive identification of the causative fungal organism, limiting detailed discussion of organism-specific antifungal susceptibility patterns and optimization of treatment strategies based on organism characteristics. Organism identification would have been valuable for guiding optimal antifungal selection and predicting treatment response. The retrospective nature of this case report precludes detailed documentation of sequential presentation photographs or advanced imaging that would enhance clinical documentation and enable precise morphological comparison. The four-month follow-up period, while demonstrating encouraging short-term outcomes, may be inadequate for detecting potential long-term disease recurrence, progressive stromal scarring, late-onset endophthalmitis, or subtle posterior segment involvement. A longer follow-up would be valuable for confirming treatment durability. These limitations reflect the practical constraints of clinical practice in resource-limited settings where comprehensive diagnostic modalities and long-term research follow-up infrastructure are unavailable.[23,24]

However, this case possesses several significant strengths and noteworthy contributions to clinical knowledge. It demonstrates detailed clinical documentation of the entire disease course from initial presentation through successful healing and functional improvement. The patient clearly benefited from an aggressive therapeutic approach specifically adapted to the clinical context and available resources in a resource-limited tropical setting, including the pragmatic clinical decision to treat presumed fungal keratitis without definitive microbiological confirmation when standard diagnostic methods yielded negative results. The successful outcome, with preservation of useful functional vision and complete clinical healing without corneal perforation or need for corneal transplantation, is noteworthy and encouraging in the context of such a severe initial presentation with substantial stromal involvement. The case illustrates successful conservative medical management enabling avoidance of keratoplasty despite initial substantial stromal infiltration, a particularly relevant and encouraging message for resource-limited settings where corneal transplantation may be unavailable, technically unavailable, or financially inaccessible to patients. The detailed documentation of clinical reasoning and the decision-making process provides practical guidance for ophthalmologists managing similar presentations in resource-limited tropical environments. This case reinforces that aggressive empiric antifungal therapy is justified in culture-negative cases with convincing clinical evidence of fungal disease.[19,20]

This case reinforces the important clinical principle that empiric antifungal treatment remains appropriate and justified when clinical presentation strongly suggests fungal keratitis, even when definitive microbiological confirmation is unavailable, provided that treatment is initiated promptly with careful clinical monitoring for therapeutic response and potential adverse effects from intracameral injection.

Understanding the pathophysiology of fungal keratitis is essential for rational therapeutic decision-

making and interpretation of clinical findings. Fungal organisms, predominantly filamentous forms including Fusarium and Aspergillus species, invade the corneal stroma following breach of the epithelial barrier. Fungal hyphae are highly motile and invasive, actively growing through corneal stromal tissue and causing direct mechanical damage through their penetrating growth. In addition to direct mechanical injury from hyphal invasion, fungal organisms produce and secrete numerous virulence factors including proteolytic enzymes, collagenases, and other tissue-destructive substances that degrade corneal collagen matrix and further weaken corneal structural integrity. These proteolytic enzymes cause collagen degradation and progressive corneal melting, leading to progressive corneal thinning, deepening corneal ulceration, and eventually corneal perforation if left untreated. The extent of enzymatic tissue destruction is often disproportionate to visible morphological changes on clinical examination, meaning substantial stromal invasion and collagen degradation may be occurring beneath areas of apparently intact corneal surface.[24,25]

The host immune response to fungal infection is a complex interplay of innate and adaptive immune mechanisms. Initial recognition of fungal pathogens occurs through pattern recognition receptors on corneal epithelial cells and innate immune cells, including macrophages and dendritic cells. Fungal antigens activate Toll-like receptors and other innate immune recognition mechanisms, triggering production of pro-inflammatory cytokines including TNF-alpha, IL-1, IL-6, and IL-8. These inflammatory mediators recruit leukocytes to the site of infection. The resulting anterior chamber reaction and hypopyon formation, while indicative of active immune response, also contribute to anterior chamber inflammation and pain. Th17 cell-mediated immune responses promote antifungal immunity through production of IL-17 and recruitment of neutrophils and other effector cells. However, excessive inflammatory response can exacerbate corneal tissue damage through the release of destructive proteolytic enzymes from activated immune cells. The balance between antifungal immune response sufficient to control infection and inflammatory response that causes excessive collateral tissue damage is delicate, and therapeutic strategies should aim to support beneficial immune responses while minimizing destructive inflammation. In our patient, the progressive hypopyon resolution documented in Table 2 and Figure 2 (middle panel) indicates successful control of both infection and inflammation following intervention.[4]

This case report adds to the limited but growing literature documenting successful medical management of fungal keratitis without keratoplasty in resource-limited settings. The combination of epithelial keratectomy with intracameral fluconazole injection represents a rarely reported approach with favorable outcomes, particularly when conducted in conjunction with intensive topical and systemic antifungal therapy. The case demonstrates that culture-negative fungal keratitis can be successfully managed based on clinical morphological assessment when definitive microbiological confirmation is unavailable. The patient's outcome was favorably influenced by several factors: timely recognition of fungal disease etiology despite culture negativity based on clinical suspicion and morphological assessment, prompt initiation of aggressive antifungal therapy without waiting for culture confirmation, selection of appropriate antifungal agents with activity against likely tropical pathogens, intensive multimodal antifungal therapy combining topical, systemic, and intracameral routes to maximize drug delivery to infected tissue, careful clinical monitoring for treatment response and complications, and prolonged follow-up to document healing and ensure absence of recurrence. These factors collectively contributed to successful outcomes and the achievement of useful functional vision.[19,20,8,10]

Previous case reports demonstrate variable outcomes with intracameral antifungal injection, ranging from excellent results with complete healing and good vision to cases requiring keratoplasty for

infection control or corneal structural support. Variation in outcomes likely reflects differences in disease severity at presentation, fungal organism involved, patient immune status, compliance with medical therapy, duration and intensity of antifungal treatment, and timing of therapeutic intervention. Earlier intervention and more intensive therapy appear to be associated with more favorable outcomes. This case demonstrates encouraging results with relatively conservative intracameral therapy (fluconazole) combined with mechanical epithelial debridement and intensive topical/systemic antifungals. The favorable outcome suggests this approach deserves consideration in resource-limited settings where advanced diagnostic modalities and surgical expertise may be limited.[14,22,25]

4. Conclusion

This case demonstrates that timely invasive antifungal intervention guided by sound clinical judgment and careful morphological assessment of corneal characteristics can achieve favorable functional and anatomical outcomes in culture-negative suspected fungal keratitis. In the absence of definitive microbiological confirmation, clinical presentation characteristics, including a well-documented history of agricultural or environmental trauma, distinctive ulcer morphology with characteristic features, presence of satellite lesions, and pattern of stromal infiltration, serve as essential diagnostic criteria that appropriately justify empiric antifungal therapy. The successful preservation of useful functional vision through medical management without the need for corneal transplantation underscores the significant value of aggressive early treatment in resource-limited settings where surgical rehabilitation options are constrained and transplantation is often unavailable. This case highlights the critical importance of maintaining appropriate clinical suspicion for fungal keratitis in tropical regions and demonstrates that favorable therapeutic success can be achieved through appropriately selected empiric treatment when definitive laboratory confirmation is unavailable or negative.

Future research priorities should focus on developing and improving diagnostic methodologies accessible to resource-limited settings, including point-of-care diagnostic platforms requiring minimal infrastructure, simplified molecular testing approaches, and rapid culture techniques that provide results within 24 to 48 hours. Additionally, well-designed controlled clinical trials comparing different therapeutic approaches for fungal keratitis in tropical developing settings would provide much-needed evidence to guide optimal treatment strategies and substantially improve outcomes for patients in resource-limited regions. Development of antifungal susceptibility testing protocols suitable for use in developing nations would enable organism-directed therapy selection and improve treatment outcomes.

5. References

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