

Clinical Characteristics and Treatment Outcomes of Fungal Endophthalmitis Caused by *Neoscytalidium dimidiatum*

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Abstract: *Neoscytalidium dimidiatum* (*N. dimidiatum*) is a common fungal pathogen that primarily affects plants but can also cause rare infections in humans. In recent years, sporadic cases have been reported worldwide. Here, we report the first case of endophthalmitis in China resulting from a corneal scratch caused by an infected dragon fruit. Exogenous fungal endophthalmitis can be classified into three categories: postoperative, post-traumatic, and keratitis-associated. Currently, there is no standardized antifungal regimen for *N. dimidiatum* infections, especially for endophthalmitis, where systemic antibiotics have poor intraocular penetration. Successful management often requires surgical interventions such as amputation or drainage. Our case highlights the diagnostic and therapeutic challenges, as well as the poor outcomes associated with *N. dimidiatum* infections in humans.

Keywords: *Neoscytalidium dimidiatum*, infection, endophthalmitis, characteristics, treatment

Introduction

In recent years, advancements in diagnostic technologies have significantly improved the detection of plant fungal pathogens in human infections. However, cases of human endophthalmitis caused by direct exposure to *Neoscytalidium dimidiatum* (*N. dimidiatum*)-infected plants remain rarely reported. Endophthalmitis is a severe intraocular infection that can result in permanent vision loss. Most cases are exogenous in origin, typically occurring as complications of cataract surgery, intravitreal injections, or penetrating ocular trauma.^{1,2} *N. dimidiatum*, a dematiaceous fungus belonging to the phylum Ascomycota, is capable of infecting both plants and humans. As a phytopathogen, it can cause ulcerative diseases and dieback in plants.^{3–5} This fungus is predominantly found in tropical and subtropical regions. While scattered cases of human *N. dimidiatum* infections have been reported worldwide, with the highest incidence in Thailand,^{6,7} no cases have been documented in China to date. Here, we present a case of *N. dimidiatum*-induced fungal keratitis that progressed to endophthalmitis, ultimately requiring enucleation.

Materials and Methods

Microbiological Tests

On the second day of the patient's admission to the hospital, a specimen of atrial fluid pus from the anterior atrial lavage was taken under aseptic conditions for general bacterial/fungal culture and fungal fluorescence staining. On the same day,

the report of fungal fluorescence staining was “Occasional fungal spores and hyphae”. After 3 days of culture, no bacterial growth was seen on the blood plate. White woolly filamentous fungi were observed spreading in all directions on the SDA plate. In addition, the isolated pure strain was inoculated again and cultured for 2, 5, and 7 days. Its morphological changes were compared to the results of the sample (Figure 1A). It is worth noting that lactate phenol cotton blue staining shows a large amount of oval chain arthritis, with bamboo joint arthritis and double leaf cell arthritis being more typical (Figure 1B). Time-of-flight mass spectrometry (MALDI-TOF) results identified *Neoscytalidium hyalinum*, also known as *N. dimidiatum*.

Sanger Sequencing

Fungal specimens were taken for genome extraction, PCR amplification, and sequencing. The internal transcribed spacer (ITS) and partial sequence of the large subunit (LSU) genomic regions were amplified using the following primers: ITS1-F, 5'-CGGCCGATCCTCCACCCTT-3', ITS1-R, 5'-GCTTATTGATATGCTTAAGTTCA-3', LSU-F, 5'-CAACAGG GATTGCCTCAGTAACG-3', LSU-R, 5'-GTTCACTTTCATTACGCGCATGGG-3'. The sequencing results were searched on the National Center for Biotechnology Information website (<https://blast.ncbi.nlm.nih.gov/Blast.cgi>), and the results identified the fungus as *Neoscytalidium hyalinum*.

Drug Sensitivity Testing

The microbiology laboratory used the standard broth microdilution M38-A2 method developed by the Clinical and Laboratory Standards Institute (CLSI) to test the susceptibility of *N. dimidiatum* clinical isolates to different antifungal drugs.

Results

Index Patient

The patient is a 55-year-old woman from Yulin, Guangxi Province, residing in Gaozhou City, Guangdong Province. Six months ago, her eyes were scratched by a dragon fruit branch, leading to symptoms such as eye redness, eye pain, and vision loss. Dragon fruit exhibits typical fungal infections (Figure 1C). At the time of admission, the patient was diagnosed with type II diabetes mellitus, with no hypertension, tumors, or other diseases, and had no history of surgery.

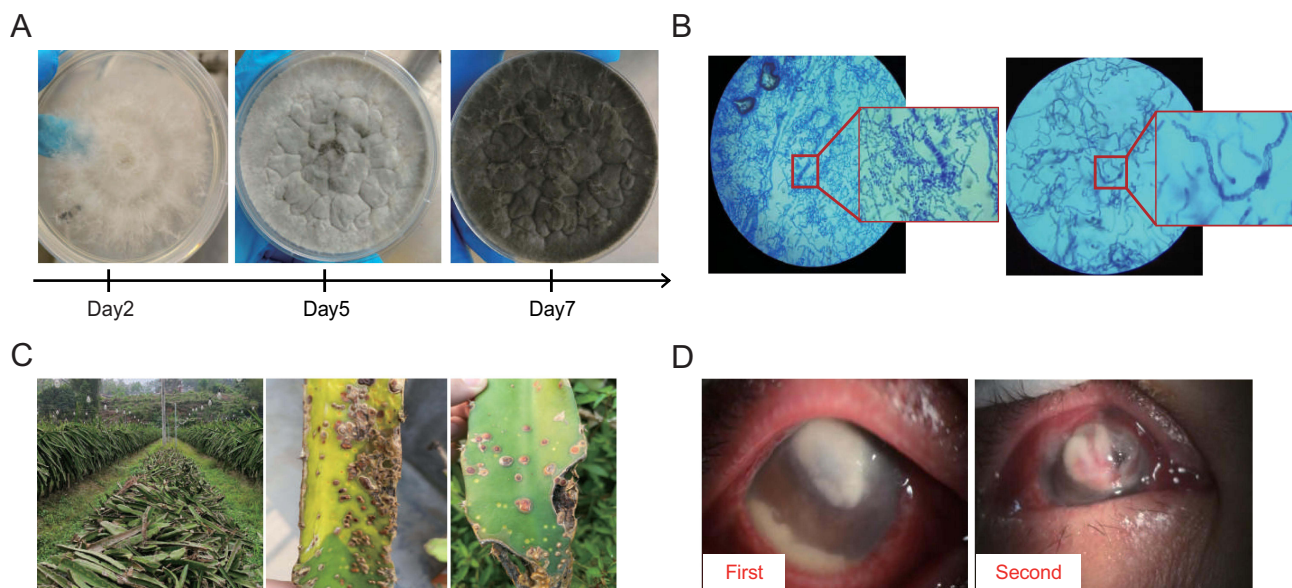


Figure 1 The morphology and infection caused by *N. dimidiatum*. (A) Fungal morphology of single colonies selected from patients' aqueous humor pus specimens and inoculated onto SDA agar plates for cultivation at 2, 5, and 7 days. (B) Lactic acid phenol cotton blue staining results of *N. dimidiatum* pure bacterial colonies. (C) The symptoms of dragon fruit infected with *N. dimidiatum* were found at a dragon fruit plantation near the patient's home. (D) The eye condition of the patient at the first and second admission.

Specialized examination showed inaccurate visual light localization in the right eye and high intraocular pressure of 32 mmHg in the right eye. There was mild redness of the right eyelid, mixed intraocular congestion (++), edema (++), brownish-black staphylococcal tissue vaguely translucent in the conjunctiva at the corneal rim above the nose, flaky grayish-white infiltrative foci visible in the cornea superiorly to the nose, measuring approximately 6×4 mm, localized corneal thinning, FL (+), corneal stromal edema +, posterior elastic lamina propria folds ++, anterior chamber below at approximately 1 CT, peripheral anterior chamber at <1/4 CT, clouding of the atrial aqueous. Anterior chamber pus was visible inferiorly temporally at a height of about 3 mm, and suspiciously thick deposits in the anterior chamber following corneal ulceration above the nose (Figure 1D). There was no abnormality in the left eye.

The patient's specimen culture and sequencing results both showed infection with the fungus *N. dimidiatum*, and no evidence of bacterial infection was observed. Based on the results of the pathogenicity test, the patient underwent anterior irrigation of the right eye, anterior chamber injection (voriconazole), and vitreous cavity injection (voriconazole). The antimicrobial drug voriconazole powder injection was used at a dosage of 100µg. After surgery, the patient's condition was stabilized. This was followed by open surgery, ophthalmic antibiotic hormone drops, and epidermal growth factor drops to promote recovery. Additionally, topical and oral voriconazole were prescribed to control the infection. Twelve days later, the patient's right eye infection worsened. A specialist examination revealed a 1.5 mm corneal perforation in the center of a grayish-white infiltrating focus in the right cornea, with outflow of anterior chamber contents. The patient's ocular infection was not well controlled, leading to the corneal perforation. Consequently, the surgeon performed an eye enucleation and conjunctival capsulorhexis with minimal intraoperative bleeding. Ocular contents obtained during the surgery were sent to the laboratory for pathogenic culture. White woolly mycelial growth was detected on SDA plates, identified by spectrophotometry, and supplemented with sensitivity testing of filamentous fungi using the microbroth dilution method. The patient recovered well from the surgery without recurrence.

During the diagnosis and treatment process, we also had concerns about *N. dimidiatum* and performed drug sensitivity testing, and the results are shown in [Supplementary Table 1](#). This result is only used to compare the minimum effective concentration (MEC) values of various drugs, as CLSI does not provide a referenceable fold value. It is evident that *N. dimidiatum* exhibits the lowest MEC value for itraconazole. However, factors such as the drug's concentration at the site, side effects, etc, must still be considered in the practical use of antifungal therapy.

Discussion

Infectious keratitis is a major global cause of visual impairment and blindness.⁸ This condition is primarily attributed to filamentous fungi belonging to the genera *Aspergillus*, *Fusarium*, and *Alternaria*, in addition to less prevalent yeast-type fungi, yeast-like fungi, and dimorphic fungi.⁹ The occurrence of fungal keratitis is frequently linked to a history of corneal trauma resulting from plant material, as well as prolonged use of corticosteroids and antibiotics. Notably, farmers constitute the majority of patients affected by fungal keratitis, accounting for 59.5% of reported cases.¹⁰

The pathogenic fungus implicated in this case is *N. dimidiatum*, a rare dark-colored fungus associated with fungal keratitis. The colony exhibits rapid growth, characterized by a wool-like appearance with sparse aerial hyphae, and can completely occupy the culture plate within three days. Initially, the surface of the fungus is colorless, gradually transitioning to white, then gray, and ultimately to a dark black hue. Under microscopic examination, *N. dimidiatum* is observed to be arranged in a chain-like formation, featuring a significant number of rectangular or cylindrical joint spores, as well as typical bamboo-like or double-celled joint spores.¹¹

The types of non-ocular diseases caused by *N. dimidiatum* infection include brain abscess, lung infection, sinusitis, foot eczema, and cellulitis.^{12–15} Patients with exogenous fungal endophthalmitis or keratitis caused by *N. dimidiatum* often have a poor prognosis. A 30-year-old Brazilian male developed a postoperative infection after undergoing left-eye corneal transplantation. Molecular analysis confirmed *Fusarium veterinarium* as the causative agent. The patient received amphotericin B therapy followed by therapeutic corneal transplantation.¹⁶ A 67-year-old male patient in Mexico presented with an ocular infection secondary to plant-related trauma. Phylogenetic analysis revealed *Neoscytalidium spp.* as the pathogenic fungus. Despite treatment with amphotericin B, natamycin, and voriconazole, his condition showed no clinical improvement. He subsequently underwent open-sky vitrectomy combined with posterior sclerotomy, retinal transplantation, and lensectomy.¹⁷ In a clinical study, 20 patients developed postoperative intraocular inflammation following cataract surgery,

with 12 cases confirmed as infections caused by *Fusarium oxysporum*. Voriconazole therapy produced suboptimal outcomes, as patients demonstrated progressive visual deterioration. A subset of these patients ultimately required enucleation.¹⁸

The drug sensitivity testing of *N. dimidiatum* isolates presented in this study indicated that itraconazole exhibited the lowest minimum effective concentration (MEC) value, while voriconazole and posaconazole also demonstrated comparatively lower MEC values. A variety of pharmacological regimens have been documented for the treatment of *N. dimidiatum* infections, including itraconazole, voriconazole, amphotericin B, natamycin, terbinafine, posaconazole, and other systemic antifungal agents or local combined systemic therapies.^{5,19} According to a review of the literature, an effective antifungal treatment regimen for *N. dimidiatum* has yet to be established. Although there have been instances of successful treatment, there is insufficient evidence regarding the distribution of itraconazole in ocular tissues, particularly in regions that are challenging for antibiotics to penetrate, such as in cases of endophthalmitis. Consequently, it is imperative to evaluate the therapeutic outcomes following antifungal treatment and to contemplate surgical intervention if deemed necessary.

Data Sharing Statement

All data generated or analyzed in this study are included in this published article.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Zhujiang Hospital, Southern Medical University. Case details may be published without additional hospital approval. Upon admission, the patient provided electronic informed consent, authorizing the use of their medical history and disease-related information for educational and research purposes, including public publication of anonymized case data.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no competing interests in this work.

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