

Fatal Invasive Pulmonary Aspergillosis Caused by *Aspergillus texensis*: First Documented Human Infection

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Case Report

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Abstract

Background

Invasive Aspergillosis (IA) is a life-threatening infection in immunocompromised patients. Although *Aspergillus fumigatus* predominates, rare and cryptic species are increasingly recognized due to advances in molecular diagnostics.

Case Presentation:

We report a fatal case of invasive pulmonary aspergillosis caused by *Aspergillus texensis* in a 39-year-old woman with classical Hodgkin lymphoma complicated by hemophagocytic lymphohistiocytosis (HLH). She developed persistent fever, pancytopenia, progressive respiratory failure, and septic shock despite broad-spectrum antibacterial therapy. Bronchoalveolar lavage (BAL) microscopy demonstrated septate hyaline hyphae. Culture yielded yellow-green colonies, and calmodulin sequencing showed > 99% identity with *A. texensis* (GenBank: PX734618). Antifungal susceptibility testing (CLSI M38-A3) revealed elevated MICs for amphotericin B (16 µg/mL) and itraconazole (8 µg/mL), intrinsic resistance to fluconazole, and lower MICs for voriconazole, posaconazole, and isavuconazole. Despite antifungal therapy, the patient died of multiorgan failure.

Conclusion

This appears to be the first documented human infection due to *A. texensis*. The case highlights the expanding spectrum of pathogenic *Aspergillus* species and underscores the importance of molecular identification and antifungal susceptibility testing in high-risk patients.

Introduction

Invasive aspergillosis (IA) remains a major cause of morbidity and mortality in patients with hematologic malignancies, prolonged neutropenia, and severe immune dysregulation (1–3). Although *Aspergillus fumigatus* accounts for most cases, molecular diagnostic advances have revealed an expanding diversity of non-fumigatus and cryptic species implicated in human disease(4, 5).

Species within section Flavi are of particular clinical relevance. *A. flavus* is a recognized cause of invasive disease in certain regions, yet closely related environmental species remain poorly characterized in clinical settings(6, 7). *Aspergillus texensis* was originally described as an aflatoxin-producing species within section Flavi, isolated from maize and agricultural soils in the United States. To date, no confirmed cases of invasive human infection have been reported, while it is able to grow at and above 37 ° C (8).

Here, we describe what appears to be the first documented case of invasive pulmonary aspergillosis caused by *A. texensis*, identified through molecular sequencing in a profoundly immunocompromised patient.

Case Presentation

In May 2024, a 39-year-old woman with a one-year history of classical Hodgkin lymphoma was admitted to Imam Khomeini Hospital Complex, Tehran, Iran, with high-grade fever (40°C), dyspnea, and pancytopenia (white blood cell count $3.08 \times 10^3/\mu\text{L}$; platelet count $23 \times 10^3/\mu\text{L}$). She was diagnosed with hemophagocytic lymphohistiocytosis (HLH) and initiated on etoposide (150 mg/m² IV twice weekly).

Her clinical course rapidly deteriorated. Blood cultures grew *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, and she received piperacillin/tazobactam and cefepime. Laboratory findings showed elevated liver enzymes and coagulopathy consistent with disseminated intravascular coagulation. Imaging demonstrated pulmonary abnormalities with associated mild-to-moderate ascites.

Despite antibacterial therapy, fever and respiratory compromise persisted. Given high suspicion for invasive mold infection in the context of profound immunosuppression, empirical liposomal amphotericin B was initiated. Bronchoscopy with bronchoalveolar lavage (BAL) was performed. Direct microscopy (10% KOH) revealed septate hyaline hyphae with acute-angle branching consistent with *Aspergillus* species (Fig. 1).

BAL cultures on Sabouraud dextrose agar at 25°C and 37°C produced yellow-green colonies within several days. Molecular identification using polymerase chain reaction amplification and sequencing of the calmodulin region demonstrated > 99% identity with *Aspergillus texensis* (GenBank accession number: PX734618), confirming species-level identification (Fig. 2). The absence of galactomannan antigen testing in BAL and serum samples represents a limitation of the present study.

Mild to moderate ascites was observed on high-resolution chest computed tomography (Fig. 3). Antifungal susceptibility testing was performed using the CLSI M38-A3 broth microdilution method(9). The isolate demonstrated the following MICs:

- Amphotericin B: 16 µg/mL
- Itraconazole: 8 µg/mL
- Fluconazole: 64 µg/mL
- Voriconazole: 1 µg/mL
- Posaconazole: 0.5 µg/mL
- Isavuconazole: 1 µg/mL
- Miconazole and anidulafungin (MEC): ≤0.008 µg/mL

As no established epidemiological cutoff values (ECVs) are available for *A. texensis*, MIC results were interpreted descriptively and, where appropriate, compared with related species within section Flavi. Given the elevated amphotericin B MIC, therapy was transitioned to intravenous voriconazole. Despite aggressive management, the patient developed refractory septic shock, progressive respiratory failure, and multiorgan dysfunction, and died 27 days after admission, in June 2024. Based on host factors, compatible clinical findings, and mycological evidence from BAL, the case fulfilled criteria for probable invasive pulmonary aspergillosis according to EORTC/MSGERC definitions.

Discussion

This report describes what appears to be the first confirmed case of invasive pulmonary aspergillosis caused by *Aspergillus texensis*, expanding the recognized spectrum of clinically relevant species within the genus *Aspergillus*. Although invasive aspergillosis (IA) has historically been attributed predominantly to *A. fumigatus*, accumulating molecular evidence demonstrates that non-*fumigatus* and cryptic species contribute increasingly to invasive disease, particularly in highly immunocompromised hosts (10). The application of molecular diagnostics has fundamentally reshaped *Aspergillus* epidemiology, revealing that species previously regarded as strictly environmental may possess unappreciated pathogenic potential(11, 12).

Traditional morphological identification methods often grouped isolates within broad species complexes, potentially masking clinically significant diversity. Sequencing of the internal transcribed spacer (ITS), β -tubulin, and calmodulin genes has led to the recognition of numerous cryptic species across sections Fumigati, Flavi, Terrei, and Nigri. Importantly, these species may display distinct antifungal susceptibility profiles and, in some cases, differing virulence attributes (3, 13, 14).

Aspergillus texensis, a member of section Flavi, was initially characterized as an aflatoxin-producing environmental species isolated from maize and agricultural soils in the United States. Section Flavi includes established human pathogens such as *A. flavus*, which is a leading cause of invasive aspergillosis in certain geographic regions and is frequently associated with sinus, pulmonary, and disseminated disease(8, 15). The identification of *A. texensis* as an invasive pathogen suggests that the clinical spectrum of section Flavi species is broader than previously appreciated. It is plausible that infections attributed historically to morphologically similar taxa may have included undetected *A. texensis* isolates in the absence of molecular confirmation(16).

The increasing detection of rare *Aspergillus* species likely reflects both improved diagnostic resolution and changing ecological pressures. Environmental azole exposure, particularly from agricultural fungicide use, has been implicated in the selection of resistant strains within section Fumigati. Whether comparable selective dynamics influence species within section Flavi remains uncertain but represents an important area for epidemiologic and environmental investigation(17, 18).

The pathogenicity of *Aspergillus* species is multifactorial, encompassing thermo-tolerance, angio-invasive capacity, conidial surface properties, oxidative stress resistance, and production of secondary

metabolites(19, 20). Although aflatoxin biosynthesis is primarily relevant to food contamination and hepatocarcinogenesis, the broader metabolic plasticity of section Flavi species may reflect adaptive traits facilitating survival in host tissues(21).

Invasive aspergillosis is fundamentally opportunistic, emerging when host immune defenses are compromised. Neutrophils are central to hyphal killing, and prolonged neutropenia remains the strongest predictor of angio-invasive disease(1). In the present case, multiple high-risk factors converged: hematologic malignancy, chemotherapy-induced cytopenia, hemophagocytic lymphohistiocytosis (HLH), and septic shock. HLH represents a state of immune dysregulation characterized by hypercytokinemia combined with impaired cytotoxic lymphocyte function. This paradoxical combination of hyperinflammation and ineffective pathogen clearance may facilitate opportunistic fungal invasion despite systemic inflammatory activation. The rapid progression to multi-organ failure in this patient likely reflects synergistic injury from polymicrobial bacterial sepsis and invasive mold infection. Unfortunately, an autopsy was not performed.

A particularly notable aspect of this case is the isolate's antifungal susceptibility profile. The markedly elevated amphotericin B MIC (16 µg/mL) and high itraconazole MIC (8 µg/mL) suggest reduced susceptibility relative to epidemiologic cutoff values reported for most related *Aspergillus* species. Although species-specific clinical breakpoints for *A. texensis* are unavailable, such elevated MICs raise important therapeutic considerations, particularly in critically ill patients receiving empirical polyene therapy. It should be noted, the absence of species-specific ECVs for *A. texensis* limits categorical interpretation of susceptibility data, and therefore, our findings should be considered exploratory and interpreted with caution.

Reduced susceptibility to amphotericin B in *Aspergillus* species has been linked to alterations in ergosterol biosynthesis pathways and membrane composition that diminish polyene binding affinity(23). In contrast, azole resistance typically involves mutations in the *cyp51A* gene, promoter alterations, or upregulation of efflux transporters; however, resistance mechanisms in section Flavi species remain less comprehensively characterized than those in section Fumigati (24). The relatively preserved activity of voriconazole, posaconazole, and isavuconazole observed in this isolate suggests that extended-spectrum triazoles may remain viable options against certain rare Flavi members, although clinical efficacy is heavily dependent on host immune recovery.

These findings underscore the limitations of extrapolating susceptibility assumptions from *A. fumigatus* to rare and cryptic *Aspergillus* species. As the diversity of recognized pathogens expands, individualized antifungal management informed by laboratory data becomes increasingly essential.

This case reinforces the indispensable role of molecular mycology in contemporary clinical practice. Morphological assessment alone would likely have led to identification at the section level without recognition of species-level identity. Calmodulin sequencing enabled definitive classification and contributes meaningful epidemiologic data to the literature(25).

Routine incorporation of molecular identification techniques in tertiary and reference laboratories may reveal that rare *Aspergillus* species are underdiagnosed rather than truly exceptional. Systematic documentation of such infections is critical to defining geographic distribution, resistance patterns, and clinical outcomes. Improved survival among patients with hematologic malignancies, expanded use of immunomodulatory therapies, environmental shifts, and antifungal selective pressures collectively create ecological niches for uncommon opportunistic fungi.

Beyond its novelty, this case reinforces several broader principles:

1. Environmental *Aspergillus* species capable of growth at human body temperature, with no prior documented human pathogenicity, may cause invasive disease in profoundly immunocompromised hosts.
2. Species-level molecular identification is critical for accurate epidemiologic characterization and may uncover emerging pathogens.
3. Antifungal susceptibility testing should be strongly considered in infections caused by uncommon species, as resistance patterns may differ from established paradigms.

Continued surveillance, genomic characterization, and susceptibility profiling of rare *Aspergillus* isolates are necessary to clarify their virulence attributes, resistance mechanisms, and optimal therapeutic strategies. As molecular diagnostics become more widely implemented, additional cases may further define the clinical significance of *A. texensis* and related taxa.

Conclusion

We report the first documented case of invasive pulmonary aspergillosis caused by *Aspergillus texensis* in a patient with Hodgkin lymphoma and HLH. The isolate demonstrated reduced susceptibility to amphotericin B and itraconazole, emphasizing the importance of molecular identification and antifungal susceptibility testing. This case broadens the recognized pathogenic spectrum of *Aspergillus* species and highlights the evolving landscape of invasive fungal infections in immunocompromised hosts.

Abbreviations

A

Invasive Aspergillosis

HLH

Hemophagocytic Lymphohistiocytosis

BAL

Bronchoalveolar Lavage

MIC

Minimum Inhibitory Concentration

MEC

Minimum Effective Concentration

ECV
Epidemiological Cutoff Value
CLSI
Clinical and Laboratory Standards Institute
KOH
Potassium Hydroxide
EORTC/MSGERC
European Organization for Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium
CT
Computed Tomography
IV
Intravenous

Declarations

Ethics approval and consent to participate

Ethical approval for publication of this case report was obtained from the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (Approval No. IR.TUMS.SPH.REC.1403.124). Written informed consent was obtained from the patient's next of kin for participation and publication of the clinical data.

Consent for publication

Written informed consent for publication of the clinical details and accompanying images was obtained from the patient's next of kin.

Competing Interests

The authors declare that they have no competing interests.

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Author Contribution

E.E. and Z.R. conceived and designed the study. E.E., H.K.S., F.H., and S.J.H. collected clinical and laboratory data and performed mycological investigations. E.F.J.M. and B.S. contributed to species identification, data interpretation, and scientific supervision. A.A., M.S., and M.K. contributed to clinical evaluation, patient management, and acquisition of clinical data. E.E. drafted the original manuscript. E.F.J.M., B.S., Z.R., and S.J.H. critically revised the manuscript for important intellectual content. All authors reviewed and approved the final manuscript.

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Data Availability

The datasets generated during the current study are available from the corresponding author on reasonable request. Sequence data have been deposited in GenBank under accession number [GenBank: PX734618].

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Figures



Figure 1

Direct microscopic examination of BAL fluid using potassium hydroxide (KOH 10%) revealed septate hyaline hyphae with acute-angle branching, morphologically consistent with *Aspergillus* species.



Figure 2

(a, b) BAL cultures on Sabouraud dextrose agar at 25 °C and 37 °C showing yellowish-green colonies after several days. (c) Microscopic features including hyaline stippled conidiophores, globose vesicles, phialides, and smooth-walled spherical conidia.

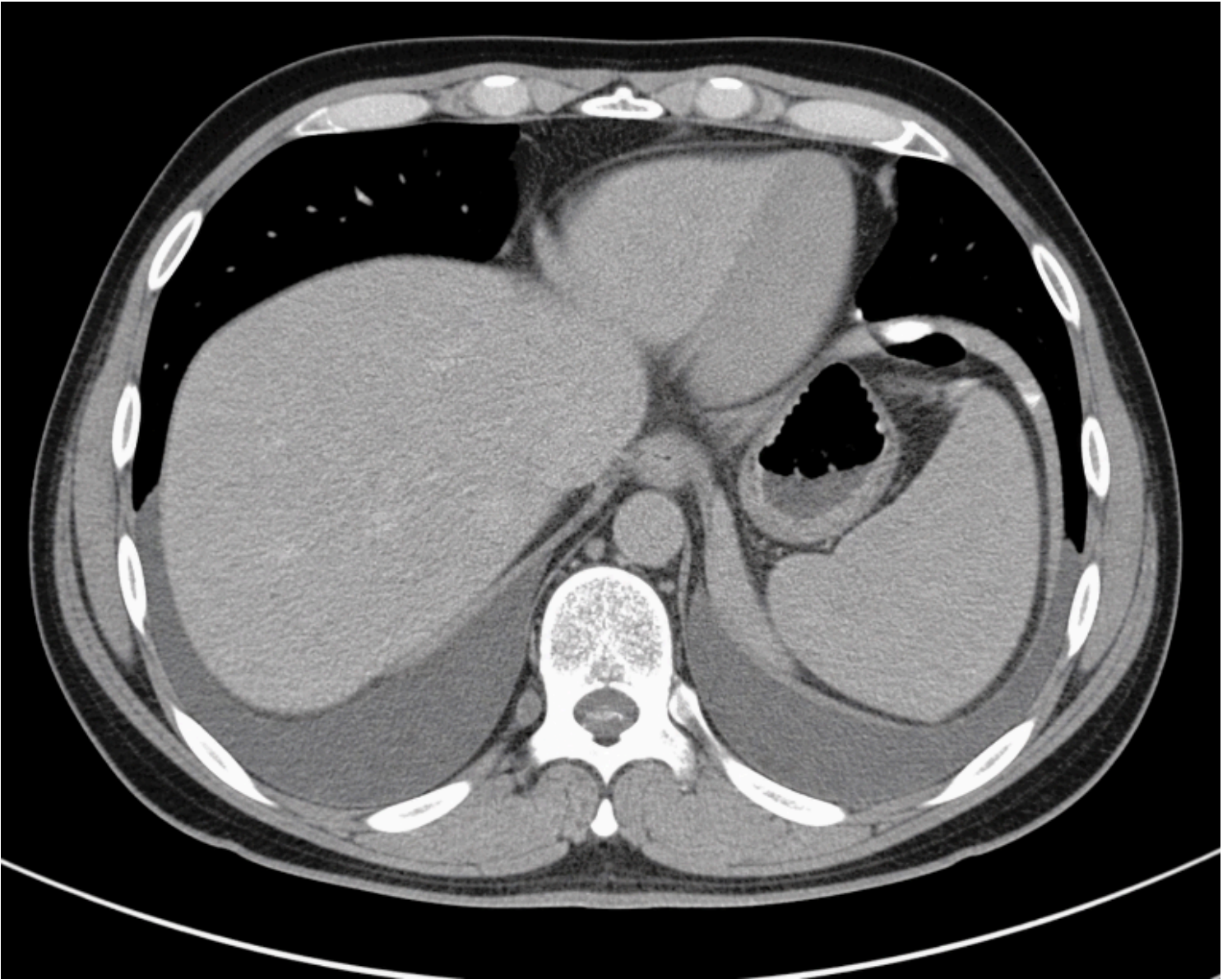


Figure 3

Mild to moderate ascites was observed on high-resolution chest CT in a patient with invasive pulmonary infection caused by *Aspergillus texensis*.