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Case Reports

Cunninghamella echinulata causing fatally invasive fungal sinusitis

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ABSTRACT

We report a fatal case of invasive fungal sinusitis caused by *Cunninghamella echinulata* in a febrile, neutropenic 15-year-old male with relapsing acute leukemia. The isolate was recovered from a nasal biopsy from the right middle meatus, and microscopic examination of the tissue revealed angioinvasion and necrosis. Human infection caused by this organism has not been well documented; however, this report alerts us to its life-threatening potential.

1. Case report

A 15-year-old male had been diagnosed with mixed lineage T-cell and myeloid acute leukemia 6 years prior to this presentation. He underwent an allogeneic bone marrow transplant from an HLA identical sibling in December 2005. His post-transplant course was complicated by severe cardiac dysfunction requiring a regimen of antihypertensive medications and diuretics, persistent neutropenia with an absolute neutrophil count ranging from 0 to 450/mm^3 (reference range: 1500–8000/mm^3), and ultimately the relapse of his leukemia involving bone marrow, mediastinal lymph nodes, and cerebrospinal fluid.

The patient was admitted for induction chemotherapy for relapsing leukemia a year prior to this presentation and subsequently received whole brain and spine radiation for persistent leukemic involvement of the cerebrospinal fluid. His course of therapy was complicated by subdural hematomas, pneumonia with respiratory failure, and cardiac decompensation requiring dopamine (20 mg/mL IV drip for 6 days). Given the severity of his cardiac disease and relapsing leukemia, he was discharged to hospice care.

One month before this presentation, he returned to the hospital with neutropenic fever, pneumonia, and a sore throat. Chest computed tomography (CT) without contrast revealed peripheral nodular ground glass opacities in the right upper lobe and a 1.9-cm nodule in the right lower lobe that was interpreted as the remnant of the larger consolidation treated in a previous hospitalization. He received piperacillin-tazobactam (4 g IV every 8 hours) and fluconazole (400 mg orally daily). Blood cultures remained negative, and his symptoms resolved over the course of 7 days. Following discharge, he received palliative radiation to his legs for bony leukemic infiltrates and completed therapy with 5-azacytidine and donor lymphocyte infusion 6 days prior to his current presentation. Five days prior to this presentation, the patient experienced right infraorbital pain with tearing in his right eye and fever to 38.1 °C.

On the day of this presentation, the patient complained about increasingly severe right-sided pain around his eye and nose. He denied visual changes, headache, and toothache. On examination, he was febrile (39.3 °C) and somnolent, but not in acute distress. His vital signs were otherwise normal. He exhibited focal tenderness over the right side of his face; however, there was no periorbital edema,

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erythema, or drainage. Cranial nerves I–XII were intact, with normal extraocular movements. Laboratory studies revealed a borderline elevated creatinine of 1.2 mg/dL (reference range: 0.6–1.3 mg/dL), potassium of 6.7 mEq/L (reference range: 3.5–5.1 mEq/L); aspartate aminotransferase of 343 U/L (reference range: 0–37 U/L), alanine aminotransferase of 221 U/L (reference range: 0–40 U/L), and alkaline phosphatase of 339 U/L (100–390 U/L); his absolute neutrophil count was 0/mm^3 (reference range: 1500–8000/mm^3) and had ranged from 0 to 450/mm^3 in the previous year. He was admitted to the hospital.

The patient was started empirically on piperacillin-tazobactam (4 g IV every 8 hours). A sinus CT revealed inflammatory paranasal sinus disease with near opacification of the right frontal sinus and mucosal thickening of the right ethmoid air cells and bilateral maxillary sinuses. No bony erosions or evidence of orbital involvement was appreciated. Nasal endoscopy was notable for an edematous right middle turbinate with focal white discoloration on the medial surface. Examination of the left nasal cavity revealed focal brown discoloration on the anterior middle turbinate. No masses or discharge was appreciated. Biopsies were performed, and the tissues were sent for histopathologic examination and culture. Liposomal amphotericin B was initiated (5 mg/kg IV per day). Histopathology from the nasal sinus biopsies revealed angioinvasive organisms with aseptate hyphae and background necrosis (Fig. 1). A mucoralean fungus grew from tissue cultures after 1 day and, on the second day, was tentatively identified as *Cunninghamella echinulata* based on phenotypic features. Liposomal amphotericin B was increased to 10 mg/kg IV per day. The family elected not to proceed with surgical debridement given the risks of prolonged anesthesia in the setting of his poor cardiac status.

Chest x-ray revealed bilateral densities with rounded infiltrates on the left side raising suspicion for fungal progression into his lungs. Shortly following this study, the patient experienced worsening right facial pain and epistaxis. He received palliative therapy with morphine nebulizers and albuterol; however, his respiratory status rapidly deteriorated, and he expired soon thereafter.

2. Histopathology

Tissue obtained from the right middle meatus and left middle turbinate of the nasal cavity and was sent for histopathologic examination. Routine hematoxylin and eosin (H&E) stains revealed respiratory mucosa with ribbon-like aseptate hyphae, angioinvasion, and necrosis (Fig. 1A). Giemsa stain confirmed the fungal morphology, highlighting numerous hyphal elements (Fig. 1B).

3. Mycology

Calcofluor white stain performed on the biopsy tissues revealed heavy fungal hyphae structure morphologically consistent with a filamentous fungus (Fig. 2). Culture from the biopsy tissues grew the fungus in several culture media including Sabouraud dextrose agar and Brain heart infusion agar (Becton Dickinson, Sparks, MD, USA) media on day 1. The organism grew at 37 °C but not at 45 °C. Colonies appeared cotton and white-gray, both on the surface and reverse. Lactophenol cotton blue stain revealed irregularly branching sporangiophores terminating in prominent, globose vesicles covered with ellipsoidal sporangiola anchored by spine-like denticles (Fig. 3A and B). The sporangiospores were echinulate (covered with spines up to 4 μm long). The microscopic features and colony morphology enabled presumptive identification of *C. echinulata*. The isolate was then referred to the Fungus Testing Laboratory, Department of Pathology, University of Texas Health Sciences Center, San Antonio, TX, accession number UTHSC 12–2507, for species confirmation and antifungal

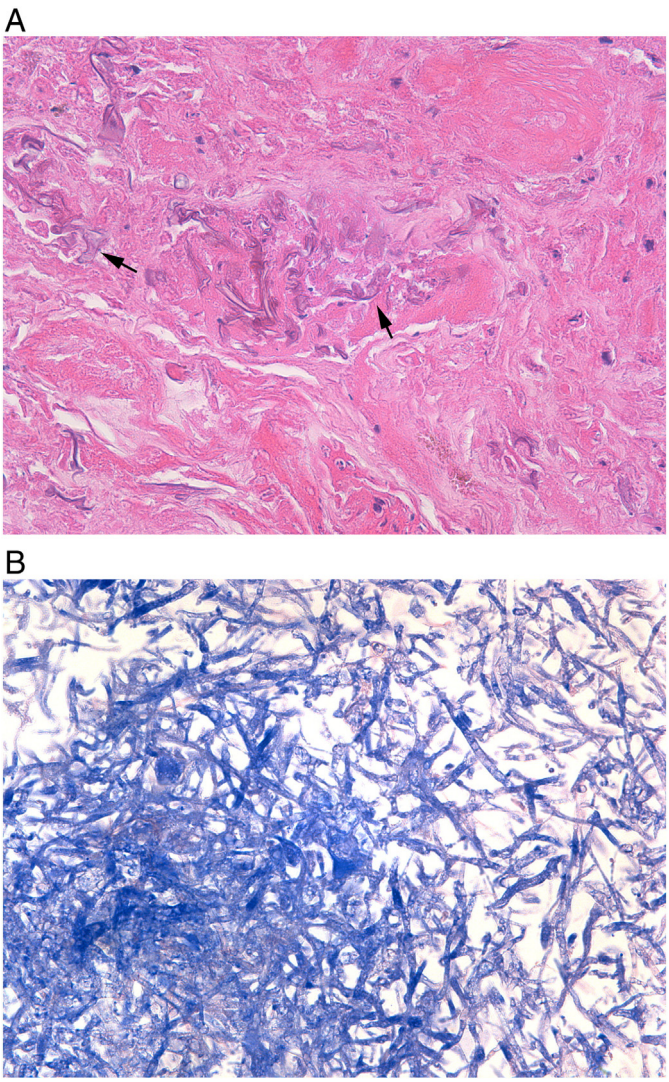

Fig. 1. Histopathologic examination 60× magnification. A) H&E stain demonstrating necrosis and invasive fungal elements (arrowheads), consistent with disease by mucoralean fungi. B) Giemsa stain highlights the organisms within an area of necrosis.

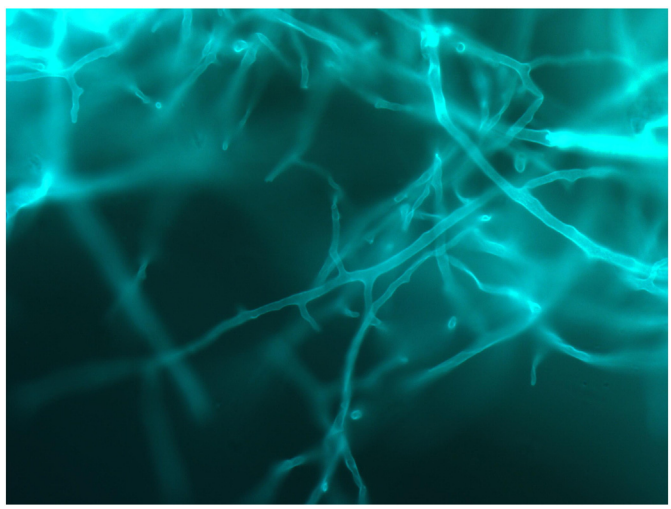

Fig. 2. Calcofluor white stain of an isolate from the middle meatus reveals filamentous fungi.