CASE REPORT

A CASE OF CENTRAL NERVOUS SYSTEM INVASIVE ASPERGILLOSIS MIMICKING ORBITAL CELLULITIS IN A PATIENT WITH UNCONTROLLED TYPE 2 DIABETES MELLITUS AND END-STAGE RENAL DISEASE

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Central nervous system aspergillosis is a rare and often fatal complication seen in immunocompromised individuals. Here, we present the case of a 60-year-old female with uncontrolled type 2 diabetes mellitus and end-stage renal disease (ESRD) who was ultimately diagnosed with CNS aspergillosis. This case underscores the diagnostic challenge and delays posed by fungal infections in patients with predisposing conditions, necessitating a multidisciplinary approach for timely diagnosis and management.

Keywords: Aspergillosis; Central nervous system; Immunocompromised

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INTRODUCTION

Central nervous system aspergillosis (CNSAG) presents a significant challenge in immunocompromised patients, often resulting in high morbidity and mortality rates exceeding 90%.[1] Among cases of invasive aspergillosis, CNS involvement is estimated to occur in approximately 10–20% of instances.[2] Notably, individuals with underlying hematological malignancies such as acute leukemia, recipients of solid organ transplants, those with AIDS, chronic pulmonary diseases, hepatic failure, Cushing's syndrome, thermal burns, and users of immunomodulation agents like alemtuzumab are at heightened risk for developing both invasive and CNS aspergillosis.[3] For patients who have undergone allogeneic bone marrow transplantation or hematopoietic stem cell transplantation, the incidence of CNS involvement is particularly elevated, ranging from 40–50%.[1] Additionally, the incidence of acute leukemia, a predisposing factor for CNS aspergillosis, stands at approximately 14%.[1]

Aspergillosis typically spreads either hematogenously from primary lung infections or through direct extension from adjacent structures such as the ear, paranasal sinuses, or mastoids.[4] Among immunocompromised individuals, hematogenous spread from invasive lung infections is the predominant mode of dissemination, whereas extension from sinusitis, mastoiditis, cranial trauma, and indwelling catheters is more commonly observed in immunocompetent hosts.[5]

Clinical manifestations of CNS aspergillosis are often nonspecific and vary depending on the specific region of the central nervous system affected. Patients may present with recurrent headaches, focal neurological deficits, or alterations in mental status. Severe CNS invasion can lead to complications such as brain abscesses, cerebritis, meningitis, cranial sinus thrombosis, seizures, and ventriculitis. Infections involving the paranasal sinuses may manifest as proptosis, visual disturbances, or cranial nerve palsies. Mycotic peripheral aneurysms, subarachnoid hemorrhage and spinal CNS aspergillosis also has been reported in the literature.

Central nervous system aspergillosis is a rare manifestation of invasive aspergillosis, primarily affecting immunocompromised individuals. The diagnosis can be challenging due to nonspecific clinical manifestations, low sensitivity of routine cerebrospinal fluid routine (CSF) examination and the need for invasive diagnostic procedures that can cause diagnostic delays and delays in prompt initiation of antifungal therapy. Here, we report a case of CNS aspergillosis in a patient with uncontrolled type 2 diabetes mellitus and ESRD, initially misdiagnosed as orbital cellulitis.

CASE REPORT

A 60 years old female, married, known type-2 diabetes mellitus and hypertensive for the past 10

years, end stage renal disease (ESRD) on maintenance hemodialysis for the last 5 years admitted to our high dependency unit under care of a nephrology team on January 25th 2024. Neuro-consult was called for right eye ptosis, right eye visual loss and numbness of right face for past 10–15 days. She also had a resolving carbuncle on her forehead. On neurological examination, she was oriented, alert, and conscious and was able to follow commands. There was complete drooping of the right eyelid, the right pupil was 8 mm dilated with no reaction to light, with no perception of light in the right eye, complete right ophthalmoplegia, and there was a loss of pain and temperature in trigeminal V1 and V2 distribution. Golden brown-colored nasal crusting was observed on bilateral nares examination, and the patient had a fruity breath odor. Before presentation to us, she was treated for presumed orbital cellulitis with broad-spectrum antibiotics. She completed antibiotics for 15–20 days without improvement and there was progression in neurological symptoms with the involvement of trigeminal V1 on the contralateral side.

Given her uncontrolled diabetes history and ESRD, rhino-orbital mucormycosis was suspected, prompting the involvement of ENT specialists and ophthalmologists for nasal tissue biopsy and assessment for surgical debridement. We advised prompt initiation of amphotericin B.

Her initial investigations showed Hemoglobin of 10.0g/dl, White cell count of 12.8 $x10^3$/ µL, and platelets $205x10^3$ µL, Creatinine 8.8 mg/dl, Urea 114 mmol/L, Glycolated hemoglobin (HbA1C) of 7.7% and intact PTH 1511pg/ml. She was on maintenance hemodialysis thrice a week and she was adequately dialyzed. CSF analysis was not performed on this patient because she was discharged for hemodyalysis appointment. Blood culture was inconclusive and yielded no growth. While the initial MRI brain was normal, a repeat MRI of the orbit and brian with contrast with a focus on the cavernous sinus was planned to further evaluate the cause and extent of the disease. Antifungal therapy with amphotericin was advised based on clinical suspicion and consultation from the primary nephrology team. A tissue biopsy from the nose was performed on the following day. She was discharged on her request from the hospital on the next day for a hemodialysis appointment. She followed up after one week with a biopsy report and brain imaging and was readmitted with stable vital signs.

MRI brain and orbit with contrast showed contrast-enhanced mucosal thickening in paranasal sinuses particularly in the right anterior ethmoid and right frontal sinus associated with increased diffuse enhancement of meninges along the frontal and temporal lobes. The inflammatory process was noted in the soft tissue along the right side of the nose, medial preseptal and medial extracoanal right sided orbital soft tissue and right premaxillary soft tissue. (Figure 1)

Histopathology showed focal viable respiratory epithelium and extensive colonies of septated fungal hyphae, revealing dichotomous branching and fruiting bodies. Fungal vascular invasion was also seen. However, no malignant cells were seen. Grocott-Gomori methenamine silver stain and Periodic acid Schiff stains were both positive for presence of fungus. (Figure 2)

Fungal culture showed growth of a fungal colony which was identified as Aspergillus flavus. It (Figure 2) had a yellowish-green, or dark green colonies surrounded by a white circle that was eventually covered by conidia. The colonies' texture was velvety or woolly with a floccose center. Microscopically, septate hyphae, rounded vesicle (fruiting bodies), with finger like extensions on more than half of its surface, and rough spiky stalk (conidiophore) helped to speciate the fungus. Slides were made using lactophenol cotton blue stain. Identification of Aspergillus flavus species was made on the basis of the colony morphology and microscopic features of the fungus.

The patient additionally presented with complaints of left lower leg weakness that ocurred 3–5 days before her readmission. Neurological examination revealed increased tone, muscle power graded at 3/5, and an upgoing left plantar reflex. She was readmitted and based on the histopathology report and brain imaging patient was diagnosed with invasive central nervous system aspergillosis (CNSAG). Intravenous Voriconazole was initiated at a dose of 6mg/kg every twelve hours on the first day, followed by 4mg/kg every twelve hours. Steroid therapy with dexamethasone was commenced at 8mg every six hours initially, but due to elevated blood sugar levels, the dosage was adjusted to 8mg every eight hours. While her left lower leg weakness showed improvement within 2–3 days of treatment initiation, there was no observed improvement in her orbital symptoms. After five days of hospitalization, the patient was discharged upon request, with an agreement to follow up with the primary care team. Unfortunately, she died on the 13th day of her treatment.

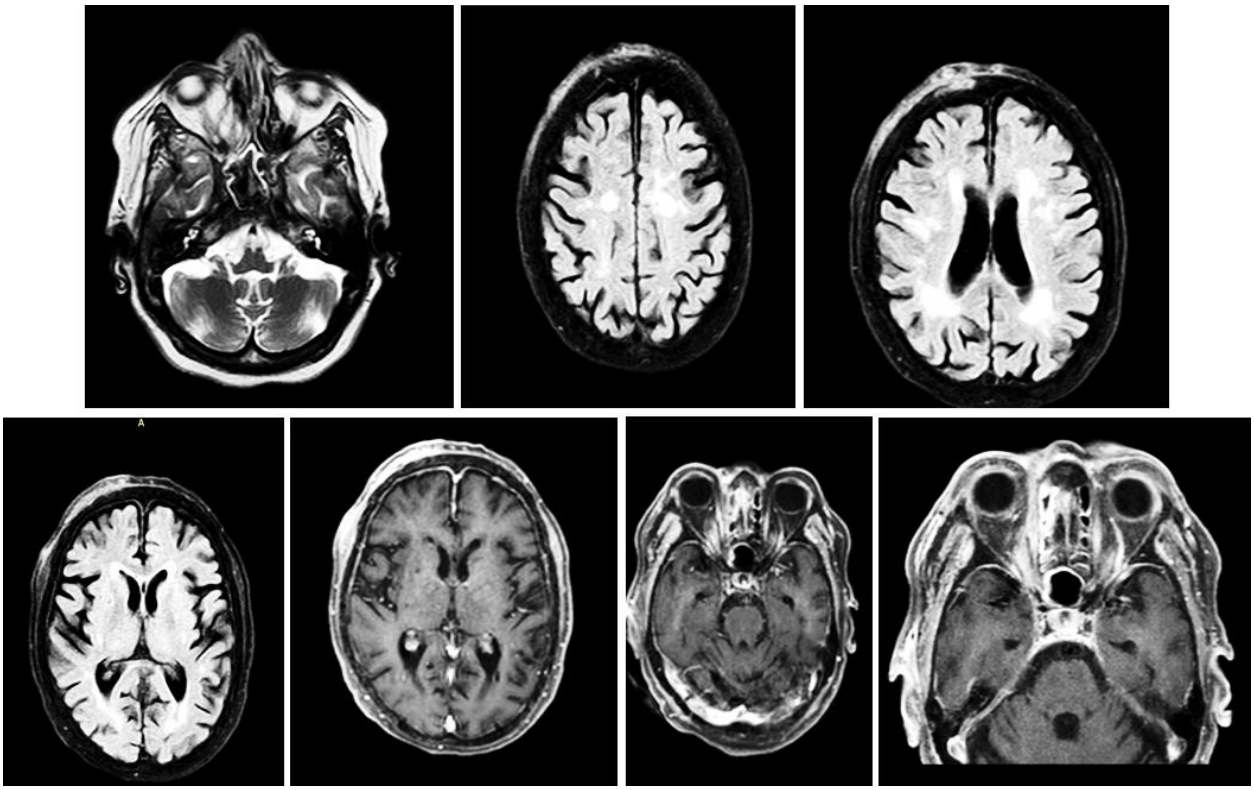

Figure-1: MRI findings in a patient with invasive central nervous system aspegillosis. MR of the brain shows contrast enhanced mucosal thickening in paranasal sinuses particularly in right anterior ethmoid and right frontal sinus associated with increased diffuse enhancement of meninges along the frontal and temporal lobes. Inflammatory process was noted in the soft tissue along right side of the nose, medial preseptal and medial extracoanal right sided orbital soft tissue and right premaxillary soft tissue.

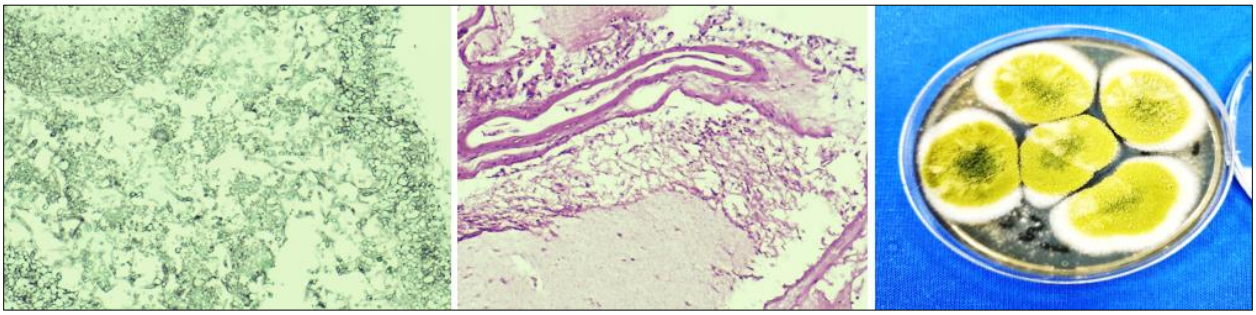

Figure-2: A-Grocott -Gomori stain , showing clearly vesicles(small arrow) and segmented hyphae(long arrow). B-Hematoxylin and Eosin stain showing vascular invasion. Yellowish-green colonies surrounded by a white circle that is eventually covered by conidia. C-The colonies' texture is velvety or woolly with a floccose center.

DISCUSSION

Central nervous system (CNS) aspergillosis poses a significant challenge in diagnosis and treatment, particularly among immunocompromised individuals. This case highlights the importance of early recognition and targeted therapy in improving patient outcomes. The patient's history of poorly controlled diabetes mellitus and end-stage renal disease underscored her immunocompromised status, predisposing her to invasive fungal infections such as CNS aspergillosis.

Clinical presentations of CNS aspergillosis can vary widely among immunocompromised patients, often manifesting atypically and complicating diagnosis.[6] In this case, initial misdiagnosis as bacterial orbital cellulitis led to a delay in recognizing the underlying fungal infection. Despite receiving broad-spectrum antibiotics, the patient's condition did not improve, prompting further

investigation and eventual admission to the hospital. The delay in definitive diagnosis, attributable to the time required for biopsy and histopathology, allowed the fungal infection to progress unchecked, exacerbating the patient's clinical course and contributing to a poor prognosis.

Diagnosing CNS aspergillosis presents several challenges, including inconclusive blood cultures and the need for histopathological confirmation[7]. Direct microscopy of affected fluid and tissue specimens may reveal characteristic fungal elements, aiding in diagnosis[7]. Prompt consideration of fungal infections, especially in cases where bacterial infection is suspected but not responding to therapy, is crucial for timely initiation of appropriate treatment.

The clinical practice guidelines of infectious diseases society of America recommend early initiation of antifungal therapy, such as amphotericin B, particularly in cases where fungal etiology is suspected pending histopathology[7]. However, in this case, delayed initiation of antifungal therapy due to concerns about exacerbating underlying end-stage renal disease further complicated the clinical management.

Multidisciplinary collaboration among clinicians, microbiologists, and pathologists is paramount in optimizing patient care for CNS aspergillosis. This collaborative approach facilitates comprehensive evaluation and integration of clinical, microbiological, and histopathological findings, minimizing diagnostic uncertainties and treatment delays. By harnessing collective expertise, the diagnostic process can be streamlined, enabling expedited management and ultimately improving patient outcomes.

In conclusion, this case underscores the importance of maintaining a high index of suspicion for fungal infections, initiating prompt diagnostic investigations, and fostering multidisciplinary collaboration in managing CNS aspergillosis. These principles are essential for mitigating diagnostic delays, guiding timely treatment initiation, and optimizing patient care, particularly in immunocompromised individuals with invasive fungal infections**.**

Learning points:

1. If a fungal infection is suspected, broad-spectrum antifungal treatment should be started based on cerebrospinal fluid reports and imaging results, and then adjusted according to culture or tissue biopsy findings.
2. The multidisciplinary team should be engaged early in the management process to facilitate timely biopsy and further management.

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