Case Report

A rare case of meningoencephalitis due to *Aspergillus fumigatus*

Un raro caso di meningoencefalite causata da *Aspergillus fumigatus*

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ABSTRACT

Cerebral Aspergillosis (CA) is an opportunistic fungal infection that usually affects immunocompromised hosts. A man was admitted for loss of consciousness and aphasia. Computed Tomography (CT) scan showed a left cerebral frontal lesion. Nasal swab showed hyphae of *Aspergillus spp*.; isavuconazole was started. Lumbar Puncture (LP) tested positive for galactomannan (index 1.9), and *Aspergillus fumigatus* grew on the Cerebrospinal Fluid (CSF) culture. Unfortunately, a new episode of fever and a general deterioration then ensued up to the death. In immunocompetent patients as well, chronic fungal rhinosinusitis deserves attention due to its potential for rapid evolution to Central Nervous System (CNS) involvement.

L'Aspergillosi Cerebrale (CA) è un'infezione fungina opportunistica che colpisce principalmente gli individui immunocompromessi. In questo case report, riportiamo il caso di un uomo ricoverato per la comparsa improvvisa di perdita di coscienza e afasia. La Tomografia Computerizzata (TC) ha mostrato la presenza di una lesione cerebrale frontale sinistra. Successivamente, il tampone nasale ha rilevato la presenza di *Aspergillus spp.*; è stato pertanto avviato un trattamento con isavuconazolo. Ulteriori indagini hanno evidenziato alla puntura lombare (PL) la positività per il galattomannano (index 1.9) e l'isolamento di *Aspergillus fumigatus* nel liquido cerebrospinale (CSF). Nonostante l'inizio del trattamento, il paziente ha sviluppato nuovi episodi febbrili e ha manifestato un generale peggioramento delle condizioni cliniche fino alla morte. Il presente caso clinico sottolinea la necessità di un'attenta valutazione della rinosinusite fungina cronica anche nei pazienti immunocompetenti, data la potenziale rapida evoluzione verso il coinvolgimento del Sistema Nervoso Centrale (CNS).

INTRODUCTION

Aspergillus is a ubiquitous opportunistic filamentous fungus that causes mold infections with a wide range of clinical syndromes in humans, and it may progress to Invasive Aspergillosis (IA). Most invasive infections are caused by members of the *A. fumigatus* species complex. In a report of 218 infections in 24 transplant centers in the United States, 67% were caused by members of the *A. fumigatus* complex, followed by *A. flavus* (13%), *A. niger* (9%), and *A. terreus* (7%). These data contrast with epidemiologic data from a decade earlier when the vast majority of cases (90%) were secondary to *A. fumigatus* species,[1] likely reflecting changes in microbial epidemiology, center-based differences, and/or changes in typing methods.

Emerging risk factors for patients with no or milder immunosuppression include: chronic obstructive pulmonary disease, with receipt of glucocorticoid therapy, Intensive Care Unit (ICU) admission[2] and certain viral infections (*e.g.*, influenza, Severe Acute Respiratory Syndrome Coronavirus 2 [SARS-CoV-2], respiratory syncytial virus).[3]

Cerebral Aspergillosis (CA) is a rare infection that occurs predominantly in previously healthy immunocompetent individuals. It is uncommon in seriously immunocompromised hosts, such as recipients of hematopoietic stem cell and solid organ transplants, patients with prolonged neutropenia, acquired immunodeficiency syndrome or haematologic malignancies, or persons undergoing treatments involving high doses of steroids.[4]

In a study of the Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI) findings associated with Central Nervous System (CNS) aspergillosis, three patterns were observed:[5] i) ring-enhancing lesions consistent with brain abscesses, ii) cerebral cortical and subcortical infarction with or without superimposed hematomas, iii) mucosal thickening of a paranasal sinus with secondary intracranial dural enhancement consistent with direct extension from the sinuses.

An increasing occurrence of CA is now being reported in immunocompetent patients who abuse cocaine by inhalation and especially in those who also have chronic rhinosinusitis.[6,7] The pathomorphosis of ventriculitis in these patients is more consistent with a cerebral aspergilloma than with ventriculitis secondary to an intracranial abscess rupture. Early diagnosis is essential for proper treatment. In this report, we present a rare case of CA in an immunocompetent patient with a history of cocaine use.

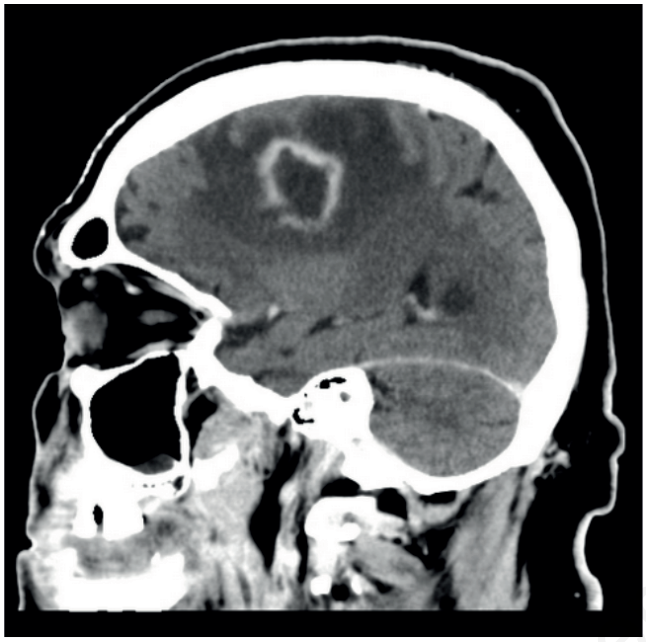

Figure 1. Computed Tomography scan demonstrating a space-occupying lesion, approximately of 3,5 cm in diameter, localized in the left-posterior frontal lobe.

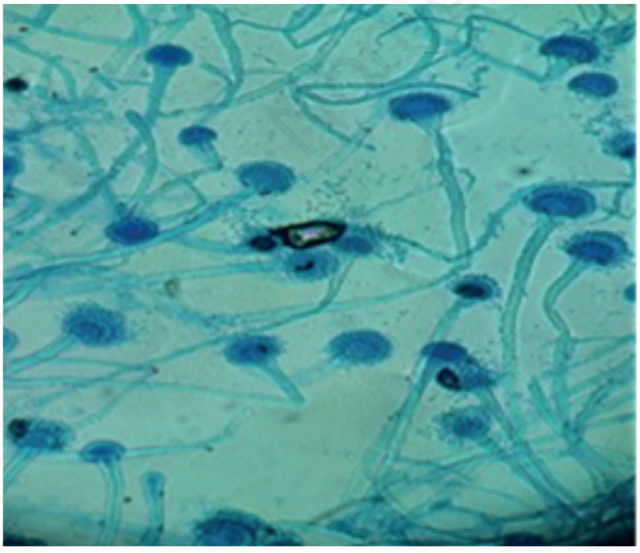

Figure 2. *Aspergillus fumigatus* culture (Sabouraud's dextrose agar) microscopic characteristics. A single series of phialides can be observed, giving origin to the rounded conidia disposed in long and parallel chains.

CASE REPORT

A 61-year-old male was admitted to the emergency department for loss of consciousness and aphasia. His Glasgow Coma Scale (GCS) score was 13 on admission. His past medical history included hypertension, non-insulin-dependent diabetes mellitus, a former smoking habit and occasional cocaine use by inhalation. A CT (Figure 1) scan showed a left cerebral frontal lesion and initial ventriculitis, which were confirmed by MRI. CSF obtained from a lumbar puncture showed 2,822 cells/mm^3 (90% polymorphonucleates), high proteinorrachia (345 g/dL) and hypoglycorrhachia (67 g/dL; blood sugar 180 g/dL). Cefepime 2 g q8 hours plus metronidazole 500 mg q8 hours were empirically started, and blood and CSF were cultured. Serum and broncho-alveolar lavage results were negative for galactomannan, despite a positive serum result for beta-D-glucan (>500 pg/mL).

Due to neurological impairment and respiratory distress, the patient was admitted to the ICU and underwent endotracheal intubation. A surveillance nasal swab showed multiple hyphae of *Aspergillus* spp., raising the suspicion of possible CA; therefore, isavuconazole 372 mg q24h (after a loading dose of 372 mg q8h for six doses) was started. A new lumbar puncture tested positive for galactomannan (index 1.9; normal value 0.5), and colonies of Aspergillus fumigatus grew on the CSF culture (Figure 2).

The patient showed progressive clinical and radiological improvement, with recovery of consciousness, respiratory weaning, and reduction in the lesion size. Then isavuconazole was stopped after 20 days, and voriconazole was started.

The following CT scan showed a volumetric reduction of the known lesion, but it revealed hydrocephalus that required mechanical drainage. Subsequently, the patient suffered a spiking fever. Blood and urine were cultured but gave negative results. He was started on ceftazidime/avibactam and linezolid because of suspected post-procedure meningitis.

During the patient's hospitalization in the ICU, a rectal swab was positive for *Klebsiella pneumoniae* KPC. Because of his persistent hydrocephalus, the patient was referred to the Neurosurgical Unit for placement of an External Ventricular Drain (EVD). At that time, his GCS was 9/15. By 15 days after the procedure, he had severe neurological impairment (GCS 3/15), and MRI indicated cerebritis.

Amphotericin-B (liposomal) was added to the voriconazole, and the EVD was replaced upon observing a good response from the neurological aspect (GCS 14/15). Ceftazidime/avibactam and linezolid were stopped after 10 days of treatment. All the subsequent CSF cultures were negative.

A new episode of spiking fever followed by septic shock caused the rapid death of the patient.

DISCUSSION

Although a rare event, CA can occur in immunocompetent patients and especially in those affected by chronic rhinosinusitis. The etiology remains unclear, but this condition usually occurs secondary to *Aspergillus* infection in tissues adjacent to the brain

or through blood transmission. The most common cause of CNS aspergillosis is *Aspergillus* infection in the nasal sinuses, followed by dental and ear infections, contamination during cerebral or cardiac surgery, and lumbar puncture.[8]

Fungi may cause invasive fungal sinusitis that typically occurs in immunocompromised hosts and is rapidly progressive. Nevertheless, our clinical case showed that in immunocompetent patients as well, chronic fungal rhinosinusitis deserves particular attention due to its potential for rapid evolution to CNS involvement. CA is a life-threatening infection, but the prognosis is more favourable in immunocompetent than in immunocompromised patients.[9] However, CA is difficult to eradicate, and when these patients recover, they often have severe deficits and consequences.

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