

Iatrogenic *Aspergillus* infection of the central nervous system in a pregnant woman

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ABSTRACT

A healthy postnatal woman succumbed to fulminant iatrogenic *Aspergillus* infection of the central nervous system, following accidental inoculation into the subarachnoid space at spinal anesthesia, during an outbreak of *Aspergillus* meningitis in Sri Lanka. Autopsy revealed extensive *Aspergillus* meningitis and culture confirmed *Aspergillus fumigatus*. The thalamic parenchyma in the brain was invaded by fungal hyphae producing necrotizing angitis with thrombosis, thalamic infarcts and fungal abscesses. The directional growth of fungal hyphae from the extra-luminal side of blood vessels towards the lumen favored extension from the brain parenchyma over hematogenous spread. The spinal parenchyma was resistant to fungal invasion in spite of the heavy growth within the spinal meninges and initial inoculation at spinal level. Modulation of the immune response in pregnancy with depression of selective aspects of cell-mediated immunity probably contributed to rapid spread within the subarachnoid space, to involve the brain parenchyma leading to clinical deterioration and death.

KEY WORDS: Aspergillosis, central nervous system infections, iatrogenic, postpartum

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A 22-year-old healthy female underwent cesarean section under spinal anesthesia. She was readmitted nine days later with remittent fever of 39°C, severe occipital headache, neck stiffness and a positive Kernig's sign.

A full blood count revealed neutrophil leukocytosis. After a diagnosis of acute bacterial meningitis, she was started on empirical intravenous antibiotics. Cerebrospinal fluid (CSF) studies, which were done after starting antibiotics, showed a leukocytosis with elevated neutrophils (400/μl) and lymphocytes (100/μl), elevated CSF protein and reduced glucose. CSF Gram's stain, cytology and polymerase chain reaction for mycobacterium tuberculosis were negative. Blood and CSF cultures failed to yield a growth of bacteria or fungi.

She deteriorated rapidly despite treatment in a neurological intensive care unit and on Day 28 of admission developed complex partial seizures. Computerized tomography scan showed a thalamic infarct. Autopsy examination of another postpartum patient who developed meningitis, following spinal anesthesia for cesarean section during this same period showed evidence of aspergillus meningitis. In view of this finding, this patient was started on intravenous amphotericin on Day 33 of admission. However, she succumbed to the illness four days later.

Autopsy revealed a congested and edematous brain with necrosis of the basal ganglia, more prominent on the right side. The CSF was turbid with basal and spinal exudates.

INTRODUCTION

Cerebral *Aspergillus* infection is encountered mainly as an opportunistic infection in immunocompromised patients.^[1] Central nervous system (CNS) infection is postulated to result from local spread of fungus localized to the rhino-cerebral region and paranasal sinuses.^[1,2] Documented cases of iatrogenic *Aspergillus* infection of the CNS have followed neurosurgical procedures such as craniotomy for cerebral tumors, trans-sphenoidal surgery for Rathke's cleft cyst and temporal clip application for anterior communicating artery aneurysm.^[3-5]

A pregnant woman is considered immunocompetent throughout the pregnancy.^[6]

This healthy postnatal woman developed fulminant iatrogenic *Aspergillus* infection of the CNS. Postulated spread of infection within the CNS following accidental inoculation into the spinal subarachnoid space, and the pathological outcomes of the infection during the postnatal period are discussed.

CASE REPORT

An outbreak of *Aspergillus fumigatus* meningitis occurred in five women following spinal anesthesia performed for cesarean section, in Colombo, Sri Lanka.^[7] Three patients succumbed to the infection. The autopsy of one patient was performed and the pathology reviewed at our institution.

Microscopic examination showed an extensive growth of fungus, morphologically compatible with *Aspergillus* within the subarachnoid space in the spinal cord and brain. The spinal parenchyma was not invaded by *Aspergillus* hyphae [Figure 1]. Tissue from the thalamic region showed hyphae invading the brain parenchyma and walls of blood vessels [Figure 2] leading to thrombosis of arteries and hemorrhagic infarction of brain tissue. Infarcted brain tissue was invaded by fungus, [Figure 3] with formation of multiple small abscesses. The cerebral cortex and the cerebellum were not involved. Culture of CSF from the autopsy specimen confirmed a pure growth of *Aspergillus fumigatus*. There was no evidence of fungal infection in any other organ.

DISCUSSION

Aspergillus is an opportunistic, saprophytic and ubiquitous fungus, found in soil and decaying vegetation. *Aspergillus fumigatus* is the commonest species to cause disease in humans.^[8]

Aspergillus infection of the CNS commonly involves the brain and less commonly the spinal cord.^[9] Investigations on the iatrogenic CNS *Aspergillus fumigatus* meningitis

outbreak in Sri Lanka revealed that the fungus was probably introduced directly into the subarachnoid space of the spinal cord through improperly stored, contaminated disposable syringes and needles used for spinal anesthesia at cesarean section.^[7] The relative immune-protected environment of the subarachnoid space would have promoted the heavy fungal growth seen within the spinal subarachnoid space, with subsequent ascending spread of infection to the brain to involve mainly the basal ganglia with invasive parenchymal disease. The pathological outcomes of intracranial *Aspergillus* infection reported include meningitis, brain abscesses, fungal granulomas and fungal necrotizing angitis with vascular occlusion by fungal thrombi leading to cerebral infarctions. Rupture of blood vessels leading to subarachnoid hemorrhage and aneurysm formation has occurred following weakening of the vessel wall by invading fungal hyphae. This vascular tropism exhibited by *Aspergillus* hyphae is a characteristic feature of cerebral aspergillosis.^[8] In this woman, it appears that the fungal hyphae invaded blood vessels from the extra-luminal adventitial aspect towards the lumen rather than from the luminal aspect to exterior, which would have occurred if the spread was hematogenous [Figure 2]. Infarcted brain tissue from the thalamic region contained fungal hyphae with focal abscess formation. Epithelioid granulomata described in *Aspergillus* infection were absent except for a foreign body type granuloma seen in spinal meninges.

It was interesting to note that although the fungus was introduced into the subarachnoid space of the spinal cord leading to the heavy fungal growth in the spinal meninges, the cord parenchyma was uninvolved and appeared to be resistant to invasion by fungal hyphae.

Pregnant women are considered immunocompetent during pregnancy, however, the maternal immune response may be modulated away from cellular immunity, towards humoral immunity.^[6,10] It is speculated that selective aspects of cell-mediated immunity are also depressed in pregnancy. Therefore fungal infections, against which the host defenses are primarily cell-mediated, are likely to be more virulent

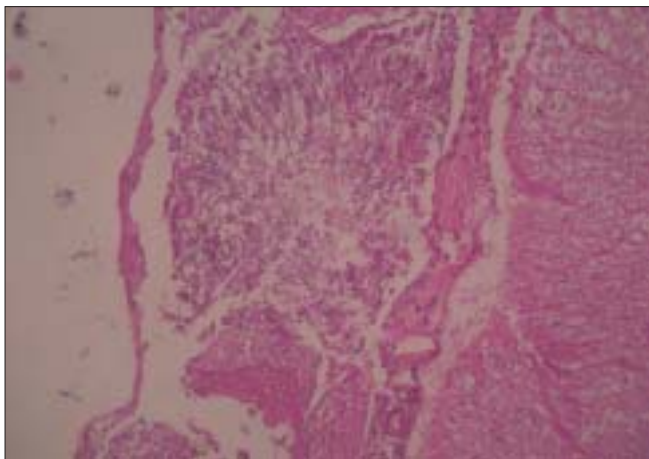


Figure 1: Fungus in spinal meninges, (H and E, x100)

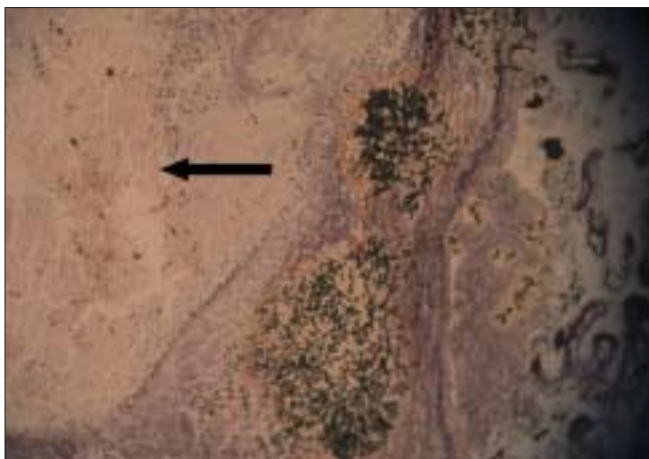


Figure 2: Fungal colonies invading the wall of a blood vessel in the brain, (Grocott stain, x100) Arrow points to vessel lumen

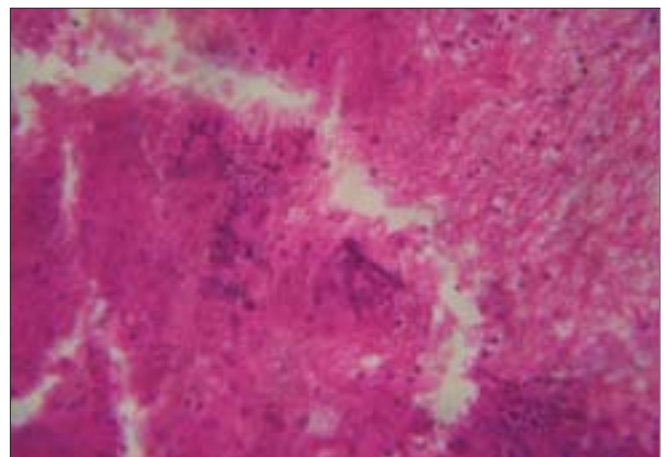


Figure 3: Fungus within a brain infarct, (H and E, x400)

during pregnancy.^[10] Granuloma formation requires an intact cell-mediated type of immunity which is not favored by the immune modulation that occurs during pregnancy. This may have contributed to the absence of well-defined granulomata observed in this case.

The pathological outcome of iatrogenic *Aspergillus* infection of this healthy postnatal woman, was characterized by fulminant necrotizing thromboarteritis, infarcts and fungal abscesses in the thalamic region of the brain together with cerebral and spinal meningitis. The spinal cord appeared more resistant than the brain for invasive disease. Fungal granulomata described, as a prominent feature in the morphological spectrum of *Aspergillus* infection were absent. Although pregnant women are considered immune competent, the modulation of the immune response with depression of selective aspects of cell-mediated immunity may have contributed to the rapid spread of fungus within the subarachnoid space to involve the thalamic region of the brain leading to rapid clinical deterioration with seizures, a stroke due to a thalamic infarct and death.

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