Angioinvasive cerebral aspergillosis presenting as acute ischaemic stroke in a patient with diabetes mellitus

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ABSTRACT
Cerebral angioinvasive aspergillosis is a rare manifestation of disseminated aspergillosis which may result in stroke in immunocompromised individuals. Reports of such disease in patients with diabetes mellitus are rare. We describe a 45-year-old man with diabetes mellitus who presented with a three-day history of right-sided limb weakness and aphasia. Cerebral computed tomography showed features of an acute infarct involving the left anterior and middle cerebral arteries. He was initially treated for an acute ischaemic stroke. Further history revealed that he was investigated for a growth in the sphenoid sinus two months earlier. Culture of the biopsied material from the sphenoid sinus grew Aspergillus fumigatus. Magnetic resonance imaging showed an extension of the growth to the brain, causing the acute ischaemic stroke. He was subsequently diagnosed with angioinvasive cerebral aspergillosis and was commenced on intravenous amphotericin B. Unfortunately, he succumbed to his illness despite treatment.

Keywords: acute stroke, angioinvasive cerebral aspergillosis, Aspergillus fumigatus, brain infection, diabetes mellitus

INTRODUCTION
Invasive cerebral aspergillosis is a devastating disease, with a high mortality rate of 85%–100% despite antifungal treatment\(^1\). It occurs in 10%–15% of patients with disseminated aspergillosis\(^2-3\). Patients who are immunocompromised, especially those with haematological malignancies and organ transplants, are particularly susceptible\(^4-9\). It is, however, rarely reported in patients with diabetes mellitus. The unique ability of the fungus to digest elastin within the vessel wall makes it highly angioinvasive, leading to a wide spectrum of neurological sequelae\(^2-3\). We report the occurrence of cerebral angioinvasive aspergillosis in a patient with diabetes mellitus presenting clinically and radiologically as an acute infarct.
magnetic resonance (MR) imaging of the brain (Figs. 3a–b) confirmed this and showed an extension of the growth from the ethmoid and sphenoid sinuses to the brain, causing the acute ischaemic stroke. Screening for human immunodeficiency virus was negative for both IgM and IgG. Septic screen was also negative. Chest radiograph was normal. He was immediately started on intravenous amphotericin B, with close monitoring of renal and liver functions. However, despite aggressive management, he succumbed to his illness and died ten days later.

**DISCUSSION**

Invasive cerebral aspergillosis occurs in 10%–15% of all cases with the disseminated disease. Involvement of the central nervous system by *Aspergillus* spp. had been
recognised as long ago as the 1930s\(^1\), and is usually as a result of haematogeneously spread from another primary source such as the lungs or the gastrointestinal tract\(^1\). The unique ability of the fungus to digest elastin within the vessel walls makes it a highly virulent and angioinvasive organism\(^2-5\). A recent review found that most cases of cerebral invasive aspergillosis occurred in the severely immunocompromised patients\(^6\), such as those with organ transplant\(^2\). In addition, haematological malignancies\(^7\), such as leukaemia\(^8\) and lymphoma, carry an additional risk, compared to other sources of immunosuppressive illnesses such as AIDS\(^9\), diabetes mellitus, steroid use or chemotherapy\(^10\). There has been little data on cerebral invasive aspergillosis in patients with diabetes mellitus, thus making our patient an atypical subject. As the chest radiograph of our patient was normal, the fungal dissemination in this patient must have occurred from the paranasal sinuses. This is unusual as cerebral invasive aspergillosis is most commonly haematogeneously spread from the lungs or the gastrointestinal tract, rather than as a direct extension of sinonasal disease\(^1,3\).

The pathophysiology of aspergillosis sets it apart from other infectious organisms. It causes an infective vasculopathy leading initially to acute infarction or haemorrhage, and later extending into surrounding tissue as infectious cerebritis which may later evolve into an abscess\(^3-6\). It has an affinity for the perforating arteries, such as the lenticulostriate and thalamoperforator arteries, leading to infarcts or petechial haemorrhages within the basal nuclei and thalamus\(^1\). The angioinvasive nature of the fungus is due to its ability to digest elastic tissue by producing elastase. As the perforator arteries have a narrower lumen, they tend to be affected much earlier. Other typical sites involved include the corpus callosum and the midbrain\(^2,3\). As pyogenic infections and thromboembolic events rarely involve the corpus callosum, the involvement of the latter should raise the suspicion of cerebral aspergillosis. Hyphal elements may also grow through the vessel wall thus compromising the structural integrity of the vessel wall leading to the formation of mycotic aneurysms\(^1,3-6\) of the larger arteries leading to rupture and massive haemorrhage. In addition, the lumen of the vessels may be completely occluded by the hyphal elements leading to ischaemic stroke. This is the most likely explanation in our patient who presented with an acute infarct in the both the ACA and superior division of MCA territory. The close proximity of the sphenoidal sinus to the cavernous carotid artery may have provided the opportunity for invasion of the ACA and the superior division of the MCA as demonstrated on the initial brain CT.

The simultaneous involvement of the superior division of MCA and ACA in this patient suggests two possibilities. Firstly, an extension of infection from the internal carotid artery, leading to growth of hyphal elements into the MCA territory might have occurred, or alternatively, the fungal elements from the carotid artery might have embolised into the superior division of MCA. The latter seems more likely, given the fact that only the superior division of MCA was involved, rather than the entire MCA. On the other hand, the involvement of ACA could also have resulted in the direct spread of the fungus through the brain parenchyma to involve the superior division of MCA. However, this is less likely as the involvement of ACA and the superior division of MCA was simultaneous.

The cerebrospinal fluid is usually sterile with mild elevation of protein levels and organisms are rarely cultured. Serology of aspergillus antigen in blood and cerebrospinal fluid remains experimental. Confirmation of diagnosis is usually difficult, as special staining and histopathological analysis is required\(^1\). A lumbar puncture was not done in our patient, given the initial suspicion of a purely vascular event. Neuroimaging studies are useful in the diagnosis of central nervous system aspergillosis. On CT of the brain, the lesions generally have low attenuation and may be accompanied by areas of haemorrhage\(^2,3\). The similar lesions often appear hyperintense on T2-weighted or proton density MR images and exhibit restricted diffusion on diffusion-weighted MR images indicating infarction\(^2,3\). There is usually subtle or no enhancement of the lesions following contrast administration on both CT and MR imaging. Dural enhancement, however, is often visible, whereas ependymal and leptomeningeal enhancement are rare\(^2,3\). Abscesses or granuloma formation are rare, especially in the severely immunocompromised patients whose immune system is deficient\(^1,10-12\).

The prognosis of cerebral angioinvasive aspergillosis is poor, with a high mortality rate of 85%–100% despite aggressive therapy\(^1,6,13-15\). This patient died despite the institution of systemic antifungal therapy. The survival depends on the disease burden and the extent of involvement. The development of mycotic aneurysms\(^12\) heralds a grave prognosis. Aggressive systemic antifungal therapy, either with or without intrathecal therapy, may be necessary to decrease the mortality rate associated with this aggressive disease. Reports have suggested that newer antifungals such as variconazole\(^10\) (a novel triazole) may be promising in treating this potentially fatal disease. In conclusion, cerebral angioinvasive aspergillosis may also occur in patients with diabetes mellitus and who are relatively immunocompetent. Hence, a high index of suspicion is necessary for early institution of therapy to reduce the significant mortality associated with this potentially-fatal illness.
REFERENCES