Central nervous system aspergillus infection complicating renal transplantation

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SUMMARY

A case of catastrophic intracerebral haemorrhage secondary to aspergillus infection in an immunocompromised renal transplant patient is presented. The pathological features and related images are described and the radiology of CNS aspergillus infection is reviewed.

Key words: central nervous system aspergillus infection; renal transplantation.

CASE REPORT

A 37-year-old woman was admitted with abdominal pain. She had recently received a cadaveric renal transplant following failure of the previous live donor kidney. Gastroscopy showed changes suspicious of cytomegalovirus (CMV) gastroduodenitis and she was treated with gancyclovir, with resolution of her symptoms. While in hospital her creatinine began to rise. The renal biopsy was suggestive of cyclosporin toxicity and the cyclosporin level was raised 537 mg/mL (normal 160–360 mg/mL).

Several days later, she developed slurred speech and weakness in her right arm. Non-contrast CT showed multifocal regions of low attenuation over the right temporal convexity, within the basal ganglia, inferior frontal lobe and corona radiata on the left side (Fig. 1). Magnetic resonance imaging on the same day showed multiple areas of high signal on the FLAIR images, some of which contained central areas of low signal (Fig. 2). There was no significant enhancement post gadolinium (Fig. 3) but several of the lesions showed increased signal on the diffusion-weighted images (Fig. 4), reflecting cytotoxic oedema. In the clinical context of a stroke-like illness and raised cyclosporin levels, changes were interpreted as being likely secondary to a microangiopathy relating to cyclosporin toxicity despite the atypical distribution. Cyclosporin was changed to tacrolimus.

Over the next two days, the patient deteriorated clinically with worsening right-sided weakness. The patient had a low-grade fever but there were no other clinical findings to suggest an infective process and blood cultures and cerebrospinal fluid (CSF) were negative. The chest radiograph showed long-standing pleuropulmonary scarring on the right side (Fig. 5).

Three days later the patient became clinically septic. Chest radiographs showed air space opacity within the left upper and lower lobes (Fig. 6). Bronchoscopy at this time was unremarkable. Repeat CT showed an increase in the size of the cerebral lesions with haemorrhagic transformation of the right basal ganglia mass (Fig. 7a). A further lesion with a peripheral dense rim on the non-contrast images was identified in the right cerebellar hemisphere (Fig. 7b). The possibility of a vasculitis secondary to a fungal infection was raised.

Two days later the patient became comatose with CT showing a large intracerebral haematoma in the left basal ganglia, intraventricular blood and hydrocephalus (Fig. 8). The patient died soon afterwards.

Post-mortem examination showed multifocal cerebral haemorrhage associated with necrotizing vasculitis and aspergillus infection. Aspergillus infection was also demonstrated involving the left lung, myocardium, pericardium and thyroid.

DISCUSSION

Cerebral aspergillosis is a recognized opportunistic fungal infection associated with immunosuppression. Aspergillus fumigatus is the most common human pathogen of the genus aspergillus. Humans are typically infected by inhaling their spores, with the lungs being the primary site of...
Fig. 1. The initial unenhanced CT scan shows patchy areas of low density within the left basal ganglia (black arrow) and inferior frontal lobe (white arrow).

Fig. 2. (a,b) Magnetic resonance FLAIR images performed on the same day as the initial CT show more numerous focal areas of increased signal (selected lesions arrowed).
Fig. 3. No significant contrast enhancement was demonstrated following the administration of gadolinium (white arrow).

Fig. 4. (a,b) Several of the hyperintensities on the FLAIR and T2-weighted images show a marked increased signal on the diffusion-weighted images (white arrow).

Fig. 5. Chest radiograph at this time shows chronic pleuropulmonary scarring within the right lung (white arrow). The left lung is normal in appearance.
Fig. 6. Subsequent chest radiograph taken when the patient was in intensive care. It shows airspace opacity within the left upper lobe (white arrow).

Fig. 7. (a) Repeat CT shows an increase in the size of the focal cerebral lesions, some of which have undergone haemorrhagic transformation (white arrow). (b) A further lesion with a peripheral dense rim on the non-contrast images is identified in the right cerebellar hemisphere (white arrow).

Fig. 8. Final non-enhanced CT scan shows a large intracerebral haematoma extending from the basal ganglia (black arrow) with associated intraventricular haemorrhage (white arrow).
infection. Central nervous system (CNS) involvement is usually by haematogenous dissemination, although direct extension from the nasal cavity or paranasal sinuses can occur.1

Organ transplant recipients are at risk of acquiring systemic aspergillosis with an estimated frequency of 1–10%. The CNS is affected in 80% of patients with disseminated invasive aspergillosis. Cytomegalovirus infection is a risk factor for invasive aspergillosis.

Following haematogenous spread, aspergillus hyphae lodge and block cerebral vessels, resulting in infarction that is typically haemorrhagic. The sterile infarct is converted to a septic infarct when the fungus erodes through the vessel wall, usually with associated cerebritis and abscess formation. This may be complicated by erosion into the subarachnoid space with meningitis/meningoencephalitis or mycotic aneurysm formation. There is typically a paucity of inflammatory reaction histologically in the immunocompromised patient.

The clinical and laboratory diagnosis is difficult. The presenting symptoms are non-specific (typically stroke-like symptoms or seizures) and fever may be absent. Cerebrospinal fluid findings are usually minimally abnormal and the organism is rarely cultured from CSF.

Imaging shows multiple foci, usually in the anterior and middle cerebral artery territories and often involving the basal ganglia.

Five patterns of CT abnormality have been described:2

1. Brain abscess pattern (43%). Single or multiple ring-enhancing lesions with surrounding oedema and typically located at the corticomedullary junction.

2. Haemorrhagic infarction pattern (12%). Broad hypodense area associated with small high-density areas that do not change after contrast administration.

3. Parenchymal haemorrhage pattern (12%).

4. Diffuse necrotic encephalitis pattern (6%). Multiple hypodense lesions without mass effect or contrast enhancement.

5. Mixed pattern (22%). Characterized by the presence of several coexisting lesions (ring enhancing, hypodense and hyperdense).

Magnetic resonance typically shows multiple areas of homogenous high signal on T2-weighted images with a low signal peripheral rim if there is associated haemorrhagic infarction. There is usually minimal contrast enhancement, although large lesions show intravascular and meningeal enhancement as expected in acute infarction. There is usually minimal oedema but the lesions can show increased signal on diffusion-weighted imaging secondary to cytotoxic oedema. The lesions are usually multiple and more numerous on MR than on CT.3

The differential diagnosis includes other infections (e.g. pyogenic and toxoplasmosis) and lymphoma. The presence of a true ring or nodular enhancement consistent with abscess and granuloma formation in these processes militates against aggressive cerebral aspergillosis. Cryptococcus infection is usually associated with meningeal disease.

The neurotoxicity associated with cyclosporin is typically reversible and sometimes referred to as reversible posterior leukoencephalopathy syndrome, although the cortex is typically involved. A similar pattern is seen in cyclosporin toxicity, tacrolimus toxicity, hypertensive encephalopathy and eclampsia.4,5 The cause is thought to be related to endothelial injury whereby endothelium releases endothelin, which is a potent vasoconstrictor, as well as prostacyclin and thromboxane A2, which are associated with thrombotic microangiopathy. Magnetic resonance shows both cortical and white matter abnormalities within the posterior circulation. These consist of focal areas of decreased signal on T1-weighted images and increased signal on T2-weighted images. There is a paucity of literature regarding the diffusion imaging appearances, although follow-up MR does show a significant reduction in the size of the signal abnormality in the majority of cases.4

CONCLUSION
This case illustrates the difficulty in making a premorbid diagnosis of CNS aspergillosis. The diagnosis of early cerebral infarction in a patient considered at risk for invasive aspergillosis, even without overt pulmonary disease, is an indication to institute antifungal therapy.3

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REFERENCES