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INSIDIOUS SINUSITIS LEADING TO CATASTROPHIC CEREBRAL ASPERGILLOSIS IN TRANSPLANT RECIPIENTS

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Cerebral aspergillosis is an important cause of mortality in organ transplant recipients and is typically associated with concomitant pulmonary infection.¹ Herein we describe two patients with insidious *Aspergillus* sinusitis leading to catastrophic CNS infection.

Case reports

Patient 1

A 56-year-old man with pancreas and kidney transplant was transferred to our tertiary care facility with meningoencephalitis and cerebral infarction. He had a history of new onset headache of 6 weeks with fever. His immunosuppressive regimen consisted of mycophenolate mofetil, prednisone, and tacrolimus with prophylactic sulfamethoxazole/trimethoprim and valganciclovir. He had a temperature of 38.9 °C, opened eyes to voice only but followed commands, and neurologic examination showed neck stiffness, dysarthria, right-sided anisocoria, and a left sided hemiparesis. Empiric antimicrobial therapy was started, including fluconazole. CT showed fluid and membrane thickening within paranasal sinuses. Cranial MRI demonstrated enhancement involving the basilar meninges and sphenoid sinus (figure, A). Diffusion-weighted images demonstrated restricted diffusion in the right pons, right cerebellum, and right caudate head consistent with acute infarction (figure, B). Cerebral angiogram demonstrated narrowing of arteries around the basal cisterns and occlusion of the right superior cerebellar artery, consistent with vasculitis secondary to basal meningitis. Lumbar puncture (LP) revealed CSF leukocytes of 1,200/mm³ (94% neutrophils), protein of 73 g/L, and glucose of 64 mg/dL. Fluconazole was changed to voriconazole. Cultures of CSF remained negative. The serum galactomannan antigen test was normal (0.39 index), but CSF galactomannan antigen titers were elevated (6.47 index). Otolaryngology evaluation showed cheesy material in the right sphenoid sinus; fungal smear of the specimen revealed septated hyphae and cultures grew *Aspergillus fumigatus* susceptible to voriconazole. Three weeks after admission, his level of consciousness suddenly worsened. CT showed right frontal cerebral hemorrhage with extension to the ventricles, and hydrocephalus. An external ventricular drain was inserted. The patient died 4 weeks after admission. Autopsy showed frontal hematomas with extension into the ventricular system resulting in midline midbrain herniation (figure, C). Microscopy showed

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focal vascular invasion of *Aspergillus* species, and subarachnoid and intraparenchymal hemorrhages (figure, D).

Patient 2

A 62-year-old woman with kidney transplant was transferred to our tertiary care facility with chronic meningoencephalitis and altered consciousness. She had a history of headache of 6 months duration. LP 3 months prior to admission showed leukocytes of $101/\text{mm}^3$ (27% neutrophils), protein of 47 g/L, and glucose of 40 mg/dL; empiric antimicrobial treatment was initiated. Diagnostic tests on serum and CSF had been negative. Her immunosuppressive regimen consisted of mycophenolate mofetil, prednisone, and tacrolimus with prophylactic sulfamethoxazole/trimethoprim. Neurologic examination showed disorientation to place and time but was otherwise normal. CT showed membrane thickening within the sphenoid sinuses and MRI showed an enhancing suprasellar mass extending into the sphenoid sinus with meningeal enhancement over the tentorium and falx. LP showed leukocytes of $286/\text{mm}^3$ (90% neutrophils), protein of 83 g/L, and glucose of 27 mg/dL. Amphotericin B lipid derivative treatment was added to the empiric regimen. Although serum galactomannan antigen titers were normal (0.06 index), CSF galactomannan was antigen titers were elevated (2.72 index). Biopsy of sphenoid showed inflammation but cultures remained negative. Twelve days after admission, she suddenly became unresponsive. CT demonstrated subarachnoid hemorrhage (figure, E through F). She died and autopsy showed cerebral aspergillosis.

Discussion

Sinusitis should be recognized as an early sign of aspergillosis and often presents with new onset headache. Untreated, it can be followed by symptoms of chronic meningitis and ischemic or hemorrhagic stroke. *Aspergillus* species have an affinity for invading blood vessels and spreading along the internal elastic lamina of these vessels, inducing vasculitis and thrombosis.

Fungal cultures of CSF often remain negative. Galactomannan applied to serum can be used as screening tools for the identification of patients with invasive aspergillosis.² The sensitivity of this test in immunocompromised patients has been reported up to 90% (specificity 93–99%), but is decreased by antifungal therapy.² A few studies have reported detection of galactomannan in CSF in patients with cerebral aspergillosis.^{3–7} CSF galactomannan sensitively detected cerebral aspergillosis with 12 of 13 reported patients having elevated CSF indexes.^{3–7} Serum antigen titers were reported in seven of these patients and all were substantially elevated. Serum galactomannan antigen titers were normal in our patients, whereas CSF indexes were elevated. Detection of circulating galactomannan in serum requires substantial leakage of antigens from the site of infection into the circulation, which might not be present in isolated cerebral aspergillosis. A prospective multicenter study on the diagnostic value of galactomannan in patients with cerebral aspergillosis is needed. Our findings indicate that, in cases of cerebral aspergillosis, galactomannan antigen may be detected in CSF when serum indexes are normal.

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Figure. Sinusitis leading to catastrophic cerebral aspergillosis

Patient 1: Axial T1-weighted contrast enhanced MRI obtained on day 4, demonstrating extensive enhancement within the sphenoid sinus and adjacent skull base (A). Diffusionweighted images ($b = 1,000 \text{ mm}^2/\text{second}$) and corresponding ADC maps showing restricted diffusion in the right pons, right cerebellum, and right caudate head consistent with evolving acute infarcts (B). Autopsy showed fatal lobar hemorrhage (C); microscopy demonstrated focal vascular invasion by hyphal elements of *Aspergillus* (D, magnification $\times 200$). Patient 2. On day 12, head CT demonstrates interval development of a large volume subarachnoid hemorrhage within the basilar cisterns, and additional intraventricular hemorrhage within the third and fourth ventricles (E and F). There is marked hydrocephalus and increased fluid and high attenuation material within the sphenoid sinuses and sphenothmoidal recesses.