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Disseminated *Pseudallescheria boydii* infection successfully treated with voriconazole

A 56 year old, right handed African-American man with past history of left knee osteoarthritis, remote intravenous drug use, remote alcoholism, and seropositivity for hepatitis C was admitted to a local hospital for fatigue, chest pain, 13.6 kg weight loss, night sweats, and vision loss. On examination, a loud systolic murmur was present. An electrocardiogram (ECG) displayed T wave alternans and a transoesophageal echocardiogram revealed severe mitral regurgitation with mitral valve vegetations, ruptured chordae tendineae, and left ventricular ejection fraction of 75%. He was diagnosed as having endocarditis and cytomegalovirus endophthalmitis, and was treated with ceftriaxone, vancomycin, ganciclovir, foscarnet, aspirin, metoprolol, lisinopril, nifedipine, and intravenous esmolol. He developed fever (39.3℃) and his mental status declined. A head computed tomography (CT) scan showed left occipital haemorrhage. His left leg became cold and pale with an ankle:brachial index of 0.4. Blood cultures grew yeast. Amphotericin B was started and he was transferred to our hospital for further care.

Upon arrival his temperature was 36.4℃, pulse was 80 beats per minute and regular, respiratory rate was 25 per minute, and blood pressure was 106/76 mm Hg on the right and 160/83 mm Hg on the left. On auscultation a II/VI holosystolic murmur over the apex and bibasilar rales were heard. His left leg was cold with pulses detectable only by Doppler. He was alert and oriented to person and place only, and recalled 1/3 items after short delay. His speech was fluent and well articulated. He had light perception on the right and was only able to count fingers centrally on the left. He displayed mild left leg weakness, normal reflexes and flexor plantar responses, mild right pronator drift, and diminished left sided proprioception. Ophthalmological examination disclosed dense bilateral vitreous infiltrates, retinal lesions, segmental retinal detachments, and scattered choroidal inflammation worse on the right. Flucytosine was added.

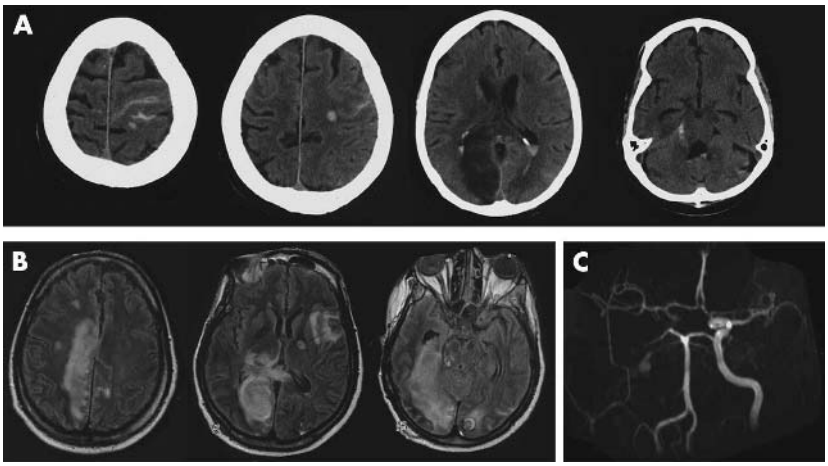

Figure 1 (A) Head computed tomography scan showing left parietal intraparenchymal, subarachnoid, and intraventricular haemorrhages, right middle cerebral and anterior cerebral arteries, bilateral posterior cerebral arteries and left insular artery ischaemic infarcts. (B) In addition, a brain magnetic resonance imaging (MRI) scan shows right thalamic and left internal capsule lacunes, and the initial left occipital ischaemic infarct with haemorrhage. (C) A magnetic resonance angiogram showing no flow in the right internal carotid artery.

An ECG revealed a prolonged QT interval, Q waves in II, III, and AVF leads, and signs of left ventricular hypertrophy. The laboratory studies revealed a white blood cell count of 25 600/μl with 69% neutrophils, 23% lymphocytes, 6% monocytes, 1% eosinophils, and 1% bands; haematocrit, 30%; platelets, 207 000/μl; troponin T, negative; aspartate aminotransferase (AST) and alanine aminotransferase (ALT), mildly elevated at 79 U/l and 99 U/l, respectively (a finding attributed to active hepatitis C); alkaline phosphatase 96 U/l; and the erythrocyte sedimentation rate (ESR) 26 mm/hr. Serological examination for human immunodeficiency virus (HIV) was negative.

A thoracoabdominal CT scan disclosed a 2×2 cm mass in the right subclavian and common carotid arteries and a right renal infarct. The left iliac artery was occluded. Intravenous heparin, in attempt to salvage the left leg, resulted in left parietal subarachnoid, intraparenchymal, and intraventricular haemorrhages. The causative organism was identified as *Pseudallescheria boydii* resistant to amphotericin, flucytosine, and fluconazole. On day 13 voriconazole was begun. He underwent urgent mitral valve replacement and left superior and profunda femoral, and iliac embolectomy. Heparin was discontinued, and he remained in prolonged coma. A head CT scan displayed new right frontoparietal, right anterior cerebral artery (ACA), right posterior cerebral artery (PCA) and bilateral small cerebellar infarcts (fig 1A). A follow up brain magnetic resonance imaging (MRI) scan revealed several new small left frontal and parietal haemorrhages and ischaemic infarcts of the right thalamus, ACA, and PCA along with the left insula, basal ganglia, and parietal lobe (fig 1B). The right internal carotid artery was occluded (fig 1C). The findings were attributed to infectious emboli and haemorrhaging from mycotic aneurysms.

On day 38 of hospitalisation the patient's coma resolved. He was eventually able to follow simple commands, and sit and stand, although expressive aphasia and left hemiparesis remained. His vision improved to 20/800 on the left. He was subsequently discharged to a long term care facility.

Discussion

Pseudallescheria boydii (anamorph or asexual phase: *Scedosporium apiospermum*) is a ubiquitous saprophytic fungus commonly found in soil, manure, decaying vegetation, and polluted water. Its commonest clinical presentation in the USA is as mycetoma, a chronic limited subcutaneous infection in immunocompetent individuals engendered by minor trauma, and is characterised by grain formation and local tissue destruction.[1] However, *P. boydii* has recently emerged as an agent of invasive fungal disease as well, a phenomenon linked to the increasing prevalence of immunosuppression in the community.[1–3] Although endocarditis and endophthalmitis have been described,[1] lung, bone, joint, or central nervous system (CNS) involvement is more typical of this organism.[4] Infections are classically acquired through penetrating trauma[1] or massive inoculation through inhalation, such as may occur in near drowning in stagnant or polluted water.[5] Disease subsequently results from contiguous extension and haematogenous dissemination. It is likely that our patient acquired his infection through prior intravenous drug use, resulting in endocarditis with secondary dissemination to eye, kidney, extremities, and brain.

Among the various types of invasive fungal disease attributable to *P. boydii*, survival rates

appear to be particularly poor with central nervous system and/or valvular involvement. A relatively recent literature review revealed that of 39 patients with documented CNS disease, only nine were known to have survived[3]; no prior reports exist of survivors of endocarditis.[1] Intrinsic resistance to amphotericin B, a mainstay in the treatment of most invasive fungal diseases including aspergillosis and mucormycosis, has been reported repeatedly, a trait undoubtedly associated with poor survival in patients in whom the diagnosis is delayed.[1–3] We describe the first immunocompetent survivor from *P. boydii* native valve endocarditis complicated by multiple ischaemic and haemorrhagic strokes and peripheral embolisation.

Successful treatment of invasive disease due to *P. boydii* hinges upon surgical resection with institution of appropriate antifungal therapy. Miconazole, an imidazole derivative used topically for many dermatophyte infections, was previously the treatment of choice in the light of this organism's resistance to many commonly used systemic antifungals, including amphotericin B and fluconazole. However, its poor CNS penetration,[3] toxicity profile, and unavailability in the USA as an intravenous formulation[1–3] render it less than desirable. Of the azole antifungals, voriconazole, a newly licensed triazole derivative, appears to be the most viable due to its spectrum of activity and excellent CNS penetration. It is steadily becoming the treatment of choice.[3] Although both itraconazole and ketoconazole have been used successfully in treatment of pulmonary pseudallescheriasis,[3] their poor CNS penetration significantly impairs their therapeutic utility in the treatment of brain abscess.

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The patient described in this letter consented to his details being published

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Ocular tilt reaction and anterior inferior cerebellar artery syndrome

The ocular tilt reaction (OTR) is an eye-head postural reaction consisting of ipsilateral head and neck tilt, skew deviation, and ocular torsion. OTR indicates either a unilateral peripheral vestibular deficit (inner ear or vestibular nerve) or a unilateral lesion of brain stem pathways from the vestibular nuclei to the interstitial nucleus of Cajal in the rostral midbrain.

The anterior inferior cerebellar artery (AICA) supplies the lateral inferior pontine tegmentum and middle cerebellar peduncle, vestibulocochlear nerve including the root entry zone, inner ear, and anterior inferior cerebellum.[1] Although there has been one report of skew deviation owing to an AICA infarction,[1] the cardinal features of the OTR have not previously been documented. We describe two patients with AICA infarction, each of whom had ipsiversive OTR—one with complete OTR, the other with skew deviation and tonic ipsiversive ocular torsion.

The first was a 58 year old man with long standing hypertension who presented with sudden vertigo and imbalance. On neurological examination, he had bilateral gaze evoked horizontal nystagmus, left peripheral facial weakness and numbness, dysmetria of the left limbs, and gait ataxia. There was no caloric response on the left side. Pure tone audiometry showed 65 dB sensorineural hearing loss on the left side. The subjective visual vertical with binocular viewing was tilted 17 degrees to the left (that is, counterclockwise from the patient's point of view). Fundus photography showed 25° extorsion of the left eye and 12° intorsion of the right eye. He had a skew deviation with a right hypertropia of 20 prism diopters in primary gaze (fig 1). Magnetic resonance imaging (MRI) including diffusion images showed acute infarcts in the left middle cerebellar peduncle and the left lateral inferior pontine tegmentum (fig 1).

The second patient was a 58 year old woman with type 2 diabetes mellitus and hypertension who developed severe vertigo, hearing loss, tinnitus on the left side, dysarthria, and imbalance. She had bilateral gaze evoked nystagmus with a horizontal-rotatory component. There was left peripheral facial weakness and numbness, dysmetria of the left limbs, and gait ataxia. Pure tone audiometry showed a 65 dB sensorineural hearing loss on the left side. Fundus photography showed 14° extorsion of the left eye and 3° extorsion of the right eye. Prism testing showed a skew deviation with a right hypertropia of 6 diopters in the primary position. Subjective visual vertical with binocular viewing was tilted 13° to the left (that is, counterclockwise from the patient's point of view). Caloric response was absent on the left side. MRI showed new infarcts in the left middle cerebellar peduncle, left lateral inferior pontine tegmentum, and anterior inferior cerebellum, possibly including the flocculus. Two months later the subjective visual vertical was normal. Fundus photography

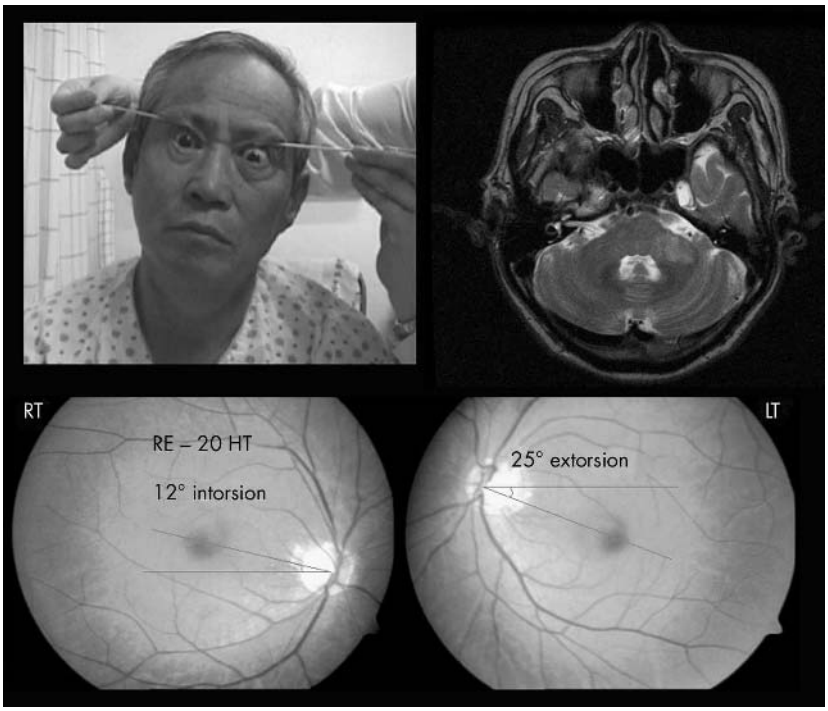

Figure 1 Tonic ocular tilt reaction in patient 1. Note sustained head tilt and concurrent vertical divergence of the eyes (skew deviation). T2 weighted axial magnetic resonance imaging of the brain showed acute infarcts in middle cerebellar peduncle and lateral inferior pontine tegmentum. There is conjugate leftward torsion of the eyes (that is, counterclockwise from the patient's point of view): a 25° extorsion of the left eye and a 12° intorsion of the right. HT, hypertropia; LT, left; RE, right eye; RT, right. Patient consent was obtained for publication of this figure.