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Single Case – General Neurology

Disseminated Aspergillosis with Mediastinal Invasion Causing Fatal Stroke in an Immunocompetent Young Man

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Abstract
Introduction: *Aspergillus flavus* is a common cause of aspergillosis. ***Case Presentation:*** A previously fit and well, immunocompetent 27-year-old male living in Australia developed disseminated *A. flavus* complex infection with mediastinal and cardiac invasion, superior vena cava obstruction and stroke, with fatal haemorrhagic transformation. ***Conclusion:*** *Aspergillus Flavus* is a rare but important cause of serious disease in the immunocompetent.

Introduction

Aspergillus flavus complex is a common species cause of invasive aspergillosis, second only to *Aspergillus fumigatus*, accounting for 13% of cases in one study of infections from transplantation centres in North America [1]. It usually affects immunocompromised hosts, in particular those with prolonged neutropenia, allogeneic haematopoietic stem cell transplant recipients, solid organ transplant recipients, advanced acquired immunodeficiency syndrome

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(AIDS) patients and those on high-dose corticosteroids. It rarely causes invasive disease in the immunocompetent and risk factors are poorly defined but likely include diabetes mellitus, intravenous drug use, and indwelling venous catheters [2, 3].

Case Report

A 27-year-old Indian male was admitted to the Royal Adelaide Hospital in Adelaide, Australia, in August 2021 with a right middle cerebral artery acute ischaemic stroke (AIS). He had no significant medical history, was systemically well, and had lived in Australia since 2014. He awoke with left arm/leg weakness. On initial examination, he was afebrile and in sinus rhythm, with a moderate left facial droop, hemi-hypoesthesia, and mild left-sided neglect. Multimodal computed tomography (CT) brain imaging demonstrated a proximal right M2 occlusion with a moderately sized perfusion lesion (Fig. 1a–c). He was initially treated with aspirin and clopidogrel (endovascular thrombectomy and/or thrombolysis were precluded by mild symptoms and prolonged time from last-known-well to presentation).

On day two post-symptom onset, he developed a junctional bradycardia with absent atrial contraction, suggesting a cardioembolic source for his AIS. On review, the inferior aspect of his CT angiogram demonstrated a mediastinal mass. Given the small infarct volume on magnetic resonance imaging and strong clinical suspicion of malignancy-related cardioembolism he was changed from aspirin and clopidogrel to apixaban (5 mg twice daily).

He underwent a CT Chest/Abdomen/Pelvis which demonstrated a large superior mediastinal mass causing superior vena cava obstruction. Given chronic (asymptomatic) bronchiectasis, tuberculosis was an initial diagnostic consideration and he was placed in isolation on full respiratory precautions. Following subsequent clinical deterioration (below) review of imaging further disclosed a 70 mm × 15 mm left anterior thigh superficial fascia lesion without inguinal or subdiaphragmatic lymphadenopathy, and multiple subtle sclerotic metastatic-appearing lesions throughout the axial skeleton and sternum (Fig. 2a–f).

Pathology results are shown in Table 1. Transthoracic echocardiography showed a distorted aortic root with a mass in the interatrial septum towards the aortic root, with probable extension along the roof of the left atrium suspicious for neoplasm or infection. Left ventricular ejection fraction was normal (approx. 65%) with no mitral or aortic valvular abnormalities. Left atrial size was reduced due to the mass, with flow turbulence. Right ventricular size and function were normal.

On day 3, the patient deteriorated neurologically, with progressive left hemiparesis and obtundation culminating in bilateral fixed and dilated pupils. Repeat non-contrast CT (Fig. 1d) demonstrated a large right parietal intraparenchymal haemorrhage with intraventricular and subdural haemorrhagic extension, obstructive hydrocephalus, 17 mm of midline shift and both parafalcine and uncal herniation. He received emergency right hemicraniectomy with haematoma evacuation and intracranial pressure monitor insertion.

On day 4 of admission, a left thigh lesion was noted on further radiological review, then palpated and biopsied. The patient was started on empiric meropenem (2 g 3 times daily) and voriconazole (6 mg/kg twice daily) therapy. Biopsy cultures ultimately grew *A. flavus* complex.

On day 6 of admission, there were no clinical signs of neurological recovery and he met clinical criteria for brain death [4]. Autopsy showed disseminated *A. flavus* complex infection involving the brain, mediastinum and left thigh. Angioinvasive right middle cerebral artery embolism with infiltration of the right frontoparietal brain parenchyma was present as the cause of haemorrhagic transformation, presumably embolic from aortic invasion. The 120 mm × 80 mm superior mediastinal mass-forming *A. flavus* complex infection

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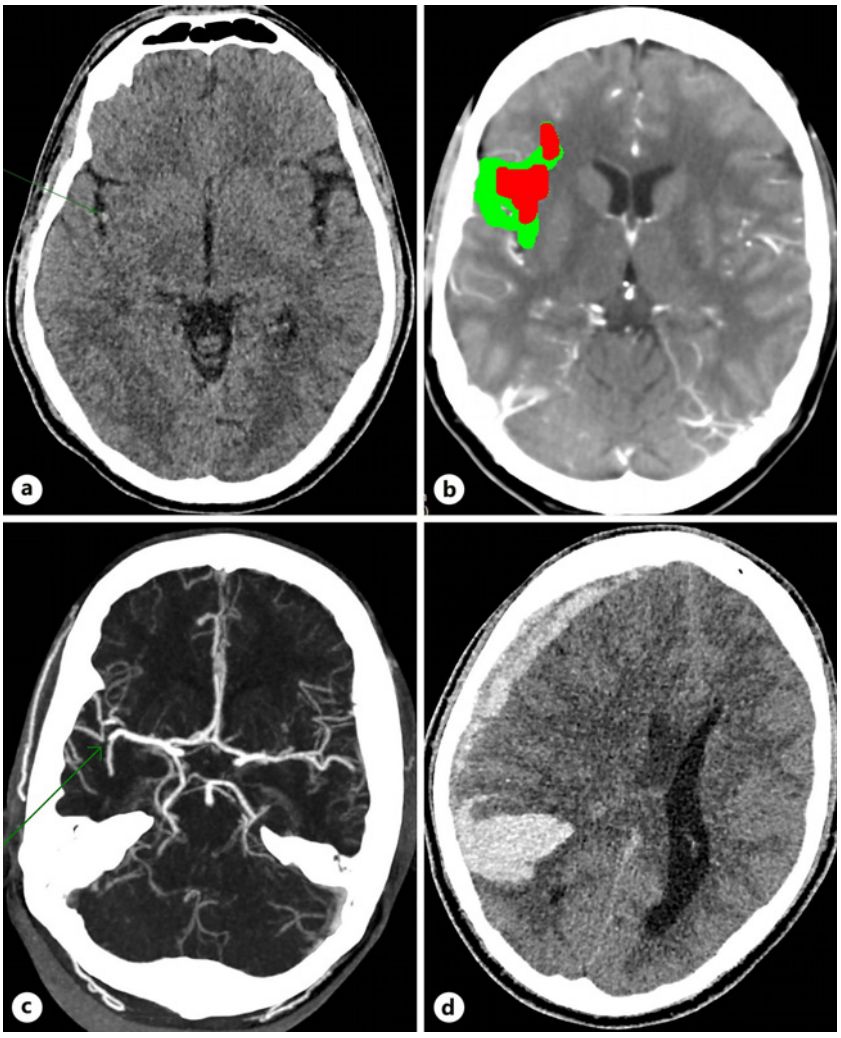

Fig. 1. **a** Top left. **b** Top right. **c** Bottom left. **d** Bottom right.

demonstrated necrotising granulomatous and eosinophilic inflammation encasing the aorta, right pulmonary artery and the superior vena cava, and infiltrating both atria and right ventricular myocardium and endocardium. The 80 mm left thigh soft tissue lesion was confirmed to be granulomatous *A. flavus* complex mass.

Discussion

A. flavus is a common cause of cutaneous aspergillosis, fungal sinusitis, and keratitis but is only responsible for 10% of pulmonary infections [5]. Mediastinal and intracardiac Aspergillus infection is a rare phenomenon [6]. *A. flavus* infection leading to AIS was reported in an immunocompetent child [7], but mediastinal invasion leading to septic embolism resulting in adult stroke appears hitherto unreported.

Fungal pathogens most commonly implicated in AIS include hyphae-forming moulds such as Aspergillus and Mucor species, as well as yeasts including Candida and Cryptococcus species [3, 8]. These moulds are angioinvasive, increasing the likelihood of

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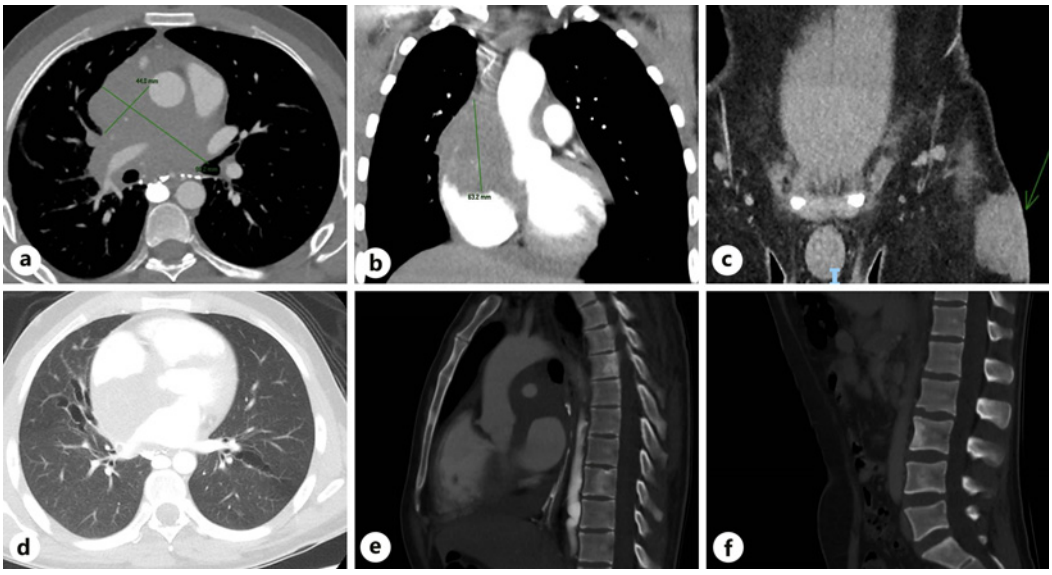

Fig. 2. **a** Top left. **b** Top middle. **c** Top right. **d** Bottom left. **e** Bottom middle. **f** Bottom right.

arterial thrombosis and embolism, in contrast to yeasts which may be more likely to cause multiple punctate strokes due to meningitis and effects on the microvascular circulation [3, 9].

Established risk factors for invasive aspergillosis in immunocompromised hosts include neutropenia and glucocorticoid therapy. Invasive aspergillosis in immunocompetent hosts is exceedingly rare, of unclear cause and was unsuspected in the current case.

Given the rapidly progressive course of invasive aspergillosis, early diagnosis and treatment are essential to prevent dissemination. In cases where cutaneous aspergillosis is suspected, skin biopsy and histopathological examination are required to confirm diagnosis. Similarly to this case, histopathology usually demonstrates diffuse nodular granulomatous mixed infiltrate consisting of lymphocytes, histiocytes, giant cells, septate hyphae, neutrophilic microabscesses, and eosinophils in the dermis. Diagnosis is confirmed via culture.

Once diagnosed, disseminated *A. flavus* infection should be treated with Voriconazole [10]. Other antifungal regimens containing Amphotericin B and Azoles are less effective [11]. Morbidity and mortality despite antifungal therapy remains high although this may be confounded by patient comorbidities.

It is important to maintain a high index of suspicion in order to identify patients with invasive fungal disease early. In patients who present with AIS, additional features suspicious for invasive fungal disease include fever, headache, risk factors (including immunocompromise, indwelling venous catheters or intravenous drug use) and unusual imaging findings such as a mediastinal mass or leptomeningeal enhancement (which may be seen in central nervous system yeast infection) [3].

In the current case, septic embolism was not initially suspected given the absence of fever and systemic symptoms. Haemorrhagic transformation rates in the setting of bacterial endocarditis-related stroke are high with both thrombolysis and anticoagulation [12]. The risk of such treatments may be higher yet in septic fungal emboli, due to angioinvasion, although it is possible that fatal haemorrhagic transformation may have supervened even with anticoagulant avoidance. Nevertheless, stroke treatment caution in the setting of suspected fungal mediastinal invasion would be warranted in future cases.

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Table 1. Pathology results

Test	Reference range, SA pathology	On presentation to hospital	Day 3 of admission
Haemoglobin, g/L	135–175	129	99
White cell count, $\times 10^9$	4–11	12.2	18.64
Neutrophils, $\times 10^9$	1.8–7.5	6.9	16.67
Lymphocytes, $\times 10^9$	1.1–3.5	1.36	1.12
Monocytes, $\times 10^9$	0.2–0.8	0.6	0.5
Eosinophils, $\times 10^9$	0.02–0.5	3.2	0.2
Basophils, $\times 10^9$	<0.1	0.21	0.15
Platelets, $\times 10^9$	150–450	370	550
Prothrombin time, s	12–16	19.2	28.7
International normalised ratio	0.9–1.2	1.4	2.2
Activated partial thromboplastin time, s	24–38	33	31
Apixaban level – anti-Xa activity assay, µg/L	40–230		124
Sodium, mmol/L	135–145	136	141
Potassium, mmol/L	3.5–5.2	4.3	4.8
Chloride, mmol/L	95–110	102	110
Bicarbonate, mmol/L	22–32	22	21
Urea, mmol/L	2.7–8.0	3.2	3.4
Creatinine, µmol/L	60–110	95	70
eGFR, mL/min/1.73m^2	>60	>90	>90
Corrected calcium, mmol/L	2.10–2.60	2.45	2.44
Phosphate, mmol/L	0.75–1.50	0.82	0.77
Albumin, g/L	34–48	34	26
Globulin, g/L	21–41	59	48
Bilirubin, µmol/L	2–24	8	15
Gamma glutamyl transferase, U/L	0–60	46	30
Alkaline phosphatase, U/L	30–110	118	78
Alanine aminotransferase, U/L	0–55	27	14
Aspartate aminotransferase, U/L	0–45	18	25
Lactate dehydrogrenase, U/L	120–250	206	190
Glucose, mmol/L	3.2–5.5*	5.6	9.7
HbA1c, %	≤7	5.5	
C-reactive protein, mg/L	0.0–8.0	55.4	
Erythrocyte sedimentation rate, mm/h	1–10	37	
NT-pro brain natriuretic peptide, ng/L	0–124	602	
25-hydroxy vitamin D3, nmol/L	60–160	5	

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Table 1 (continued)

Test	Reference range, SA pathology	On presentation to hospital	Day 3 of admission
Thyroid stimulating hormone, mIU/L	0.50–4.50	2.92	
Angiotensin-converting enzyme, U/L	20–70	36	
Alpha fetoprotein	≤7	1	
Human chorionic gonadotropin tumour marker, IU/L	≤0.3	<0.3	
Beta-2 μglobulin, mg/L	0.6–2.9	2.3	
Homocysteine, μmol/L	4–14	10	
Alpha-galactosidase activity DBS 4MU, nmol/h/mL	2.0–6.9	4.7	
Antithrombin, %	80–125	88	
Protein C, %	65–130	77	
Protein S, %	65–155	85	
Lupus anticoagulant (via dRVVT)		Negative	
Beta-2 glycoprotein 1 antibody, GU	≤19	<1	
Cardiolipin IgG, GPL units	≤8	3	
F2 (prothrombin) common variant gene F2:c.*97G>A		Not detected	
F5 (factor V) common variant gene F5:c.1601G>A		Not detected	
Anti-nuclear antibody		Speckled; 1:80	
Extractable nuclear antigen		Negative	
Anti-neutrophil cytoplasmic antibody		Negative	
Rheumatoid factor, IU/mL	≤13	<13	
Total IgG, g/L	7.00–16.00	28.12	
IgG1, g/L	3.76–7.96	11.71	
IgG2, g/L	2.25–7.41	5.81	
IgG3, g/L	0.21–1.16	1.18	
IgG4, g/L	0.12–0.96	6.10	
IgA, g/L	0.70–4.00	2.48	
IgM, g/L	0.40–2.30	1.83	
IgE, kU/L	≤119	1,693	
Tryptase, μg/L	<11.9	4.0	
Paraprotein, g/L		0†	
Kappa-free light chain, mg/L	3.00–19.00	54.75	
Lambda-free light chain, mg/L	6.00–26.00	24.93	
Kappa/lambda-free light chain ratio	0.25–1.65	2.20	

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Table 1 (continued)

Test	Reference range, SA pathology	On presentation to hospital	Day 3 of admission
Complement C3, g/L	0.90–1.80	1.58	
Complement C4, g/L	0.10–0.40	0.27	
Flow cytometry (blood)		‡	
HIV 1/2 (p24 core antigen + HIV antibody)		Not detected	
Mycobacterium tuberculum interferon-gamma release assay, IU/mL		Negative	
Schistosoma IgG, s/co	Equivocal: 0.9–1.1	0.94	
Strongyloides IgG, s/co	Not detected: <0.9	0.32	
Toxoplasma gondii IgG, IU/mL	Not detected: <1.0	0.18	

*Reference range shown for fasting glucose; actual specimens were not fasting.
†Electrophoresis shows a diffuse hypergammaglobulinaemia.
‡An expanded population of eosinophils was detected based on CD45 and side scatter. They comprised approximately 27% of total nucleated cells. There is no atypical expression of lymphoid markers. Interpretation: There is no evidence of B cell monoclonality. There is no atypical expression of T cell markers.

In summary, this report describes a rare occurrence of fulminant disseminated and mediastinal *A. flavus* complex infection causing stroke with fatal haemorrhagic transformation in an immunocompetent man. There were no clinically apparent risk factors for disseminated Aspergillosis although it was possible that mild bronchiectasis was a predisposition, or that both represented an undiagnosed immunodeficient state. Thorough skin examination at the time of admission may have led to earlier diagnosis and avoidance of anticoagulation. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536594).

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interests to declare.

Funding Sources

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Author Contributions

R.Y. and R.G. were each major contributors in writing the manuscript; E.P.R., K.S., and T.K. each contributed to editing of the manuscript and analysing the case. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

1 Garcia-Giraldo AM, Mora BL, Loaiza-Castaño JM, Cedano JA, Rosso F. Invasive fungal infection by *Aspergillus flavus* in immunocompetent hosts: a case series and literature review. Med Mycol Case Rep. 2019;23:12–5.
2 Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the infectious diseases society of America. Clin Infect Dis. 2016;63(4):e1–60.
3 George P, Ramiro JI, Gomes JA, Newey CR, Bhimraj A. Central nervous system fungal infection-related stroke: a descriptive study of mold and yeast-associated ischemic stroke. J Stroke Cerebrovasc Dis. 2020;29(6):104759.
4 Australia and New Zealand intensive care society. Death and Organ Donation [accessed 26/09/2022]. Available from: https://www.anzics.com.au/death-and-organ-donation/.
5 Pegues CF, Daar ES, Murthy AR. The epidemiology of invasive pulmonary aspergillosis at a large teaching hospital. Infect Control Hosp Epidemiol. 2001;22(6):370–4.
6 Demaria RG, Dürrleman N, Rispail P, Margueritte G, Macia JC, Aymard T, et al. *Aspergillus flavus* mitral valve endocarditis after lung abscess. J Heart Valve Dis. 2000;9(6):786–90.
7 Gupta J, Chakrabarty B, Singh G, Singh S, Kumar A, Xess I, et al. A rare infective cause of stroke in an immunocompetent child. Brain Dev. 2021;43(1):152–6.
8 Hier DB, Caplan LR. Stroke due to fungal infections. In: Caplan LR, Bogousslavsky J, editors. Uncommon causes of stroke. 2nd ed. Cambridge: Cambridge University Press; 2008. p. 47–52.
9 Practical Neurology. Unusual Causes of Stroke: Infectious Causes of Stroke [accessed 2024 Jan 14]. Available from: https://practicalneurology.com/articles/2020-jan/infectious-causes-of-stroke.
10 Johnson EM, Szekely A, Warnock DW. In-vitro activity of voriconazole, itraconazole and amphotericin B against filamentous fungi. J Antimicrob Chemother. 1998;42(6):741–5.
11 Denning DW, Tucker RM, Hanson LH, Stevens DA. Treatment of invasive aspergillosis with itraconazole. Am J Med. 1989;86(6 Pt 2):791–800.
12 Masuda J, Yutani C, Waki R, Ogata J, Kuriyama Y, Yamaguchi T. Histopathological analysis of the mechanisms of intracranial hemorrhage complicating infective endocarditis. Stroke. 1992;23(6):843–50.