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Locally extensive angio-invasive *Scedosporium prolificans* infection following resection for squamous cell lung carcinoma

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ABSTRACT

We report a case of *Scedosporium prolificans* infection in a patient following surgery for squamous cell lung carcinoma. Combination therapy with voriconazole and terbinafine was commenced for intrathoracic infection and mycotic vasculitis. In spite of antifungal treatment, he developed culture-positive sternal and rib osteomyelitis four months later. Scedosporiosis is not commonly reported in patients with solid organ malignancies, and this case highlights its aggressive nature and propensity for direct local invasion.

1. Introduction

Scedosporium prolificans is a ubiquitous dematiaceous filamentous fungus. Clinical disease can range from asymptomatic colonisation of the respiratory tract, invasive infection involving adjacent and deep structures, and disseminated infection involving distant sites. In the immunocompetent host, infection can also result from penetration of spores due to direct trauma or surgery. *S. prolificans* is an emerging pathogen in immunocompromised hosts, particularly those with prolonged neutropenia. It is highly resistant to antifungals from multiple classes, although synergy has been demonstrated with various combinations of antifungal agents. Here we report a case of locally invasive and aggressive *S. prolificans* in a non-neutropenic patient where *S. prolificans* was still able to be cultured after four months of combination antifungal therapy and whose treatment course was complicated by highly variable plasma voriconazole levels.

2. Case

A 44-year old man was admitted to our institution for resection of a right-sided apical squamous cell carcinoma of the lung (T4N0M0). He had been diagnosed 3 months earlier in the context of non-resolving right apical chest radiographic changes, haemoptysis, Horner's syndrome and right arm motor weakness. Imaging confirmed an apical Pancoast tumour with local invasion of the subclavian vessels and brachial plexus. He underwent local irradiation and chemotherapy (cisplatin, etoposide) two months prior to arrival at our hospital. Due to extensive local invasion he was referred for specialist thoracic, vascular and neurosurgical intervention for tumour resection. His other relevant medical history was malignancy-associated bilateral pulmonary emboli and deep venous thrombosis treated with enoxaparin and inferior vena cava (IVC) filter.

Surgical resection (day 0) was prolonged and technically difficult due to tumour infiltration of surrounding perineural and vascular structures, however histology of the resected tissue revealed post-radiotherapy changes with no residual neoplasia. Surgical margins and surrounding lymph nodes were also negative for malignancy. The immediate post-operative period was unremarkable and he was discharged home on day +9. He returned on day +16 with pleuritic chest pain, dyspnoea and fever. Computed tomography (CT) of his chest revealed a large loculated complex collection containing solid and fluid components in his right thoracic cavity (Fig. 1A). The collection extended into the mediastinum and retrosternal region adjacent to his sternotomy wires, and caused mediastinal shift to the left. He underwent video-assisted thoracopic surgical (VATS) drainage of the collection on day +17. Postoperatively (day +19) he survived three episodes of cardiac arrest requiring cardiopulmonary

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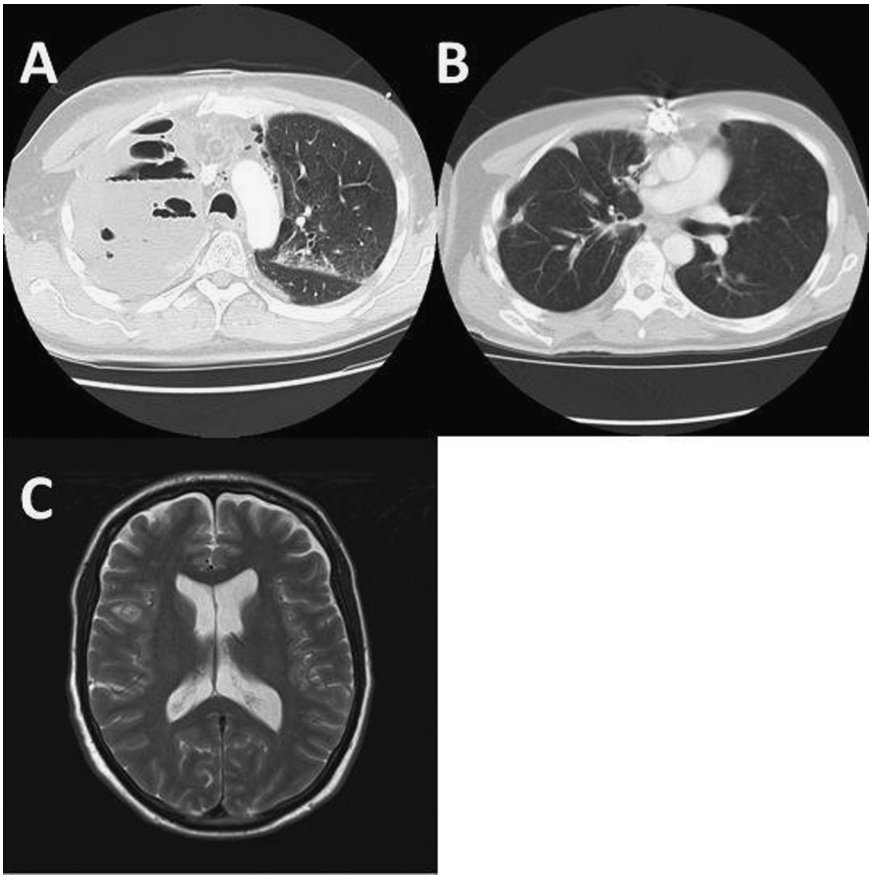

Fig. 1. Radiographic images of chest and brain. (A) Computed tomography of chest (day +16) demonstrating a massive collection within the right hemithorax comprising solid and fluid components and multiple gas locules. There is extension to the retrosternal region without bony erosion or destruction. (B) Computed tomography of chest (day +108) demonstrating 8 mm pulmonary nodule in left lower lobe and resolution of previous right hemithorax changes. (C) Magnetic resonance imaging of brain (day +284), T2-weighted signal, demonstrating right frontotemporal lobe ring-enhancing lesion with some surrounding oedema at the grey-white matter interface.

resuscitation, exploratory right- and left-sided thoracotomies and internal cardiac massage. Massive bleeding from the right subclavian artery was noted and required ligation. Decortication of the right middle and lower lobes was also performed. Twelve days later (day +31) he developed incipient pericardial tamponade and required a left anterolateral thoracotomy for pericardial fluid drainage and pericardial window formation. Other post-operative complications included atrial tachy-arrhythmias managed with sotalol, difficult pain control, depression and physical deconditioning.

Pleural fluid and tissue obtained from the VATS procedure contained moderate numbers of neutrophil polymorphs and cultured *S. prolificans* with no other bacterial pathogens. Antifungal susceptibility testing demonstrated *in vitro* resistance to posaconazole (minimum inhibitory concentration [MIC] > 8 mg/L), voriconazole (MIC > 8 mg/L), amphotericin B (MIC > 8 mg/L) and flucytosine (MIC > 64 mg/L). Synergy testing was not performed on this isolate. Histology of the subclavian artery revealed an acute necrotising vasculitis associated with proliferation of fungal spores and septate hyphae at the adventitial aspect of the blood vessel consistent with mycotic vasculitis (Fig. 2A–C). Unfortunately this tissue was not submitted for microscopy and culture. Pericardial fluid revealed mild active chronic pericarditis but was culture negative for bacteria, mycobacteria and fungi. He was commenced on intravenous (IV) voriconazole (6 mg/kg loading dose for 48 h then 4 mg/kg twice-daily) and oral terbinafine 250 mg twice daily. Electrocardiographic monitoring was mandated by the combined use of voriconazole and sotalol but did not reveal any QT interval prolongation. Routine CT scanning of his brain and sinuses did not reveal any evidence of fungal disease. An immunodeficiency screen was unremarkable (human immunodeficiency virus serology, immunoglobulins, immunoglobulin G subclasses, serum protein electrophoresis), and he had normal white blood cell and neutrophil counts with a mild lymphopenia (0.8×10^9/L; reference 1–4×10^9/L). The absolute CD4 count was low (262 cells/μL; reference 330–1310 cells/μL) but was consistent with his lymphopenia, and CD4 percentage was normal (36.2%; reference 35–59%). A repeat CD4 count was not performed. Further history was obtained from the patient, and he reported spending time in a newly created vegetable garden following diagnosis of his lung carcinoma.

Voriconazole therapy was complicated by variability in plasma levels. Initial steady state trough levels were supratherapeutic (12.8 mg/L) and were associated with visual hallucinations; the subsequent maintenance dose of oral voriconazole was 250 mg twice daily in combination with terbinafine. Despite these initial problems with voriconazole toxicity, maintaining plasma voriconazole trough levels within the target range (1–5.5 mg/L) was subsequently difficult after two months of therapy (Table 1). None of his concomitant medications are known to be associated with increased voriconazole metabolism, so autoinduction of hepatic metabolism was suspected. Apart from increasing voriconazole to 400 mg twice daily, pantoprazole 40 mg twice daily was also added for cytochrome P450 inhibition. He developed hepatic dysfunction, with elevated alkaline phosphatase (255 U/L; reference 35–110 U/L) and gamma glutamyltransferase (395 U/L; reference 5–50 U/L). Hepatic aminotransaminases and bilirubin were normal, and ultrasound and CT scanning of the abdomen did not reveal any anatomical hepatobiliary abnormalities or subdiaphragmatic metastatic disease.