Aspergillus vertebral osteomyelitis and epidural abscess

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ABSTRACT

We present the first reported case of *Aspergillus* vertebral osteomyelitis and epidural abscess in Singapore in a 50-year-old man with post-tuberculous bronchiectasis. The patient presented with acute urinary retention and flaccid paraplegia. Despite surgical debridement and treatment with voriconazole, the patient developed multiorgan failure and died two weeks after presentation. Early diagnosis and prompt initiation of treatment are emphasised in the hope of improving the outcome of this aggressive condition.

Keywords: *Aspergillus* spp., epidural abscess, osteomyelitis, vertebral osteomyelitis

Singapore Med J 2009;50(4):e151-e154

INTRODUCTION

Vertebral involvement in aspergillosis is rare and carries a high mortality.[1] To our knowledge, this is the first reported case in Singapore of *Aspergillus* vertebral osteomyelitis with epidural abscess causing a rapidly-progressing compressive myelopathy.

CASE REPORT

A 50-year-old man, with a background history of pulmonary tuberculosis, diabetes mellitus and bronchiectasis, was admitted to our department in October 2007. He had a history of pulmonary tuberculosis in 2004 and completed a course of anti-tuberculosis therapy. His condition was subsequently complicated by bronchiectasis and recurrent haemoptysis. In May 2007, he experienced massive haemoptysis and underwent right middle lobe lobectomy, following a failed bronchial artery embolisation. The histology of the resected lung showed chronic granulomatous inflammation with cavitations and pleural adhesions, and *Aspergillus* fungal balls. Systemic antifungal treatment was not started then, as the patient was improving clinically and the lesion had been surgically excised.

In October 2007, he presented with cough with increased sputum production, shortness of breath and right-sided chest pain, made worse on movement and inspiration. Examination on admission showed a cachexic man, with reduced chest expansion and breath sounds of the right lung. The haematological profile showed haemoglobin of 10.2 g/dL, white cell count of 16.2×10^9/L (differential count: neutrophils 84.8%, lymphocytes 10.3%, monocytes 4.7%, eosinophils 0.1%, basophils 0.1%). The albumin level was reduced to 25 g/L. Blood urea and serum creatinine levels were normal. The chest radiograph showed a lucent postsurgical cavity in the right hemithorax, consolidation and pleural thickening of right lower zone and reticulonodular shadowing in the left mid zone (Fig. 1), which was similar to the previous chest radiograph taken in September 2007. He was treated for infective exacerbation of bronchiectasis with a course of amoxicillin-clavulanate.

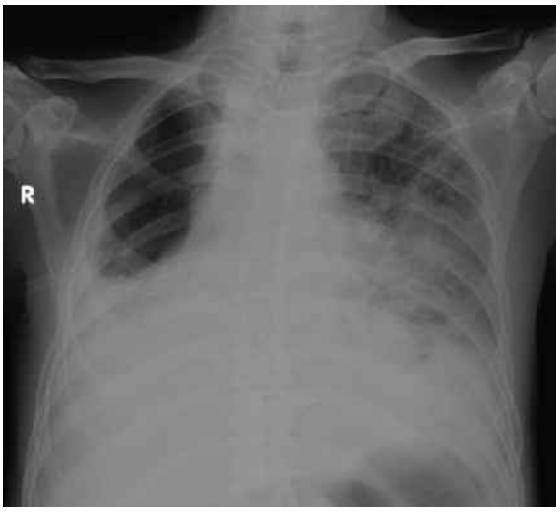

Fig. 1 Chest radiograph taken in October 2007 shows a lucent postsurgical cavity in the right hemithorax, consolidation and pleural thickening of right lower zone and reticulonodular shadowing in the left mid zone.

During the course of the admission, he developed acute urinary retention and rapidly progressive flaccid paraplegia within one week. There was no fever, back pain or history of trauma. Examination revealed bilateral lower limb flaccid paraplegia and absent deep tendon reflexes. There was diminished sensation in his lower limbs. The anal tone was reduced and an indwelling catheter was inserted to relieve the acute urinary retention. Urgent magnetic resonance (MR) imaging of the thoracolumbar spine was done in November 2007. It showed osteomyelitis involving T2–T8 vertebral

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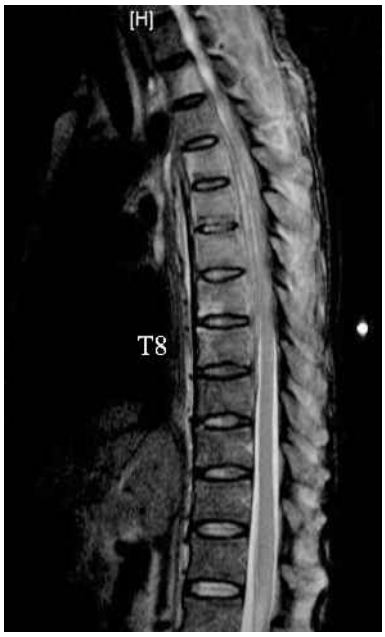

Fig. 2 Sagittal T2-W MR image shows marrow oedema of T2–T8 vertebral bodies and an anterior epidural fluid collection.

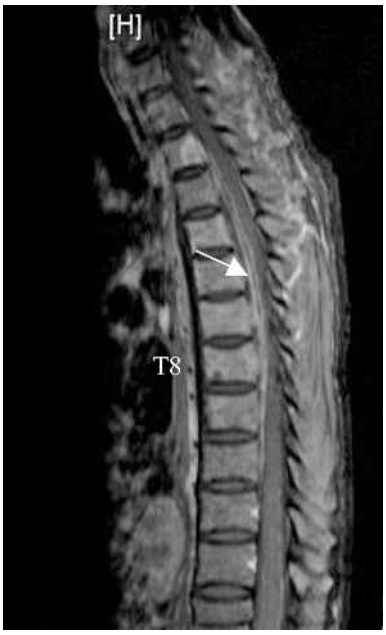

Fig. 3 Contrast-enhanced sagittal T1-W MR image shows enhancement of T2–T8 vertebral bodies with an anterior epidural abscess (arrow) and cord compression.

bodies with associated paravertebral tissue and posterior element bone and soft tissue infective changes, worse on the right side. There was an anterior epidural abscess extending from T2 to T9 levels, resulting in moderate spinal cord compression (Figs. 2–4).

The patient underwent emergency surgical exploration, which showed a small anterior epidural collection of caseous material anterior to the spinal cord at the T4–T6 levels, necrotic paraspinal muscles, thickened dural lining, and caseous necrosis of the right side of right T4–T6 vertebrae, causing narrowing of the right T4–T6 foraminae and scarring of the exiting T4–T6 roots. T2–T8 decompression laminectomy, T4 costovertebral joint excision and anterior drainage of epidural abscess were performed. Empirical anti-tuberculosis therapy was started, based on the surgical findings. The histopathological specimen, however, showed *Aspergillus* spp. The culture of surgical tissue grew *Aspergillus (A.) fumigatus*. Blood and sputum samples for fungal smear and cultures were negative. Surgical tissue smear for acid-fast bacilli was negative. The patient was started on intravenous voriconazole at 6 mg/kg 12-hourly, and then maintained on oral formulation at 200 mg twice daily. Anti-tuberculosis therapy was stopped. Despite treatment, the patient's condition remained poor. There was no significant neurological recovery postsurgery. He developed multiorgan failure and died two weeks after the surgery.

DISCUSSION

Aspergillus spp. are ubiquitous opportunistic moulds. Of the approximately 300 species known, only a few are pathogenic. The most common species of *Aspergillus* causing clinical disease include *A. fumigatus, A. flavus, A. niger* and *A. terreus*.[2] Despite its ubiquity and prevalent exposure, tissue invasion with these fungi are rare. It occurs primarily in severely immunocompromised hosts with prolonged and severe neutropenia, haematopoietic stem cell and solid organ transplantation, advanced acquired immunodeficiency syndrome, or chronic granulomatous disease,[3] which our patient did not have. However, recent data suggests that invasive aspergillosis may also be a concern in relatively less immunocompromised patients in the intensive care unit setting, particularly those with underlying chronic obstructive pulmonary disorder on steroid therapy, and those with liver failure.[4] Our patient did not have any of the above conditions, but he had diabetes mellitus, which has been associated with *Aspergillus* spp. colonisation and which may be a risk factor for the invasive disease.[5] In addition, cases of invasive aspergillosis in apparently immunocompetent subjects have been reported.[6]

Central nervous system (CNS) involvement is the most lethal complication of invasive aspergillosis with a reported mortality of more than 95%. It occurs in 10%–20% of invasive aspergillosis, usually in the form of cerebral aspergillosis.[7] Spinal osteomyelitis and epidural abscess causing compressive myelopathy, as encountered in our case, is rare. Current literature on similar conditions is largely limited to case reports only.[6] The source in our patient is probably from the lungs, via either haematogeneous spread, given the propensity of the fungus for vascular invasion, or contiguous extension. There was no history of iatrogenic

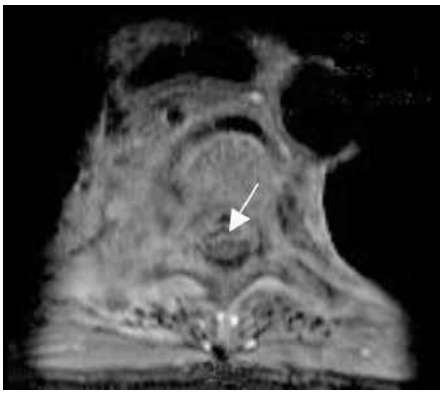

Fig. 4 Contrast-enhanced axial T1-W MR image of the T5 vertebra shows the vertebral body, right pedicular and transverse process infective changes and anterior epidural abscess (arrow).

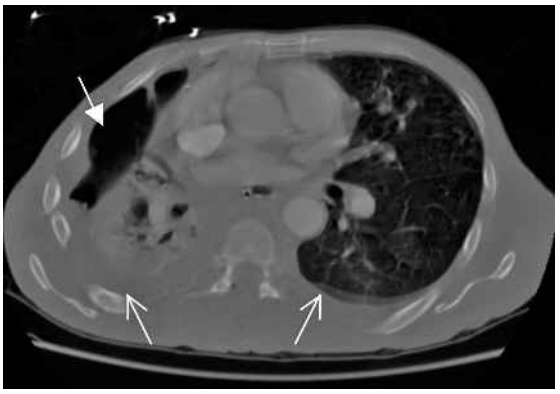

Fig. 5 CT image of the thorax shows a right pneumothorax (bold arrow) with collapse of the underlying right lung and bilateral effusions (arrows).

spinal inoculation during his previous right lobectomy. Computed tomography (CT) of the chest showed a right pneumothorax with collapse of the underlying right lung and bilateral effusions (Fig. 5). However his condition deteriorated rapidly and precluded further confirmatory investigation for pulmonary aspergillosis, including pleural fluid aspiration, bronchoalveolar lavage and biopsy.

Early diagnosis of invasive aspergillosis depends on a high index of suspicion, and differentiating it from colonisation remains a challenge.[5] Histological and cultural evidence from tissue biopsies or resection material, or positive cultures from normally sterile body fluids are the current gold standard of diagnosing invasive aspergillosis. Both methods, however, are limited by significant time delay and low sensitivity. There is a current shift in emphasis from waiting for definitive diagnosis to screening high-risk patients using non-culture methods to facilitate early initiation of antifungal therapy in the hope of improving outcome.[3] Promising assays include galactomannan and polymerase chain reaction (PCR)-based assays. Enzyme immunoassay detection of galactomannan has high sensitivity and has been validated for diagnosing invasive aspergillosis in patients with haematological malignancy.[8,9] It also allows an earlier diagnosis as the detection of galactomannan preceded diagnosis based on radiological examination or *Aspergillus* spp. isolation by up to nine days.[8] Its use however may be limited by its lower sensitivity in non-neutropenic patients and false positive reactions with certain antibiotics, such as pipercillin-tazobactam and amoxicillin-clavulanate.[10] This test is readily available in Singapore.

PCR-based detection of *Aspergillus* DNA is currently investigational but has shown good potential in clinical use. It is rapid, highly sensitive (ranging from 88% to 100%) and may even eventually allow species-specific diagnosis.[11] In addition, it can be used for cerebrospinal fluid, and has the potential to improve the diagnosis of CNS aspergillosis, where biopsy is often not feasible and culture is frequently negative.[12] However, false positive results due to environmental contamination and frequent colonisation need to be taken into consideration in the clinical setting. Diagnostic imaging with CT or MR imaging is essential for staging disease and for providing a guide for orthopaedic or neurosurgical intervention in *Aspergillus* spinal osteomyelitis. Its findings are however non-specific, and differentiating it from tuberculous spondylitis, particularly in an endemic region, is difficult. Image-guided biopsy is a useful tool in directing treatment.[13] It was not performed for our patient as he had significant compression with neurological deficits which required surgical treatment.

Treatment of invasive aspergillosis is multimodal, involving reversal of underlying immunosuppression, when possible, early initiation of antifungal therapy and surgical intervention, where applicable.[6] Numerous studies, including a large randomised controlled trial,[14] have demonstrated the superiority of voriconazole over amphotericin B in the treatment of invasive aspergillosis, with improved survival and lower toxicity. The Infectious Diseases of America has recently released its guidelines on the treatment of aspergillosis in January 2008. It recommended voriconazole as the primary treatment of invasive aspergillosis, including CNS aspergillosis. The treatment is initiated with a loading dose of voriconazole 6 mg/kg intravenously every 12 hours for two doses, followed by 4 mg/kg every 12-hourly. Intravenous voriconazole should be used cautiously in renal failure because its vehicle molecule cyclodextrin is renally cleared. The effect of accumulation of cyclodextrin in renal failure is currently not established. The oral formulation does not contain cyclodextrin and has good bioavailability. It is hence a good alternative for our patient who had renal failure. The patient should be monitored closely for adverse effects, including hepatotoxicity, visual disturbances and skin rash. As voriconazole is both a substrate and an inhibitor for CYP2C19,

CYP2C9 and CYP3A4, the patient's medication must be reviewed for potential deleterious drug interactions.[15] Combination therapy using voriconazole, amphotericin B and caspofungin may have better efficacy, but is not recommended as a first-line treatment due to higher toxicity, possible drug interactions and limited data. *Aspergillus* osteomyelitis requires combined surgical and medical therapy. Recently, voriconazole has also been used successfully either as salvage or primary therapy, albeit only in a small number of cases. The goal of surgery is to isolate the causative organism if image-guided biopsy is inconclusive or not feasible, and to perform decompression when there is spinal instability or symptoms of spinal cord or radicular compression. The extent of surgery should be individualised. Patients with epidural abscess and extensive bony destruction will require more extensive surgery, including laminectomy and abscess drainage.[1]

In conclusion, *Aspergillus* vertebral osteomyelitis and extradural abscess is a rare cause of compressive spinal myelopathy. Early definitive diagnosis remains a challenge and requires a high index of suspicion. Strategies based on non-culture methods have shown potential in allowing earlier diagnosis, and hence initiation of antifungal therapy in the hope of improving outcome. Voriconazole, in combination with surgery, is the primary treatment for *Aspergillus* osteomyelitis. Despite current treatment, the outcome of invasive aspergillosis, including *Aspergillus* osteomyelitis, remains dismal.

ACKNOWLEGDEMENT

The authors would like to acknowledge the invaluable contribution of Dr Jean-Pierre Laporte, Departments of Diagnostic Radiology and Orthopaedic Surgery, Alexandra Hospital, and the Departments of Pathology and Laboratory Medicine, National University Hospital.

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