Successful Management of Aspergillus Fumigatus Osteomyelitis In A Lung Transplant Recipient

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Citation

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Abstract

Fungal osteomyelitis is a rare, life threatening complication of solid organ transplantation often associated with long term sequelae. Here we describe the use of a multi-disciplinary management approach including combination antifungal therapy, surgery and hyperbaric oxygen therapy in the successful management of Aspergillus fumigatus osteomyelitis of the humeral head in a lung transplant recipient. To our knowledge this is only the third documented case of Aspergillus fumigatus osteomyelitis in a lung transplant patient and the first involving a patient with no known primary source of aspergillosis.

CASE REPORT

A 26 year old man underwent bilateral sequential lung transplantation for cystic fibrosis complicated by respiratory failure. The recipient was seropositive for cytomegalovirus (CMV). The peri-operative course was complicated by type 1 hypersensitivity to methylprednisolone leading to cardiac arrest requiring urgent institution of cardiopulmonary bypass via the groin and re-operation for severe intra-thoracic haemorrhage. Post-transplant immunosuppression consisted of cyclosporin (to maintain trough serum levels of 300 – 350 g/l), mycophenolate (1.5g bd) and dexamethasone (1.5mg daily). Basiliximab (Simulect, Novartis pharmaceuticals) was administered day 1 and 5 as a cyclosporine sparing agent given problems with intrapleural haemorrhage and renal impairment. Due to poor absorption, cyclosporin was changed to tacrolimus (target serum levels of 10-15 g/l) on day 15 post transplant. Valganciclovir (450mg/day), nebulised amphotericin B (10mg bd) and sulfamethoxazole/trimethoprim (twice weekly) were administered for CMV, fungal and Pneumocystis jiroveci prophylaxis respectively.

Fourteen days post transplant, fluconazole was commenced following the isolation of Candida tropicalis from pleural fluid. An area of left lung consolidation was subsequently investigated with bronchoscopy. Pseudomonas aeruginosa and Candida albicans were grown from bronchoalveolar lavage fluid and transbronchial biopsies revealed organizing pneumonia, but no evidence of rejection. His treatment continued with meropenem, ciprofloxacin and fluconazole.

The patient was discharged from hospital seven weeks post transplant with no further complications except poorly controlled diabetes mellitus during the follow-up period.

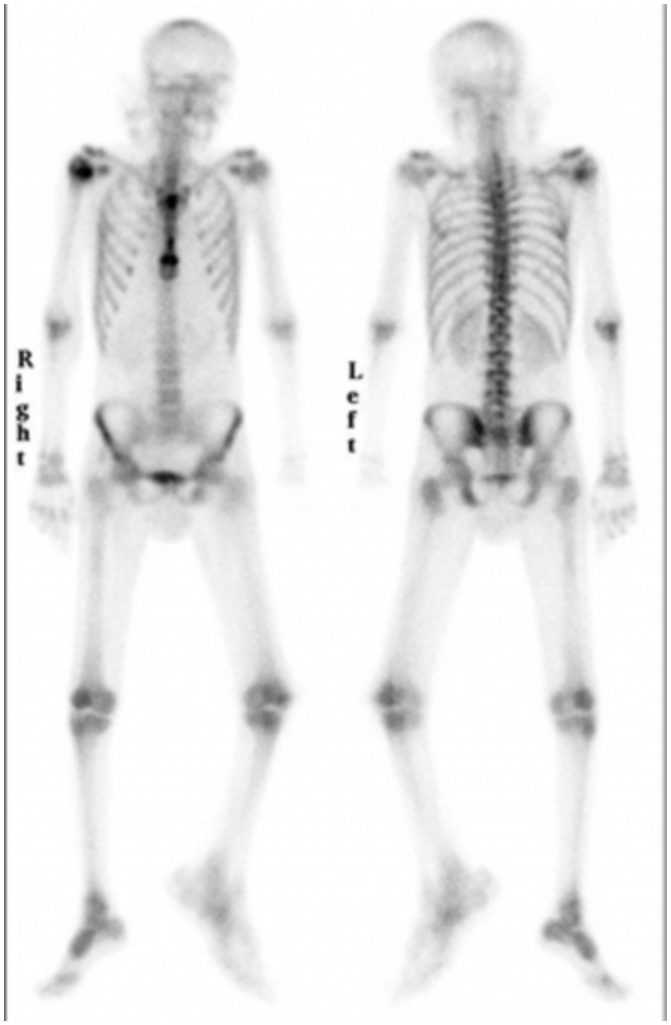
Three months post transplant, the patient presented in status epilepticus requiring intubation. The blood sugar level was 1.2 mmol/L. Investigation revealed a normal chest x-ray, mild renal impairment, no leukocytosis and a c-reactive protein (CRP) of 115 mg/L. A CT Head revealed white matter hypo-attenuation in the left frontal lobe and a lumbar puncture was negative for cryptococcal antigen and herpetic viruses. As the patient was unable to have a MRI head at this point due to an in-situ portacath, a presumptive diagnosis of seizures related to hypoglycaemia and reversible posterior leukoencephalopathy secondary to tacrolimus was made. The hypoglycaemia was corrected, tacrolimus was switched back to cyclosporin, systemic blood pressure aggressively controlled and he was admitted to the intensive care unit.

The patient's neurological state rapidly improved and he was extubated. With further clinical history now available, he reported a one week history of a painful, hot and swollen right shoulder. Fluid aspirated from the right shoulder grew Aspergillus fumigatus. Voriconazole and caspofungin were commenced in combination. A bone scan (Figure 1) showed increased vascularity and radiotracer uptake in the right shoulder. No intra-cardiac vegetations were identified on echocardiogram. A MRI was performed after removal of the portacath but due to movement artefact, only the head could be imaged. Three focal areas of increased T2 hyper-intensity were seen in the frontal lobe, occipital lobe and

frontoparietal region confirming the presumptive diagnosis of reversible posterior leuoencephalopahy secondary to tacrolimus toxicity. There were no cerebral abscesses.

Figure 1

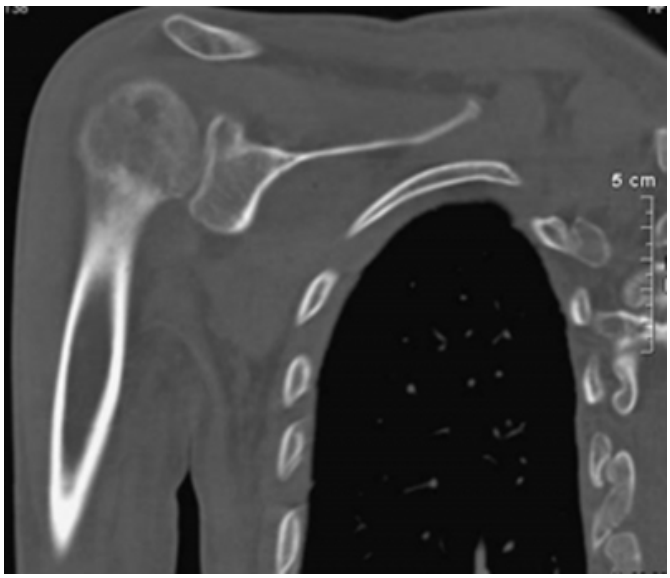
FIGURE 1: Bone scan showing increased radiotracer uptake in the right shoulder



A progress CT of the shoulder ten days after the initial presentation suggested infective collections involving the subscapularis muscle and right posterior glenohumeral head. There was also a cortical break and associated mixed lytic/sclerotic changes in the posterior humeral head confirming septic arthritis and osteomyelitis (Figure 2). Despite this there was clinical improvement and the CRP had fallen to 22 mg/L. Voriconazole was changed to posaconazole due to deranged liver function tests after thirteen days of therapy.

Figure 2

FIGURE 2: CT of shoulder confirming sclerotic changes of the posterior humeral head



Twenty days after initial presentation the patient complained of increased pain and decreased range of movement of the right shoulder, he became febrile and the CRP increased to 68 mg/L. The radiologic appearance had deteriorated with an increase in the number and size of locules in the subscapularis muscle, the development of a glenohumeral joint effusion, and an air locule in the posterior aspect of the humeral head (Figure 3). Subsequent MRI of the right shoulder showed enhancement and oedema throughout the right humeral head and extending 9.5cm into the proximal humeral shaft (Figure 4). Cyclosporin was decreased with a target C2 (2 hour post-dose) level of 300-400 and intravenous amphotericin was commenced, in addition to the caspofungin and oral posaconazole. An arthroscopic washout of the right shoulder was performed and converted to an open washout with subsequent synovectomy of the biceps sheath with removal of caseous material.

Figure 3

FIGURE 3: Repeat CT of the right shoulder 20 days after presentation. Note air locule in posterior humeral head (3A) and the air locule in the subscapularis muscle (3B)

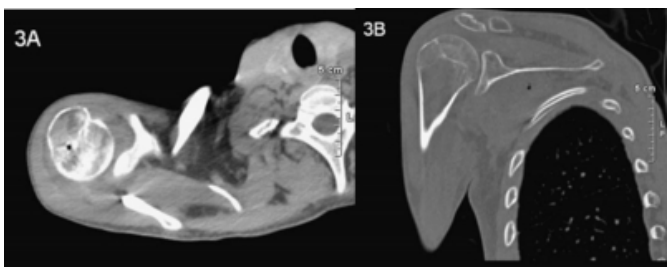
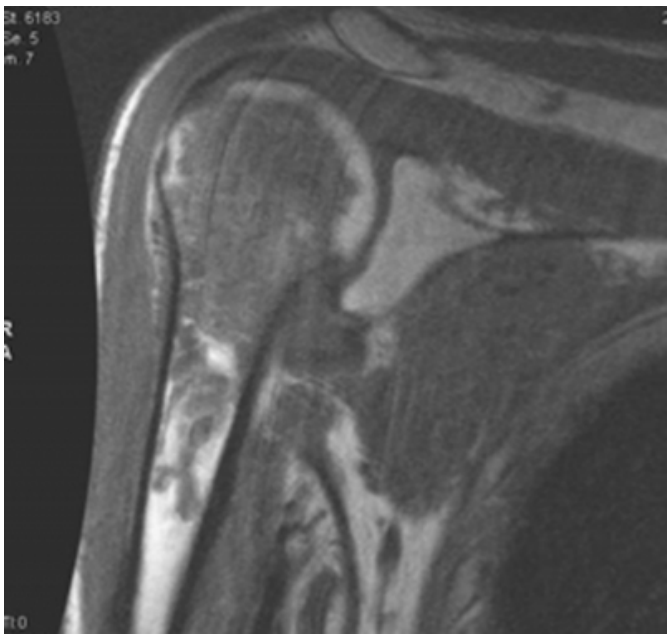


Figure 4

FIGURE 4: MRI of the shoulder demonstrating significant osteomyelitis and oedema



On day 23 the patient commenced daily hyperbaric oxygen therapy. By day 33 the patient had improved and repeat MRI at day thirty-five showed radiological improvement. His recovery was complicated by a lower-respiratory tract infection for which he received meropenem and ciprofloxacin. Forty-six days after admission the amphotericin, caspofungin and meropenem were ceased and the patient was discharged home to continue the hyperbaric oxygen therapy (to a total of 40 treatments) and posaconazole as an outpatient.

Six months after the initial presentation, the patient again presented with worsening pain in the right shoulder. Investigation revealed recurrence of osteomyelitis in the humeral head and he subsequently underwent open debridement of the humeral head and insertion of amphotericin cement beads. Posaconazole was changed back to voriconazole without a significant deterioration in liver function. The patient made a full recovery with a full range of movement at the shoulder joint, and normal allograft function 15 months after initial presentation with Aspergillus osteomyelitis.

DISCUSSION

Aspergillus osteomyelitis is rare although it is the fourth most common site of aspergillosis(1). A 2005 review identified 63 reported cases of Aspergillus osteomyelitis and joint infections between 1977 and 2003. (1) In immuno-competent patients osteomyelitis commonly results from the hematogenous spread of invasive pulmonary aspergillosis. It is estimated 6%-16% of heart and lung transplant recipients are treated for invasive pulmonary aspergillosis post-transplant (2, 5). Interestingly in our patient all routine bronchoscopy's pre and post operatively showed no evidence of pulmonary Aspergillus infection. Risk factors for invasive aspergillosis after transplantation include; dose and length of immunosuppressive therapy, presence of vascular complications, neutropenia, defective phagocytes, allograft rejection, diabetes, renal failure, malignancy, bacterial and CMV infections, use of antibiotics, parenteral nutrition, and dialysis (3).

Infections of bone and joints caused by Aspergillus are recognised as being difficult to treat and often requiring prolonged medical therapy. Unfortunately optimal treatment is yet to be defined and currently is based on a collection of small case series and single case studies.

Traditionally treatment has focused on Amphotericin B and surgical debridement. However, single use of Amphotericin B has fallen out of favour due to its poor bone/joint tissue penetration and the sub-optimal response of infection when used as a single agent. Other medical options for treatment include triazoles: itraconazole, voriconazole, ravuconazole and posaconazole; flucytosine and caspofungin. Fluconazole has no activity against Aspergillus, and our patient developed the disease while on fluconazole. Itraconazole, voriconazole and posaconazole are known to have good anti-Aspergillus activity and achieve good bone penetration. Compared with Amphotericin B (AmB) and itraconazole, posaconazole has the best in vitro activity against Aspergillus species (3, 4). Moreover, clinical success has been demonstrated with posaconazole in the treatment of invasive aspergillosis in patients in whom AmB or itraconazole therapy has failed (5). The echinocandin caspofungin has in vitro activity against Aspergillus, but has poorer bone penetration. There seems little place for caspofungin monotherapy to treat Aspergillus osteomyelitis, however it may have a role as part of combination therapy. (1) Caspofungin and voriconazole in combination have previously been examined. Singh et al. compared 40 solid organ transplant patients who received voriconazole and caspofungin as primary therapy with a control group of 47 patients who received liposomal amphotericin B. While there was no overall mortality difference between the two groups, in patients with renal failure, combination therapy was shown to be independently associated with improved

survival.(6) In the review of the literature performed by Kirby et al, the combination of amphotericin B and flucytosine resulted in successful treatment in all cases.(1)

Our patient was commenced on voriconazole and caspofungin combination therapy but later voriconazole was changed to posaconazole due to deranged liver function tests. Amphotericin B was later added to the regime, although there was initial hesitancy because of pre-existing impaired renal function. In solid organ transplant recipients, whenever possible, consideration should also be given to carefully decreasing the degree of immunosuppression as an adjunct to medical therapy for the treatment of invasive aspergillosis. Despite lowering the patient's immunosuppression he did not develop acute allograft rejection and graft function remains excellent.

Hyperbaric oxygen (HBO) is claimed to be helpful in refractory osteomyelitis. The functional definition most commonly applied to hyperbaric candidates includes failure to respond to a 4- to 6-week course of appropriate antibiotics (7). A large number of animal data and in vitro experimental studies supports the use of HBO in refractory osteomyelitis (8). Uncontrolled trials of surgery and antibiotics combined HBO in refractory osteomyelitis in the past have shown success rates as high as 85% (9). As yet there are no randomized controlled trials relating to refractory osteomyelitis. Unfortunately randomized controlled trials may be difficult to accomplish, given the relative infrequency of the illness and the varied patient and disease characteristics. HBO therapy is considered safe when used according to standard protocols, with oxygen pressures not exceeding 300 kPa and treatment duration not exceeding 120 minutes (10). Due to rapid pressure changes, adverse effects include barotrauma to the middle ear, cranial sinuses and, in rare cases, the teeth or lungs. HBO-related pulmonary toxicity is thought to be a concern in lung transplant patients due to pre-existing co-morbidities and increased susceptibility to toxic pulmonary injury (10). Throughout treatment our patient's lung function was stable.

The addition of HBO as an adjunctive therapy significantly increases the upfront cost of treatment. In complicated cases of refractory osteomyelitis, however, the long-term expenses associated with prolonged hospitalization, long courses of antimicrobial therapy, and additional surgery actually offset the differences, frequently making HBO cost effective (8)

To our knowledge, this is the first reported case of osteomyelitis in a solid organ recipient that has included hyperbaric oxygen therapy in the treatment regime and one of the few documented cases of aspergillus osteomyelitis involving a lung transplant patient.

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