Melioidotic osteomyelitis treated with antibiotic-calcium hydroxyapatite composite: case report with four-year follow-up

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Abstract

Melioidosis is caused by an infection by *Burkholderia pseudomallei*. Osteomyelitis is a recognised manifestation of melioidosis but *Burkholderia pseudomallei* is a relatively rare aetiological agent in musculoskeletal infections. We report a 32-year-old diabetic man with septicaemia due to melioidotic infection of the spleen, liver and distal femur. The osteomyelitis relapsed despite being treated with the standard radical debridement and insertion of gentamycin-impregnated polymethylmetacrylate (PMMA) beads, followed by an optimal antibiotic therapy. The PMMA-gentamycin beads were then removed. The bone defect was debrided and packed with calcium hydroxyapatite blocks filled with ceftazidime powder. The osteomyelitis was successfully treated and the patient remained free of infection four years postoperatively. Computed tomography demonstrated successful incorporation of the calcium hydroxyapatite into host bone.

Keywords: bacterial infection, bone filler, *Burkholderia pseudomallei*, melioidosis, osteomyelitis

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INTRODUCTION

Melioidosis is caused by an infection by the soil saprophyte *Burkholderia pseudomallei*. It is one of the few truly tropical diseases and is endemic in Southeast Asia and Northern Australia. This disease was discovered by Whitmore and Krishnaswami in 1911 during postmortem histopathological examination on a morphia addict who died of pneumonitis[1]. The clinical spectrum of melioidosis is variable and includes latent infection, local cutaneous lesions, subacute pneumonia, focal organ abscesses, musculoskeletal infection and lethal fulminant septicaemia. Although osteomyelitis is a well-recognised manifestation of melioidosis, it is a relatively rare aetiological agent in musculoskeletal infections and remains a clinical challenge to treat. We report on a long-term follow-up of a diabetic patient with melioidotic osteomyelitis of the distal femur that was successfully treated by a new technique in which calcium hydroxyapatite blocks filled with ceftazidime powder was used as a form of local antibiotic therapy.

CASE REPORT

A 32-year-old diabetic man presented with a week's history of an inguinal swelling. A diagnosis of right inguinal abscess was made, and an incision and drainage was performed. Culture of the pus obtained at surgery failed to identify the causative organism. Three months later, he was admitted to another hospital with a history of prolonged fever. Ultrasonography of the liver revealed multiple abscesses. A computed tomography (CT) – guided liver biopsy was performed and grew *Burkholderia pseudomallei*. He was treated with oral cotrimoxazole 500mg and doxycycline 100mg twice daily, and remained compliant with treatment.

He returned six months later with a swelling just above the left knee. Radiographs revealed changes compatible with osteomyelitis of the distal end of the left femur. His white cell count remained within normal limits. Erythrocyte sedimentation rate (ESR) was 145 mm/hour. A blood culture isolated *Burkholderia pseudomallei* which was sensitive to amoxicillin-clavulanate and ceftazidime. A serology latex agglutination test for melioidosis demonstrated a high titre >320:1. Abdominal ultrasonography revealed multiple liver and splenic abscess.

A radical debridement was performed and gentamicin-impregnated polymethylmetacrylate (PMMA) beads were placed in the distal femur and surrounding soft tissue. Pus from the femur confirmed the diagnosis of melioidotic osteomyelitis. Intravenous ceftazidime 2g eight-hourly and oral amoxicillin-clavulanate 625mg twice daily continued to be administered for six weeks before the patient was discharged with oral amoxicillin-clavulanate.

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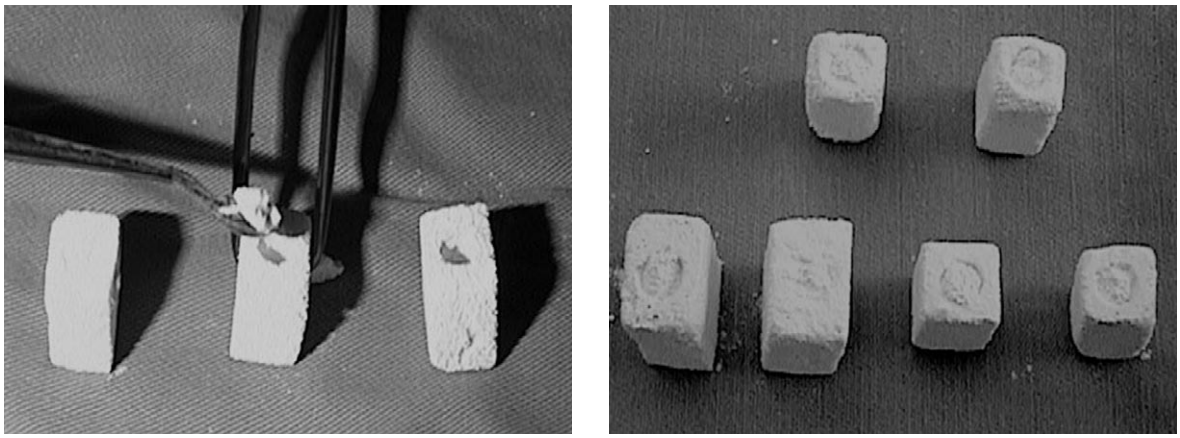

Fig. 1 Photographs show how the drill hole was made over the central portion of the calcium hydroxyapatite blocks and filled with ceftazidime powder. The opening was then covered with a small oversized calcium hydroxyapatite cap.

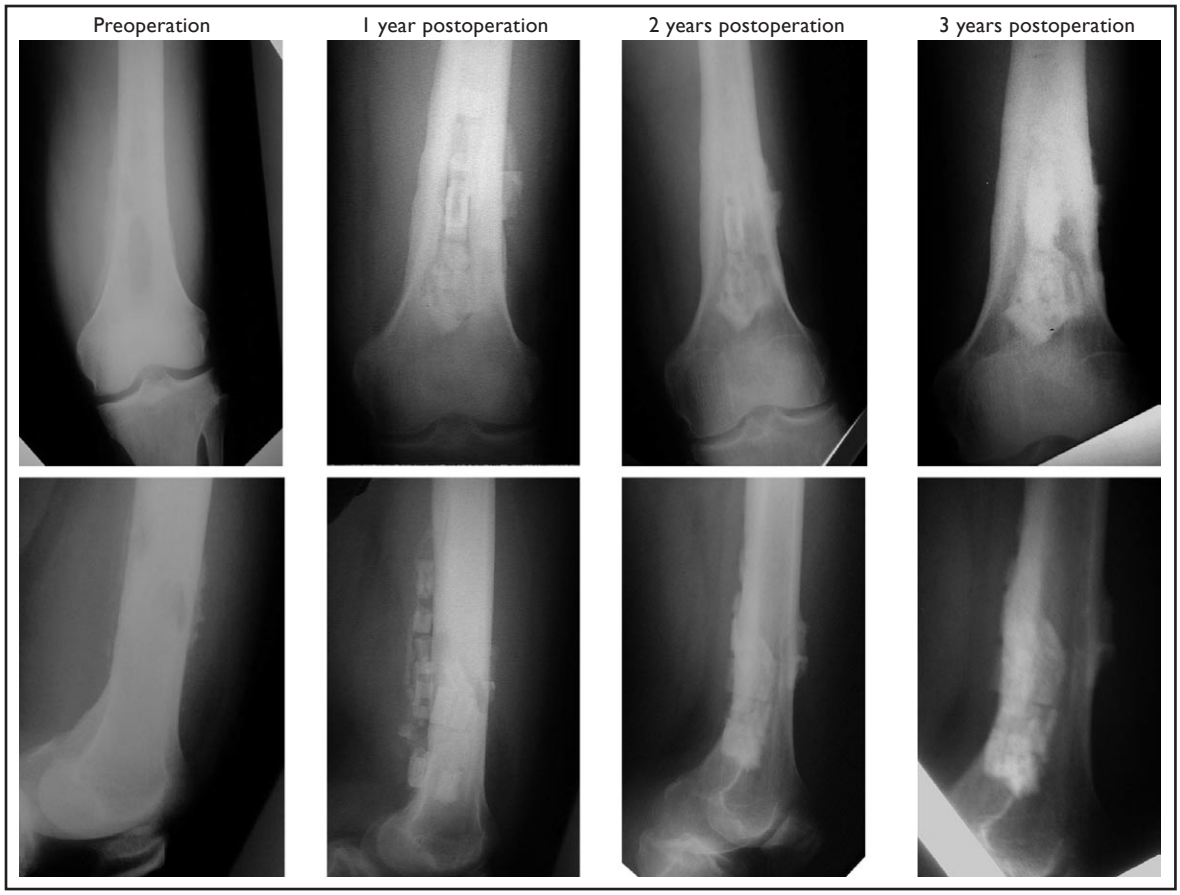

Fig. 2 Preoperative radiographs show radiological signs of osteomyelitis. Yearly postoperative radiographs show the location of the ceftazidime-calcium hydroxyapatite blocks with features of incorporation at the end of three years follow-up. No signs of chronic osteomyelitis were noted. [Top row: frontal projections; bottom row: lateral projections].

He had a recurrence of the osteomyelitis in the eighth month, despite remaining compliant with treatment with oral amoxicillin-clavulanate. Abdominal ultrasonography was repeated, and showed that the liver and splenic abscess had successfully resolved. He was admitted for intravenous ceftazidime and amoxicillin-clavulanate. A radical debridement was repeated and the gentamycin-impregnated PMMA beads were removed. The infected bone was packed with calcium hydroxyapatite blocks filled with ceftazidime powder (Fig. 1).

The calcium hydroxyapatite block used was "G-Bone MHAB2" (G. Surgiwear Limited, India). The dimension of block was 1x1x2cm with the pore size of 100-200 microns and 60% porosity. The well was created on the block using a 6mm diameter burr with the average depth of 1cm and filled with ceftazidime powder. The opening

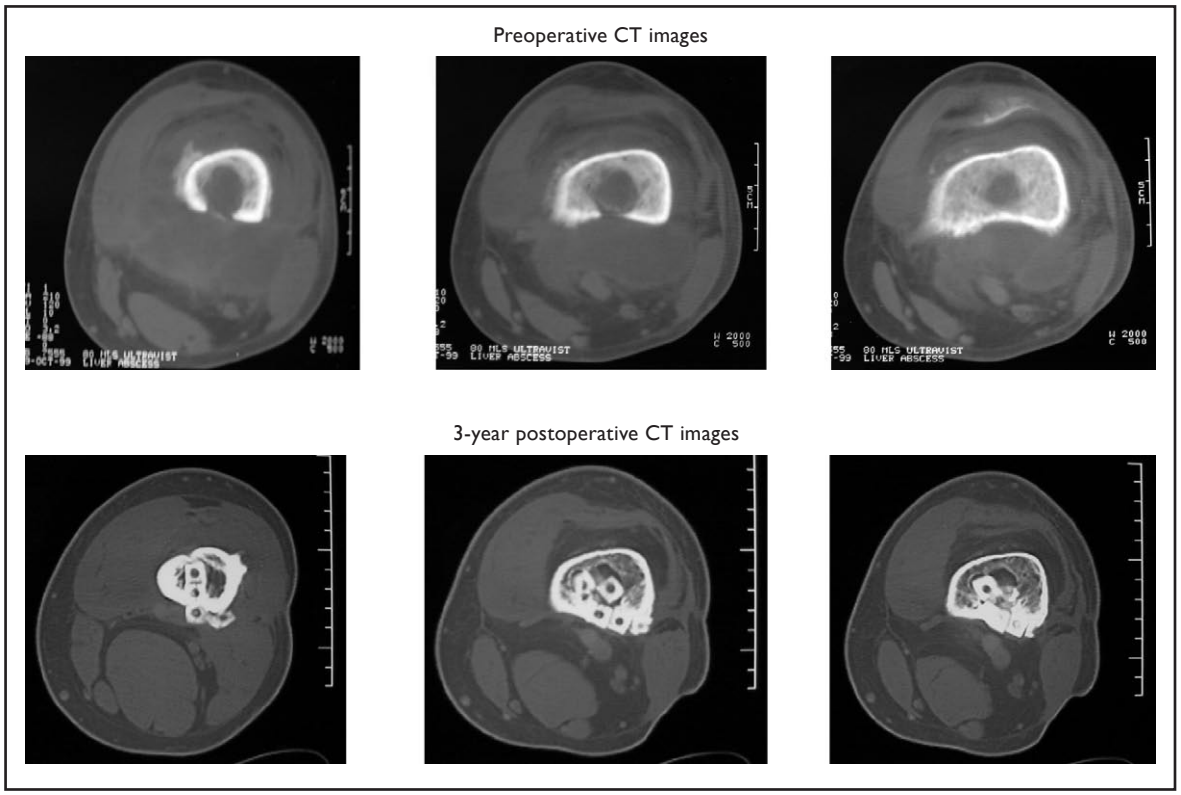

Fig. 3 The preoperative CT images (top row) show features of osteomyelitis evidenced by periosteal reaction with subperiosteal collection, especially over the posterior aspect of the distal left femur. The three-year postoperative CT images (bottom row) show resolution of the osteomyelitis with incorporation of the calcium hydroxyapatite into host bone.

was covered with a small oversized calcium hydroxyapatite cap. The ceftazidime used was from GlaxoSmithKline (Fortum), IV/IM vial 2g in a vial. A total of nine blocks were used (four intramedullry and five outside the bone) and the dosage of ceftazidime used was 5g. No supplementary bone graft added.

Over a period of four weeks, the infection resolved clinically and the ESR dropped to 34mm/hr. For the last four years of follow-up, he remained disease free with normal ESR levels. Annual radiographs that were performed did not show features of chronic osteomyelitis (Fig. 2). CT performed three years postoperatively demonstrated successful incorporation of the calcium hydroxyapatite into host bone, with complete resolution of the osteomyelitis radiologically (Fig. 3).

DISCUSSION

Burkholderia pseudomallei, a gram-negative soil saprophyte, is endemic in Australia and Southeast Asia[2] and the mode of transmission is by direct contamination with infectious soil or water through a pre-existing wound or direct inhalation of infectious particles[3]. Melioidosis involving the bone and joint is rare. Sookpranee et al reported an incidence of 8%[4]. Characteristically, the organism is susceptible to amoxicillin-clavulanate, ampicillin-sulbactam, ceftazidime, and is resistant to ampicillin, cotrimoxazole, tetracycline and ciprofloxacin. Melioidotic osteomyelitis is conventionally treated using a combination of intravenous ceftazidime and oral amoxicillin-clavulanate[5], as well as removal of infected and necrotic bone. *Burkholderia pseudomallei* is inherently resistant to intravenous gentamycin. However, Subhadrabandhu et al had reported that the use of gentamycin-impregnated PMMA beads reduce the risk of relapse by achieving a local concentration of gentamycin exceeding the minimal inhibitory concentration (MIC) for *Burkholderia pseudomonas*[6].

Despite standard surgical treatment and adequate antibiotic therapy, our patient had an early relapse of his osteomyelitis. It is unlikely that the organism was resistant to the antibiotics administered as abdominal ultrasonography done later demonstrated resolution of the liver and splenic abscesses. We felt that delivery of the appropriate antibiotic and achieving a high concentration of the antibiotic in the bone was essential and thus we utilised calcium hydroxyapatite blocks impregnated with ceftazidime. Calcium hydroxyapatite was chosen as a drug delivery system because it enabled us to deliver ceftazidime, the drug of choice in the treatment of

melioidosis. It also has excellent biocompatibility and effectiveness in filling the bone defect[7,8]. The presence of microspores and interconnecting canal permits the in-growth of bone and bone marrow cells[8,9]. The incorporation of hydroxyapatite into bone even in the presence of infection has been illustrated in our patient as well as in other studies[8,9].

Calcium hydroxyapatite appears to be superior to PMMA as a drug delivery system as there is no thermal damage to the drug during the process of preparation[8,10]. A second operation to remove the carrier is unnecessary. The removal of beads not only recreates the dead space but the surgical insult also results in an inflammatory reaction, which are both not conducive to resolution of infection. The use of antibiotic-calcium hydroxyapatite composite in melioidosis infection of bone has not been described in the literature. We believed that the antibiotic-calcium hydroxyapatite composite may have a role in the treatment of melioidotic osteomyelitis. A larger study needs to be conducted to assess the effectiveness of this new option of treatment.

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