Burkholderia cepacia infection in an infant affected by renal osteodystrophy

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Summary

We report a case of chronic osteomyelitis caused by *Burkholderia cepacia* presenting with multiple bone localizations in an infant affected by end-stage renal disease. In order to avoid the amputation of the extremities, a salvage procedure was attempted: all lesions were curetted completely and filled in with bone cement. At 24 months follow-up all lesions are completely healed.

Introduction

Osteodystrophy in end-stage renal disease is nowadays extremely rare in developed countries due to dialysis treatment, which may delay or even prevent this dangerous complication.

Osteomyelitis is a possible complication of osteodystrophy. Poor quality of bone stock, a weak immune system and the presence of artero-venous accesses used for dialysis are important risk factors for osteomyelitis.

Burkholderia cepacia is a saprophytic gram-negative bacteria; it is endemic in South East Asia and Northern Australia where these bacteria are widely present in soil and water (22).

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Some authors have suggested that there is a re-emergence of Burkholderia infection in endemic areas and that it is spreading to non-endemic areas (12,15). In particular, several cases have been identified in Africa and in travellers returning to European countries from Africa (5,10,13,14).

These bacteria are most commonly spread by percutaneous inoculation, inhalation and ingestion.

Generally systemic manifestations are prevalent (3): it commonly presents as pneumonia (51%), genitourinary infection (14%), skin infection (13%), bacteraemia without evident focus (11%), neurological symptoms (3%) and is a very rare cause of osteomyelitis and septic arthritis (4%). Septic arthritis and osteomyelitis are an uncommon presentation of the disease (17).

Osteomyelitis can rapidly evolve from an asymptomatic phase to a severe disease that can be fatal. Disseminated septicaemia can cause septic shock, which is fatal in nearly 80% of the cases (7). Between these extreme forms the infection may run a chronic or relapsing course; or it may remain latent for a long time before becoming clinically evident (4,22).

Several concomitant conditions may favour super infection by *Burkholderia* spp.: diabetes (39%); alcohol abuse (39%); chronic lung and renal disease (26-12%) (6,20).

The aetiologic diagnosis is easily missed, since Burkholderia infection mimics other infections both clinically and radiologically and the diagnosis can only be established by bacteriological and immunological studies.

Prompt treatment with long-term combination antibiotics in high dosages and surgical drainage of abscesses improves survival (14).

We report a chronic osteomyelitis caused by *Burkholderia cepacia* presenting with multiple bone localizations in an African infant affected by end-stage renal disease, highlighting the need for awareness of this entity as a differential diagnosis for persistent, recurrent, nonresponsive granulomatous infection in this age group.

Case Report

A 10 year-old boy from Eritrea with multiple discharging ulcerative lesions in the left heel and in both hands came to our attention. The patient was affected by end-stage kidney disease of unknown origin and had been treated with dialysis in his own country. An alteration of the calcium-phosphorus balance with X-rays showing a diffuse renal osteodystrophy was present. Drainage of the purulent material and antibiotic treatment (based on antimicrobial susceptibility testing, AST, report) with piperacillin and tazobactam (1.5 g/three times in a day) was performed for 45 days without clinical improvement.

A new AST showed that the causative germ had become resistant to piperacillin-tazobactam just lasting sensitivity to 3rd generation

cephalosporin. Consequently, ceftazidime 1.5 g/day was started and continued for 70 days.

After more than 3 months of antibiotic therapy with no clinical amelioration, in order to avoid the amputation of the extremities, a salvage procedure was attempted.

C-reactive protein was: 0.39 mg/100 mL (normal values <0.80) and total leukocyte were 7350/mm^3 (normal values <9000).

Radiographs showed thickening of the cortex and scalloped margins of lytic lesions. Histological analysis showed chronic non-suppurative granulomatous osteomyelitis.

A possible infection by mycobacteria was excluded by acid fast staining and no fungi were identified. A motile, non-fermenting, gram-negative bacillus oxidase positively identified as a multidrug resistant (MDR) Burkholderia was found in the cultures of all three lesions; it was identified as *B. cepacia* by Matrix-assisted Laser Desorption/Ionization mass spectrometric typing.

The patient had no systemic symptoms.

The calcaneal lesion was treated by curettage of all inner necrotic bone and a sort of cortical shell was only left; that newly formed cavity was then filled-in with bone cement (Figure 1).

The lesions of both hands were treated by curettage of the radial diaphysis and 2nd metacarpal (left) and the 4th metacarpal (right).

Based on AST report, a 3rd generation cephalosporine (ceftazidime) 1.5 g per day for 1 month after surgery was administered.

At 24 months-follow-up lesions are still healed.

Discussion

Burkholderia has been increasingly diagnosed as a cause of paediatric infection in tropical countries, with reports mainly from Thailand, Vietnam, Northern Australia, Malaysia, and India (17).

An increasing number of people from industrialized countries travel to developing countries as well as people from developing countries come to industrialized ones. Like our patient, these people are exposed to the risk of acquiring Burkholderia infection and this disease can spread from established endemic areas to developed countries.

Clinicians in developed countries should be educated on how to recognize and treat this infection; it is of paramount importance an accurate anamnesis with particular attention to the countries where patients have recently been and the presence of risk factors (14).

However, very few reports about *Burkholderia* spp. osteomyelitis in children have been published; moreover, most of them are caused by *B. pseudomallei* (22). Only a few case reports are available in the literature about *B. cepacia* osteomyelitis (Table 1).

These osteomyelitis are primarily haematogenous. However, our patient had multiple bone lesions but no history of a systemic illness suggestive of a haematogenous spread.

Considering that our patient had dialysis fistulae in all limbs, we hypothesized that these might be the primary source of the infection. Moreover, necrotic bone which characterizes renal osteodystrophy represents a fertile ground for an over infection by this saprophyte (5).

Considering that gram-negative bacilli are easily discarded as a contaminant, if clinical signs and anamnesis information are present, Burkholderia super infection must be considered (10).

Histopathology findings are useful in the diagnosis. Burkholderia causes a type IV hypersensitivity reaction similar to tuberculosis and sarcoidosis with no specific features. The differential diagnosis with these infections may be difficult and can be easily mistaken (11).

Also radiologic picture of Burkholderia osteomyelitis is the same as that for other granulomatous infection, such as tuberculosis (9). RMN may help in the pre-operative planning, showing characteristics of soft tissues involvement.

A combination therapy consisting of ceftazidime for intensive therapy and cotrimoxazole for final eradication is the emerging treatment of choice. However, it may not be sufficient to promote healing of ulcers, especially when facing MDR bacteria (6).

Antibiotics were administered according to AST results: piperacillin-tazobactam was then replaced with ceftazidime. Considering the end stage renal failure, cotrimoxazole was not used in association.

From the available evidence, a strong recommendation for surgical debridement cannot be made (4). However, in the presence of necrotic

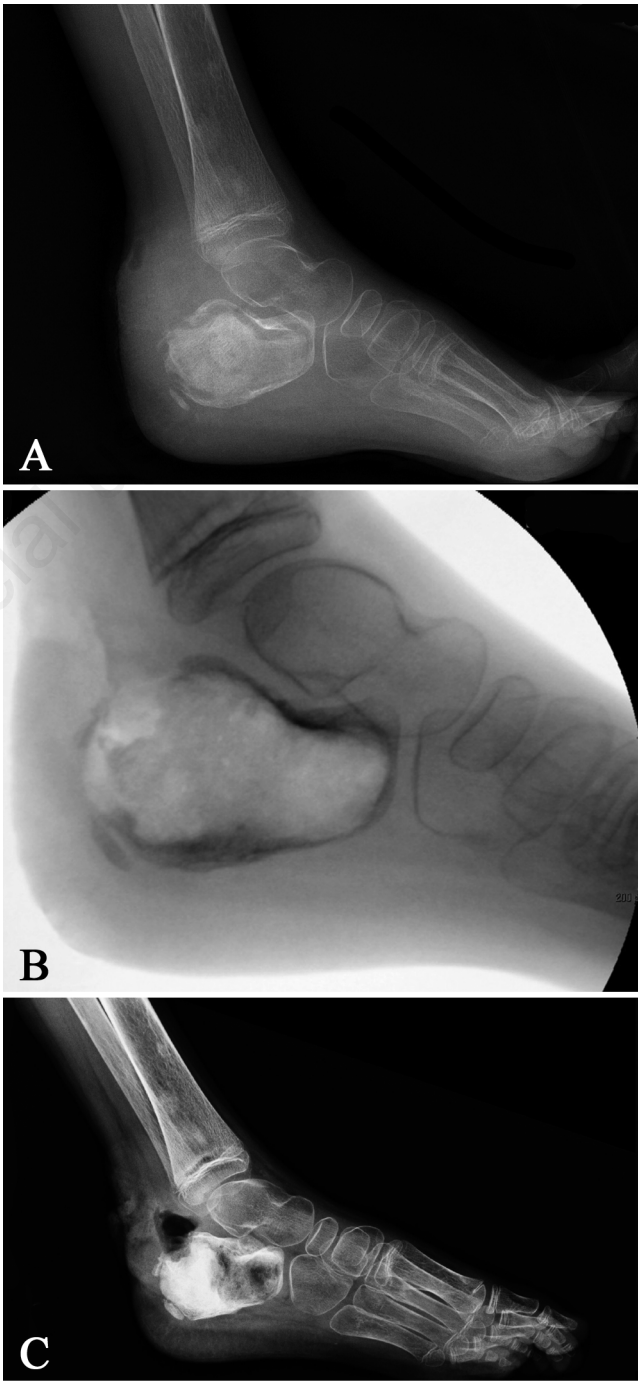

Figure 1. A) Melioidosis lytic lesion in the left heel. B) The necrotic bone was curetted in that way it remained only a sort of cortical shell of original bone. C) The newly formed cavity was filled-in with bone cement to allow early weight bearing.

Table 1. Review of the literature shows some case reports about *Burkholderia cepacia* osteomyelitis.

Author	Site of infection	Symptoms	Risk factors	Treatment	Outcome
Rodriguez *et al.* (16)	Cervical spine	Fever; neck pain	Cystic fibrosis	Antibiotic (temocillin); surgical debridement	Healed at 2 years follow-up
Weinstein *et al.* (21)	Cervical spine	Neck pain; stiffness	Diabetes; rhinoplasty	Antibiotic (meropenem)	Not available
Smith *et al.* (19)	Cervical spine	Neck pain	Intravenous drug abuse	Antibiotic (sulfamethoxazole, trimethoprim, cefoperazone)	Healed at 6 months follow-up
Olmos *et al.* (2)	Lumbar spine	Fever; back pain	Vertebroplasty	Antibiotics (levofloxacin and cotrimoxazol); surgical debridement	Healed at 2 years follow-up
Hsieh *et al.* (8)	Thoracic spine	Fever; back pain	Work with vegetables and plants	Surgical decompression; antibiotics (levofloxacin)	Dead in 2 weeks
Al Attia *et al.* (1)	Skull	Headache; fever; discharging sinus	Diabetes mellitus	Antibiotic (piperacillin and ceftazidime)	Healed

bone or soft tissue abscesses – as clearly shown in the management of this patient – we believe that formal debridement has a definite role.

Calcium hydroxyapatite blocks filled with ceftazidime powder and gentamicin-impregnated polymethylmethacrylate beads have been described in the treatment of adult Burkholderia osteomyelitis in order to achieve a sustained, high, local concentration of antibiotic (8,11). We used cement only in the calcaneal lesion in order to allow early weight bearing; since gentamicin was contraindicated because of renal disease, the cement was not impregnated with any antibiotic.

No final consensus about the duration of the antibiotic therapy has been reported (6). However, several investigators have emphasized the use of long-term antimicrobial therapy.

Even if the patient had recovered completely at 24 months follow-up, the similarity of pathogenesis and presentation with tuberculosis suggests caution: a long-term follow-up is necessary before Burkholderia osteomyelitis can be considered eradicated (13,18).

Conclusions

We reported a very rare aetiology of osteomyelitis in childhood with multiple lesions involving different anatomical sites. The diagnosis in such cases may be very difficult: a clinical suspicion must be addressed in the case of a recurrent, non-responsive chronic granulomatous lesion, whenever the patient has been epidemiologically exposed at its risk. A close collaboration between surgeons, clinicians and microbiologists is mandatory, in order to identify and properly treat these uncommon infections.

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