LOCALISED MELIOIDOTIC OSTEOMYELITIS

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Melioidosis is an uncommon infection caused by a Gram-negative bacillus, *Pseudomonas pseudomallei*. Only a few case reports of orthopaedic infection have been published in English, and most were of isolated septic arthritis or secondary to melioidosis of another organ.

We have reviewed ten patients with localised melioidotic osteomyelitis; six had underlying conditions. We discuss the importance of obtaining a bacteriological diagnosis, and of surgical debridement as well as appropriate antibiotic therapy.

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Melioidosis is an infectious disease caused by the Gram-negative bacillus *Pseudomonas pseudomallei*, and is common in Southeast Asia, Northern Australia and West Africa (Everett and Nelson 1975; Patamascon, Schaad and Nelson 1982; Sanford 1987). It has been described as the great imitator of other infectious diseases, because virtually every organ can be affected although it is most common in the respiratory system (Punyagupta 1983). It rarely involves the musculoskeletal system, and when it does it is usually part of a disseminated infection (Diamond and Pastore 1967; Borgmeier and Kalovidouris 1980; Leelarasamee and Bovornkitti 1989; Tanphaichitra 1989). Both Kowsuwon et al (1989) and Saengnipanthkul et al (1991) considered isolated or localised bone or joint involvement to be very rare. Although they recognised isolated septic arthritis only two cases of localised osteomyelitis were included in their reports.

We have reviewed ten cases of localised melioidotic osteomyelitis treated at Ramathibodi Hospital.

**PATIENTS AND METHODS**

From 1975 to 1991, 64 patients with melioidosis were treated at Ramathibodi Hospital; ten of them (15.6%) had localised melioidotic osteomyelitis (Table I) and form the basis of our report. The infection was confirmed in all cases by positive pus or blood culture, and the clinical records and radiographs were studied retrospectively. The average follow-up was 36 months (12 to 84) and the average age at presentation was 46.8 years (28 to 62). Seven patients (70%) had underlying or associated conditions including diabetes mellitus (5 cases), renal calculi (1), and AIDS (1).

The patients had all suffered from pain or swelling at the affected site, for an average period of 4.5 months (1 to 12). In four the vertebrae were involved, in four the proximal humerus, in one the proximal femur and in one the proximal tibia. White cell counts varied from 3200 to 12 000 mm$^3$ with predominant neutrophilia. The indirect haemagglutination antibody (IHA) titre was tested in six of the patients and was significantly raised in all to over 1:256 for *Pseudomonas pseudomallei*.

In the four spinal cases, plain radiographs showed destruction of the vertebral bodies with varying degrees of collapse. There was scalloping of the anterior vertebral margins, paravertebral abscesses, and varying degrees of narrowing of the involved intervertebral disc spaces (Fig. 1). In the other six cases the metaphysis of a long bone was involved, with two basic patterns: a cystic or osteolytic lesion (Fig. 2) or a circumscribed, saucer-shaped erosion of cortical bone (Fig. 3). Sequestrae and periosteal new-bone formation were rarely seen. There was a pathological fracture in one patient (case 8), and when a joint was involved there was destruction of cartilage shown by joint-space narrowing (case 4).

All ten patients had positive cultures of *Pseudomonas pseudomallei* from pus or blood specimens, but in only one were organisms seen on Gram staining. The bacillus was sensitive to co-trimoxazole, ceftazidime, doxycycline, tetracycline, chloramphenicol, and kanamycin. Microscopic examination of tissue specimens showed granulomas of closely aggregated epithelioid cells with multinucleated giant cells and some focal necrosis. The initial histopathological diagnosis was caseous granuloma.

All ten patients were initially treated by curettage and debridement. Patients treated from 1975 to 1985 (group 1) usually had a combination of drugs such as chloramphenicol and tetracycline or chloramphenicol and co-trimoxazole.
(cases 1 to 5). Those treated after 1985 (group 2) had the bacteriocidal drugs which had become available and were shown to be effective in vitro. Combinations of co-trimoxazole and ceftazidime or of co-trimoxazole and doxycycline were given to cases 6 to 10. Antibiotic therapy was continued for at least three months in all cases. We also used intramedullary gentamicin-impregnated polymethylmethacrylate (PMMA) beads in one relapsing patient (case 4) and in three other patients with severe infection (cases 7, 8 and 9).

CASE REPORTS AND RESULTS

Details of all patients are shown in Table 1; all were followed up for at least two years. Two out of the five patients in group 1 died (cases 1 and 5) and there was one relapse (case 4).

In the second group of five patients treated with bacteriocidal drugs there were no deaths or relapses, but one patient with severe disease had a pathological fracture.

Case 1. The patient had localised osteomyelitis of the proximal humerus and rapidly improved after surgical drainage combined with antibiotics. One year later, he was readmitted and developed toxic shock syndrome. Blood culture revealed Klebsiella and E. coli. The diagnosis was hospital-acquired infection. He died two weeks later.

Case 5. In 1981, a 50-year-old homosexual man with back pain developed inflammatory disease at L2 to L3. Pus drained from the retroperitoneum cultured Pseudomonas pseudomallei. He was treated with chloramphenicol and co-trimoxazole and the acute symptoms settled. Reaccumulation of pus in the retroperitoneum required re-admission on several occasions in the next four years. In 1987, he had severe haematemesis and melaena. Serum specimens were positive for antibody to human immunodeficiency virus by the Western blot technique. He died from Pseudomonas pseudomallei septicaemia. The diagnosis was recrudescent melioidosis with AIDS.

Case 4. A 43-year-old farmer relapsed with secondary septic arthritis of the shoulder five years after his first admission with osteomyelitis of the proximal humerus (Fig. 2). On his second admission he was treated by the second regime of antibiotics and intramedullary gentamicin-PMMA beads and has had no further recurrence after two years.

Case 8. A 62-year-old female farmer with diabetes mellitus had a three-month history of shoulder pain and extensive disease of the humerus (Fig. 3a). After incision and drainage she sustained a pathological fracture (Fig. 3b) and after further debridement was treated with gentamicin-PMMA beads (Fig. 3c). The fracture united, and three years later she had good elbow and shoulder movement (Fig. 3d).

DISCUSSION

Pseudomonas pseudomallei is a small, Gram-negative, obligatorily aerobic, non-spore-forming bacillus. It is a free-living organism in the natural environment, especially in stagnant water and rice paddies. Whitmore and Krishnaswami (1912) were the first to describe melioidosis in patients and the first report from Thailand was by Chittivej, Buspavanij and Choavanasai (1955). During the past decade, there have been over 800 cases of melioidosis in Thailand (Leelarasamee and Bovornkitti 1989). There is a wide geographical distribution of Pseudomonas pseudomallei with isolation rates of from 30% to 50% in various
Case 8. Figure 3a – The radiograph shows saucer-shaped erosions of cortical bone and extensive involvement of most of the humerus. There is little periosteal new-bone formation. Figure 3b – After incision, drainage of the pus and removal of all dead tissue there was a pathological fracture. Figure 3c – After repeated debridement, gentamicin-PMMA beads were introduced. Union occurred in four months. Figure 3d – Three years later. The patient had good ranges of movement at shoulder and elbow.

soil and water samples (Finkelstein et al 1966). The organisms contaminate water droplets and soil dusts, and presumably gain entrance to the body through ingestion, inhalation, or wounds. For these reasons, most patients are farmers, and men are more often affected than women and children.

The natural course may be acute, subacute, or chronic (Leelarasamee and Bovornkitti 1989). Most of our patients had the chronic form with its prolonged course. The initial clinical symptoms were usually mild fever, malaise, and inflammation, and due to delay in seeking proper medication and changes in physicians, patients presented at our hospital with the chronic form.

Osseous lesions usually involve the metaphyseal regions of long bones and the vertebral bodies, in which the radiographic appearance cannot be differentiated from that of a tuberculous lesion. The metaphyses of long bones may show either cystic change or a circumscribed erosion of cortical bone; these lesions have been mistaken for neoplasm, sarcoidosis and other granulomatous infections.
Table 1. Clinical details of ten patients with localised melioidotic osteomyelitis

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex (yr)</th>
<th>Occupation</th>
<th>Site</th>
<th>Clinical presentation</th>
<th>Duration of symptoms (mth)</th>
<th>Underlying disease</th>
<th>Positive culture</th>
<th>IHA* titre</th>
<th>Treatment †</th>
<th>Follow-up (yr)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40/M</td>
<td>Farmer</td>
<td>L proximal humerus</td>
<td>Fever, swelling, pain L shoulder</td>
<td>3</td>
<td>CXR ‡ neg</td>
<td>Blood</td>
<td>Not done</td>
<td>Chlor, Tetra</td>
<td>1</td>
<td>Died</td>
</tr>
<tr>
<td>2</td>
<td>34/M</td>
<td>Farmer</td>
<td>R proximal tibia</td>
<td>Pain, chronic ulcer</td>
<td>6</td>
<td>Renal calculi</td>
<td>CXR neg</td>
<td>Put</td>
<td>I and D Chlor, Tetra</td>
<td>4</td>
<td>No relapse</td>
</tr>
<tr>
<td>3</td>
<td>62/F</td>
<td>Farmer</td>
<td>Vertebral body L4 to L5</td>
<td>Low back pain</td>
<td>3</td>
<td>Diabetes mellitus</td>
<td>CXR neg</td>
<td>Blood</td>
<td>Not done</td>
<td>Anterior decompress and fusion TMP/SMZ, Chlor, Kana</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>43/M</td>
<td>Farmer</td>
<td>R proximal humerus</td>
<td>Swelling, pain R shoulder</td>
<td>6</td>
<td>Diabetes mellitus</td>
<td>CXR neg</td>
<td>Put</td>
<td>I and D Chlor, Tetra</td>
<td>5</td>
<td>Relapse in 5 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Last treatment I and D Gentamicin-PMMA beads, Cefaz, Doxy</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>50/M</td>
<td>Merchant</td>
<td>Vertebral body</td>
<td>Back pain</td>
<td>1</td>
<td>CXR neg</td>
<td>Put</td>
<td>Not done</td>
<td>Anterior decompress and fusion TMP/SMZ, Chlor</td>
<td>6</td>
<td>Died from recrudescent melioidosis with AIDS and sepsis</td>
</tr>
<tr>
<td>6</td>
<td>43/M</td>
<td>Farmer</td>
<td>Vertebral body L1 to L2</td>
<td>Back pain</td>
<td>5</td>
<td>CXR neg</td>
<td>Put</td>
<td>Not done</td>
<td>Anterior decompress and fusion TMP/SMZ, Cefaz</td>
<td>3</td>
<td>No relapse</td>
</tr>
<tr>
<td>7</td>
<td>49/M</td>
<td>Farmer</td>
<td>Vertebral body</td>
<td>Fever, back pain</td>
<td>12</td>
<td>Diabetes mellitus</td>
<td>CXR neg</td>
<td>Put</td>
<td>1:640</td>
<td>Anterior decompress and fusion Gentamicin-PMMA beads, TMP/SMZ, Cefaz</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>62/F</td>
<td>Farmer</td>
<td>L proximal humerus</td>
<td>Fever, swelling, pain L shoulder</td>
<td>3</td>
<td>Diabetes mellitus</td>
<td>CXR neg</td>
<td>Put</td>
<td>1:320</td>
<td>I and D Gentamicin-PMMA beads, TMP/SMZ, Doxy</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>57/M</td>
<td>Merchant</td>
<td>R proximal humerus</td>
<td>Swelling, pain R shoulder</td>
<td>12</td>
<td>Diabetes mellitus</td>
<td>CXR neg</td>
<td>Put</td>
<td>1:640</td>
<td>I and D Gentamicin-PMMA beads, TMP/SMZ, Doxy</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>28/M</td>
<td>Engineer</td>
<td>R proximal femur</td>
<td>Pain R hip</td>
<td>6</td>
<td>CXR neg</td>
<td>Put</td>
<td>1:320</td>
<td>I and D TMP/SMZ, Doxy</td>
<td>2</td>
<td>No relapse</td>
</tr>
</tbody>
</table>

* indirect haemagglutination antibody
† Chlor, chloramphenicol; Tetra, tetracycline; I and D, incision and drainage; TMP/SMZ, co-trimoxazole; Kana, kanamycin; Cefaz, ceftazidime; doxy, doxycycline
‡ CXR, chest radiograph
As with a number of other chronic infections, *Pseudomonas pseudomallei* may provoke a state of delayed hypersensitivity. The specific allergy is related to the prolonged survival of organisms in the body and the formation of granulomatous tuberculoid lesions. The histopathology of the granuloma in our cases was indistinguishable from that induced by tuberculosis, and therefore bacteriological study is the mainstay of diagnosis. Gram staining of the pus is the most rapid approach, but its identification by bipolar staining is rarely possible (Puapermpoonsiri and Puapermpoonsiri 1983). Microbiological culture may be the only way to make a firm diagnosis. Another approach to diagnosis is by serological testing. IHA has a high degree of sensitivity and specificity and an antibody titre of over 1:40 is generally accepted as serological evidence of infection (Jones and Hambie 1980). Antibody titres ranging from 1:40 to 1:160 are, however, frequently found in healthy people and in patients with other illnesses who live in endemic areas such as Thailand. Leelarasamee (1985) pointed out that a single titre of 1:80 to 1:320 is suggestive of active melioidosis, and a single titre of more than 1:640 is diagnostic of highly active melioidosis. Our findings support these statements.

Melioidotic infection is often associated with other underlying diseases such as diabetes mellitus, chronic renal failure, cirrhosis of the liver and systemic lupus erythematosus (Sanford and Moore 1971), and six of our patients had other disorders; five had diabetes mellitus and one had renal calculi. None of this group died from the disease, and, as reported by Saengnapanthkul et al (1991) for isolated articular melioidosis, underlying disease did not seem to influence the severity of isolated bone lesions. It should be noted that patients with immunosuppression and with AIDS are also at increased risk.

Extensive debridement of the infected bone and appropriate antibiotic therapy are essential for successful treatment. In our early cases we used either chloramphenicol and tetracycline or chloramphenicol and co-trimoxazole, but there were some treatment failures. More recently, ceftazidime, co-trimoxazole and doxycline in various combinations, according to sensitivities, have been used. We recommend that these combinations of drugs should be continued for at least six weeks. After this co-trimoxazole or doxycline should be given usually for a year. Careful follow-up is needed to ensure remission is maintained after completion of the course of treatment. We found that the organism was resistant in vitro to the aminoglycosides (except kanamycin), and the minimum inhibitory concentration (MIC) of gentamicin was from 32 to 120 mg/l, higher than the serum concentration which can be provided by the intramuscular injection of doses of 3 to 5 mg/l (Vorachit, Jayanetra and Boonsong 1989). In contrast, the local application of gentamicin-impregnated PMMA beads can provide much higher concentrations in wound secretions (up to 200 mg/l and averaging 50 to 80 mg/l). These levels exceed even the MIC for *Pseudomonas pseudomallei* (Wahlig 1981). For this reason, we have started using gentamicin-PMMA beads at the sites of melioidotic bone infection, and hope that this will reduce remissions and the time in hospital. It is too early, and the number of patients too small to give any firm conclusion.

**Conclusions.** Melioidosis is endemic in many tropical and subtropical areas. Orthopaedic diagnosis, especially of spinal cases, necessitates differentiation from other granulomatous infections such as tuberculosis. This requires culture and sensitivity studies. A high index of suspicion and effective microbiological culture are needed. Surgical debridement is an important part of successful treatment and gentamicin-PMMA beads may be useful. Combination antibiotic therapy is essential for at least six weeks, followed by either co-trimoxazole or doxycycline alone for a year.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

**REFERENCES**


