

# *Candida albicans* vertebral osteomyelitis in chronic renal failure

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**Summary:** Invasive candidal infections are encountered with increasing frequency in compromised hosts but bone infection is uncommon. A woman with systemic lupus erythematosus and end-stage renal failure managed by continuous ambulatory peritoneal dialysis developed a painful thoracic kyphosis and a lytic lesion in the vertebral bodies of T10 and T11. Blood cultures were sterile but bone biopsy material contained *Candida albicans* which also grew on culture. Circulating immune complexes were measured in high levels and contained candida antigens and specific anti-candida antibody as determined by isoelectric focusing, immunoblotting and immunoprinting techniques. Pain persisted after anti-fungal therapy had sterilized the lesion necessitating surgical excision of affected vertebrae, kyphosis correction and iliac crest bone grafting. The titres of circulating immune complexes and anti-candidal precipitins closely paralleled the clinical course.

## Introduction

Haematogenous osteomyelitis usually occurs in the spine in adults, the metaphyses of long bones in children, and involves multiple sites in neonates.<sup>1</sup> *Staphylococcus aureus* is the commonest infecting agent accounting for over 90% of cases but other organisms may be implicated, particularly in patients predisposed by immune suppression, chronic disease or drug abuse.<sup>2</sup>

We report here the case of a 36 year old woman with chronic renal failure who developed vertebral osteomyelitis due to *Candida albicans*. This organism is an infrequent cause of osteomyelitis but in adults shows a predilection for the spine. Few guidelines for the treatment of vertebral osteomyelitis exist and information on prognostic indicators is not available. The investigation, diagnosis and management of candidal spinal osteomyelitis is discussed in the light of our experience.

## Case report

A 36 year old European woman was admitted with a 4-week history of continuous back pain localized to the mid-thoracic area. The pain was exacerbated by movement, especially respiration, and was only partially alleviated by rest. At the age of 14 years she had

developed systemic lupus erythematosus (SLE) with associated nephropathy, which in the year before admission had progressed to end-stage renal failure. This was managed by continuous ambulatory peritoneal dialysis (CAPD). Spinal and other radiographs had indicated a degree of demineralization consistent with renal osteodystrophy, and areas of extraosseous calcification within the capsules of the interphalangeal joints of the hands. In the past immunosuppression had been with azathioprine and prednisone, and at admission was 30 mg prednisone/day.

The patient weighed 55 kg, was pyrexial (38.2°C) and moved with considerable hesitancy due to thoracic pain. Spinal movements were decreased and a pronounced kyphosis was evident located approximately at T10. There was pain on percussion of the apex of the kyphosis. Neurological examination revealed no abnormality.

Radiographs of the thoracic spine showed narrowing of the T10–T11 disc space, but no paraspinal soft tissue mass. Tomography demonstrated a lytic lesion within the bodies of T10 and T11 and a small central sequestrum (Figure 1). A technetium-99 polyphosphonate bone scan demonstrated increased uptake in the lower thoracic spine.

Haematological investigations indicated a haemoglobin of 80 g/l, a total white cell count of  $9.5 \times 10^9/l$  and an erythrocyte sedimentation rate of 145 mm/hour. Blood cultures were repeatedly negative.

A provisional diagnosis of osteomyelitis of the

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**Figure 1** Lateral radiograph of thoracic spine showing sequestrum.

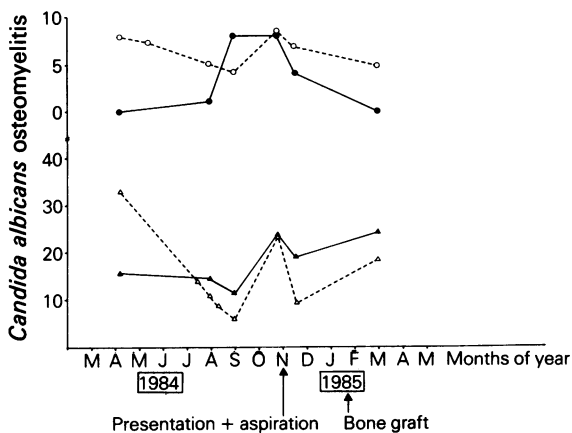
thoracic spine was made and since standard microbiological investigations failed to indicate a cause the involved area was biopsied. Examination of the biopsy specimen revealed yeast cells and the histological appearance was typical of acute on chronic osteomyelitis and secondary hyperparathyroidism. Cultures yielded a heavy growth of *Candida albicans* sensitive to both 5-flucytosine and amphotericin B.

Immunological investigations provided further support for the diagnosis of candidal infection. High levels of circulating immune complexes were detected by polyethylene glycol (PEG) precipitation and by solid phase micro ELISA Clq binding (aggregated IgG equivalent) (Figure 2). Characterization of the components of the immune complexes by iso-electric focusing of PEG-precipitated material, immunoblotting and immunoprinting revealed candida antigens and specific anti-candidal antibody.<sup>3</sup> Anti-candidal precipitating antibodies were detected in low titre in samples of stored sera which had been collected up to 7 months before the onset of symptoms. Precipitins were

present in high titre at presentation and throughout the ensuing period of antimicrobial therapy. Following surgery, levels declined to zero and Clq binding immune complex levels fell in parallel (Figure 2).

Initial antimicrobial treatment was directed against a presumed staphylococcal cause but with the isolation of candida was altered to a combination of oral 5-flucytosine (750 mg/day) and amphotericin B (50 mg/day) given via a central venous Hickman catheter. The onset of neutropenia necessitated the early withdrawal of 5-flucytosine, and amphotericin B was thereafter given alone for a period of 4 weeks. The patient was mobilized slowly as pain would allow and was discharged after one month's treatment.

Two months later incapacitating back pain necessitated readmission. There were no new physical findings but radiographs indicated an increase in the degree of thoracic kyphosis with no evidence of bone healing. Complete bed rest for 2 weeks did not alleviate the symptoms and operative intervention was considered necessary. The vertebral bodies of T10 and T11 were excised, the kyphosis was partially corrected, and a bone graft taken from the left iliac crest was inserted into the defect. Cultures of surgical specimens did not yield candida. Following operation, pain relief was immediate and almost total. The patient was managed on a Stryker bed for 4 weeks followed by mobilization in a posterior spinal orthosis. CAPD continued uneventfully as renal replacement therapy. Six months after the initial onset of symptoms there



**Figure 2** Levels of immune complexes and candida precipitins: ○—○, Clq solid phase IgG in µg/ml; ●—●, candida precipitin titre (reciprocal); △—△, polyethylene glycol precipitated IgG in mg/dl; ▲—▲, serum IgG in g/l.

was no pain and radiographs showed evidence of healing of the lesion (Figure 3).

### Discussion

Invasive candidal infections are being encountered with increasing frequency in compromised hosts but infection of bone has been only rarely described. Fogarty, in 1983, found 16 such cases in a review of the literature and in half of the adult cases the infection involved vertebrae.<sup>4</sup> A number of diverse underlying factors have been associated with the development of candidal osteomyelitis including treatment with hyperalimentation,<sup>5</sup> broad-spectrum antibiotics,<sup>2</sup> surgical procedures,<sup>6</sup> prolonged periods of intensive care<sup>4</sup> and intravenous drug abuse.<sup>7,8</sup> In the case reported here the underlying SLE, renal failure, peritoneal dialysis and long term immunosuppression produced the ideal *milieu* for the acquisition of spinal candidiasis.

In the majority of cases candida reaches bone by haematogenous spread during episodes of fungemia.



**Figure 3** Lateral radiograph of thoracic spine following bone grafting.

The reason for the predisposition of the spine in adults is not clear but it has been shown that the vertebral vascular supply in the adult is increased compared to that in the child.<sup>9</sup> There is speculation also that direct venous spread from the pelvis may occur, this being a site of primary infection in women.

A frequent mode of presentation in previously reported cases of candida osteomyelitis has been severe back pain; there has been no comment about the development of a painful kyphosis,<sup>10</sup> which was such a prominent feature in our case. Conversely, with some other causes of spinal infection, such as tuberculosis, although kyphosis is frequently described,<sup>11</sup> associated back pain is not a feature. However, following trauma, 90% of patients who develop a kyphosis of greater than 45° have severe back pain and the cause is presumed to be mechanical.<sup>12</sup> Surgical bone specimens from our patient were sterile, and we suggest that the pain was due to failure of spontaneous interbody fusion, and stress on the posterior soft tissues or the facet joints.

The indications for early debridement and anterior bone grafting in non-tuberculous vertebral osteomyelitis have not been established. The persistence of pain in the case reported, despite adequate antibiotic treatment lead to effective surgical therapy. Clearly, in patients with a painful and increasing kyphosis early surgery should be considered.

The diagnosis of candidal infection can reliably be made only when the organism is isolated directly from the lesion. Positive blood cultures provide evidence of acute candidaemia but once the early stage of haematogenous dissemination has passed it is rarely possible to isolate the organism from subsequent blood samples. In the absence of positive cultures the confirmation of candidal infection may be difficult. A variety of immunological tests have been developed in an attempt to improve this situation and serum levels of precipitating and agglutinating antibodies to *Candida* are frequently measured. However, the interpretation of the results of these tests is seldom straightforward. It has been shown for example, that a rise in anti-candida immunoglobulin commonly occurs post-operatively in cardiac surgery patients.<sup>13</sup> The entirely non-specific nature of such antibody responses obviously weakens interpretation of anti-candidal precipitin data.

Newer serological techniques may hold more promise as reliable indicators of candida infection. For example, our case demonstrated beyond doubt the value of immune-complex measurement and characterization. Complexes contained both candida-specific antibody and candidal antigens indicating that in the absence of candidaemia the presence of antigenaemia predicted a focus of infection which was confirmed by culture. Moreover, the serum levels of immune complexes closely paralleled the clinical

progress, peaking at the height of the illness, persisting throughout antifungal therapy and eventually falling after surgery. The levels of candida precipitins also showed the same trend but as discussed their presence alone may not be sufficient to secure a firm diagnosis.

How long one should treat candidal osteomyelitis has not been firmly established but in many reports, including ours, one month of amphotericin B appears optimal. The use of 5-flucytosine alone cannot be recommended since resistant strains emerge rapidly during treatment. Miconazole is usually very active against candida but in one reported case of neonatal candida osteomyelitis the infection failed to respond to this agent.<sup>14</sup>

Finally, it is of interest to note that four patients with Candida osteomyelitis have apparently recovered

without the use of specific antifungal therapy.<sup>10</sup> Spontaneous healing of these lesions may occur when susceptibility factors, such as the use of antibiotics and immunosuppressive agents, and the presence of infected catheters no longer operate, but we believe that there would have to be exceptional reasons for withholding therapy from patients with proven candida infection.

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