Osteomyelitis and infective endocarditis

M.E. Speechly-Dick and R.H. Swanton

Department of Cardiology, The Middlesex Hospital, Mortimer Street, London W1N 8AA, UK

Summary: Osteomyelitis is thought to occur as a complication of infectious endocarditis in as many as 6% of cases of endocarditis. We describe this association in three patients. Osteomyelitis may be difficult to diagnose in patients with endocarditis because symptoms such as fever, bone pain and stiffness are common to both illnesses, therefore physicians need to have a high index of suspicion to avoid missing this important complication. We recommend that patients with endocarditis and persistent or localized musculoskeletal symptoms should be investigated to exclude osteomyelitis. Plain radiographs can be normal in 50% of cases of osteomyelitis in the early stages or show only minor abnormalities, but bone scans are highly sensitive. We suggest that a bone scan is performed if radiography is unhelpful, since a diagnosis of osteomyelitis can effectively be excluded if the bone scan is normal. We advocate close follow-up of these patients with prolonged antibiotic treatment consisting of at least 6 weeks of intravenous therapy, and 3 months or longer of oral therapy.

Introduction

We describe three cases of osteomyelitis in patients with endocarditis, two due to *Staphylococcus epidermidis* and one due to *Staphylococcus aureus*. Musculoskeletal symptoms are very common in patients with endocarditis and this makes it difficult to determine which patients warrant investigation to exclude osteomyelitis. Up to 6% of all cases of endocarditis are complicated by osteomyelitis¹ and it occurs slightly more frequently in cases with *Staphylococcus aureus* endocarditis.² There is no consensus of opinion on the length of treatment for this condition, and we review the literature and advocate a management regime.

Case reports

Case 1

A 64 year old man was admitted because of 3 weeks of lumbar backache, malaise and night sweats. Six years earlier he had undergone a homograft aortic valve replacement for severe aortic regurgitation due to rheumatic fever in childhood.

He was pyrexial (40°C), with a tachycardia of 120/minute and a blood pressure of 180/70 mmHg. There were no stigmata of endocarditis. On auscul-

tation there was a soft ejection systolic murmur at the left sternal edge radiating to the aortic area. There was a tender area in the right lower lumbar area. Neurological examination was normal.

Investigations revealed a haemoglobin of 12.2 g/dl, white cell count of $28 \times 10^9/l$ (of which 86% were neutrophils), ESR 115 mm/hour, C-reactive protein (CRP) 190 mg/l, and mean cell volume (MCV) 104 fl. The chest radiograph was normal except for a mildly enlarged heart and sternal wires from previous surgery. The electrocardiogram showed sinus tachycardia, left ventricular hypertrophy and a PR interval of 0.2 seconds. Echocardiography revealed a normal aortic homograft with no evidence of aortic regurgitation or vegetations.

A diagnosis of probable infective endocarditis was made and treatment was started with intravenous gentamicin (60 mg 12 hourly) and high dose benzyl penicillin (1.2 g 4 hourly). Blood cultures grew a penicillin-resistant *Staphylococcus epidermidis* from all bottles on day 3. The antibiotic therapy was changed to flucloxacillin and gentamicin. Thoracolumbar spine radiographs on day 2 showed extensive degenerative disease in the thoracic and lumbar spine, which was especially marked at the level of L2–L3 with anterior bridging osteophytes.

The temperature settled and the ESR fell to 56 but he still complained of severe back pain so a bone scan was performed (Figure 1). This suggested infection of the lumbar vertebrae L2 and L3. This was confirmed by magnetic resonance imaging of the thoracolumbar spine, which showed evi-

Correspondence: M.E. Speechly-Dick, B.Sc., M.R.C.P., Department of Academic and Clinical Cardiology, University College London Hospitals, Grafton Way, London WC1E 6DB, UK.

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Figure 1 Bone scan showing increased concentration of tracer at the level of the second lumbar vertebra (L2), which would be compatible with neoplasia or osteomyelitis.

dence of osteomyelitis and discitis at L2, and inflammation of the surrounding soft tissue (Figure 2). A diagnosis of osteomyelitis secondary to endocarditis was made. To improve bone penetration and because of gradually deteriorating renal function fusidic acid (500 mg 8 hourly) was substituted for gentamicin.

On day 13 an aortic regurgitant murmur developed. Echocardiography confirmed severe aortic regurgitation and revealed an aortic root mycotic aneurysm. The PR interval on the electrocardiogram (ECG) had not changed. The patient became pyrexial again and intravenous teicoplanin (400 mg once daily) was added to the therapy.

Acute heart failure developed on day 14 and emergency aortic valve replacement was carried out. At surgery the valve was found to be attached to the annulus over only 1 cm of its circumference. There was a large aortic root mycotic aneurysm, which was removed, and its cavity was obliterated by oversewing. The valve was replaced with a homograft because of the possible problems of anticoagulation as he was a heavy drinker. Post-

operative recovery was uneventful and after a total of 2 months of intravenous therapy the patient was discharged home on a 3 month course of oral flucloxacillin (1 g 6 hourly) and fusidic acid (500 mg 8 hourly).

The back pain did not recur and radiographs of the lumbar spine improved after 2 months. The antibiotics were discontinued after 3 months and the patient remains well more than 2 years later.

Case 2

A 65 year old man was admitted with a 2-month history of anorexia, weight loss, intermittent fever, myalgia and, more recent, low thoracic and lumbar backache. He had a past history of submucous resection for a transitional cell carcinoma of the bladder and was undergoing follow-up with annual cystoscopies, the most recent examination being nearly a year earlier.

He was pyrexial (38°C), and looked unwell. There were no stigmata of infective endocarditis. There was moderate mitral regurgitation but no evidence of cardiac failure. Dental examination

Figure 2 Magnetic resonance imaging scan showing discitis of the second lumbar vertebra (L2) with surrounding soft-tissue inflammation indicative of osteomyelitis.

revealed an infected left lower molar (there was no history of recent dental treatment). Neurological examination was normal, and the spine was mobile and non-tender.

Investigations revealed a haemoglobin of 10.2 g/dl, a white cell count of $8.4 \times 10^9/l$ and an ESR of 50 mm/hour. The chest radiograph showed cardiomegaly with clear lung fields. Echocardiography confirmed a dilated left ventricle with volume overload, moderate mitral regurgitation but no vegetations on the mitral valve. Blood cultures grew *Staphylococcus epidermidis*, which was fully sensitive to penicillin.

A diagnosis of probable endocarditis had been made on admission and treatment was started with intravenous penicillin (1.2 g, 4 hourly) and gentamicin (80 mg, 12 hourly). When the blood culture results were available, intravenous flucloxacillin (500 mg, 6 hourly) was substituted for penicillin. The infected tooth was extracted with antibiotic cover.

The backache did not improve and a lateral thoracic spine radiograph was performed, which showed slight wedging of the 10th thoracic vertebra (T10). A subsequent bone scan revealed dense uptake of isotope at T10, raising the possibility of either malignant infiltration or infection. In view of the history, a diagnosis of osteomyelitis secondary to infective endocarditis was made. The pain gradually improved with bed rest and antibiotics. A repeat lateral thoracic spine radiograph 6 weeks later showed wedging of three vertebral bodies but intact disc spaces with appearances more suggestive of osteoporotic collapse.

A total of 6 weeks of intravenous antibiotics and a further 2 months of oral flucloxacillin (500 mg 6 hourly) and probenidol (500 mg 6 hourly) were given. Post-discharge follow-up was close to monitor the resolution of the endocarditis and osteomyelitis, and to follow-up the mitral regurgitation.

The mitral regurgitation gradually deteriorated and 9 months later the patient underwent a mitral valve replacement. There was no evidence of a recurrence of endocarditis. Repeat thoracic spine radiographs showed gradual improvement over several months. The patient remains well 3 years later.

Case 3

A 41 year old man was admitted to another hospital with a 2 month history of malaise, weight loss, night sweats and diarrhoea. He was known to have a bicuspid aortic valve but had had dental treatment 3 months earlier without antibiotic prophylaxis. He had a history of a suppurating skin wound 2 months before. One week before admission he had noticed black spots on his scalp, fingers and toes. Blood cultures grew *Staphylococcus aureus*, and echocardiography showed a bicuspid aortic valve with vegetations on the anterior valve leaflet and a dilated aortic root. A diagnosis of infective endocarditis was made, but despite intravenous treatment with vancomycin and ciprofloxacin, his condition continued to deteriorate haemodynamically. He was then transferred to a cardiology unit with cardiothoracic surgery facilities.

On admission he was pyrexial with splinter haemorrhages and Osler's nodes, mild splenomegaly and early cardiac failure. Investigation revealed a haemoglobin of 10.4 g/dl, white cell count of 10.7×10^9 and ESR of 92 mm/hour. Echocardiography revealed that a fistula between the aortic root and the right ventricle had developed, and there was severe aortic regurgitation. The antibiotics were changed to a combination of teicoplanin (800 mg 12 hourly) and gentamicin (80 mg 8 hourly). Aortic valve replacement (AVR) with a Starr-Edwards prosthesis and patch repair of the fistula were carried out. Five days postoperatively complete heart block developed and a permanent VVI pacemaker was inserted. He became afebrile on antibiotics and made steady improvement. Two weeks after surgery he developed atrial flutter and underwent cardioversion. His renal function started to deteriorate and therefore gentamicin was discontinued and rifampicin was added. Three weeks after the initial surgery, he developed worsening cardiac failure. Echocardiography revealed that the fistula between the aortic root and right ventricle was patent again, and that the patch had come away. Surgical repair was attempted for

a second time and the prosthesis was also replaced. Active infection was seen around the site of the patch closure. Two days postoperatively cardiac tamponade developed requiring emergency aspiration. A Hickman line was inserted for the administration of long-term antibiotics.

The patient had 6 further weeks of intravenous therapy with teicoplanin following the second operation and steadily improved. He gained weight and participated in active physiotherapy. He complained of mild lumbar back pain 5 weeks after surgery, but there were no abnormal findings on clinical examination or on X-ray and the pain resolved with mild analgesics. He was discharged home with very close follow-up. Unfortunately he was readmitted with a pyrexia of 40°C and severe back pain 2 weeks later. Samples were taken for culture and he was restarted on intravenous teicoplanin. Spinal radiographs revealed reduced height and increased lucency of the 9th thoracic vertebra (T9) indicating probable osteomyelitis and this was confirmed by a bone scan. Blood cultures confirmed a recrudescence of *S. aureus* and echocardiography showed probable vegetations on the aortic valve, and a fistula between the aortic root and right ventricle. The patient developed severe acute pulmonary oedema and could not be resuscitated from a cardiac arrest. Post-mortem examination showed that T9 was soft and surrounded by purulent exudate. There was active infection in the heart but no abscesses in the liver or spleen.

Discussion

Musculoskeletal symptoms are common in infectious endocarditis and this makes it difficult for the clinician to select those patients who need investigation for osteomyelitis. Four papers specifically examined the incidence of musculoskeletal symptoms in large groups of patients with endocarditis. Thomas *et al.*³ described musculoskeletal manifestations in 32 of 108 (29.6%) patients treated for infectious endocarditis. These symptoms included myalgia, articular pain, aseptic arthritis, low back pain and osteomyelitis. Thirteen of these patients (12%) had spinal musculoskeletal symptoms and there were four cases of osteomyelitis among them. Patients with endocarditis and musculoskeletal symptoms did not differ from those without symptoms in terms of cause of infection, cardiac history, age, sex, or coexistent clinical signs. Churchill *et al.*¹ described an incidence of 44% for musculoskeletal symptoms in a survey of 192 patients with endocarditis and in 27% these symptoms were the presenting feature. Osteomyelitis was found to be the cause of back pain in 6% of the 192 patients, a similar result to that in the study by Thomas *et al.*³

Another large retrospective study by Meyers *et al.*⁴ of the musculoskeletal manifestations of endocarditis examined the records of 180 cases of proven endocarditis and found an incidence of 28% of musculoskeletal symptoms, but they found no cases of osteomyelitis. However, there was one patient with disc-space narrowing and another with a paravertebral abscess, and it is possible that these patients had undiagnosed osteomyelitis. It would have been difficult to diagnose osteomyelitis in retrospect if patients were not investigated for it at the time. Mansur *et al.*⁵ also examined retrospectively the incidence of all complications of endocarditis in 300 patients who presented between 1978 and 1986, and found no diagnoses of osteomyelitis.

Therefore musculoskeletal symptoms, which can be a prominent complaint in anyone who is unwell, are a common feature in patients with endocarditis. The seriousness of the illness and the high incidence of musculoskeletal symptoms can mean that the possibility of osteomyelitis is overlooked. Osteomyelitis probably occurs with a frequency of approximately 6%.¹ It is a well-recognized complication of endocarditis, and is thought to be due either to microembolism of bacteria or haematogenous spread. Invasive organisms such as *S. aureus* are thought to result in a higher incidence of osteomyelitis and, for example, this diagnosis was made in 9% of 35 patients with native valve coagulase-negative staphylococcus.² Mansur *et al.*⁵ found that streptococci were the culprit organism for endocarditis in 49% of 300 cases, but that there was also a high incidence of *S. aureus* (20%) and *S. epidermidis* (5%), and all of these organisms are capable of causing osteomyelitis.

Back pain in the context of positive blood cultures should be taken seriously and the physician should investigate any patient with these findings thoroughly to exclude osteomyelitis. *S. epidermidis* is the most frequent cause of positive blood cultures in hospital but only 6.3% of these are true bacteraemia.⁶ However, we should not dismiss coagulase-negative staphylococci in blood cultures as a contaminant, especially if more than one sample is positive because *S. aureus* and *S. epidermidis* account for 60–90% of cases of isolated osteomyelitis⁷ and approximately 30% of cases of infective endocarditis.⁵

Fever, back pain and stiffness are the major symptoms of osteomyelitis and, as described above, these symptoms are also very common in endocarditis. If the back pain is persistent or severe, it would seem sensible to investigate the patient for osteomyelitis. It takes between 2 and 8 weeks from the onset of osteomyelitis before there are any obvious abnormalities on a plain radiograph.⁷ Even then, in 50% of cases the radiographs are normal early on or show changes consistent with degenerative arthritis only, the rest are abnormal

and show narrowing of the disc space, sclerosis, erosion of the endplates and destruction of the vertebral bodies.⁸ Computerized tomography (CT) may also be normal in the early stages or may disclose a reduction in disc density, an early sign of osteomyelitis.⁸ Magnetic resonance imaging may reveal abnormalities earlier than either plain radiography or CT scanning, but is not always available. However, radionuclide bone scans with either gallium or technetium have a very high sensitivity and are the diagnostic procedure of choice if plain radiographs have been unhelpful.^{8,9} Radionuclide scanning can provide evidence of bone infection within 48 hours of the infection; the radionuclide concentrates avidly at sites of increased blood flow and bone turnover. Therefore, the differential diagnosis of osteomyelitis is of metastatic malignancy, where lesions are usually multiple and scattered through the axial skeleton, arthritides and Paget's disease, which have typical distributions, and trauma, which can be differentiated by the history.¹⁰ The diagnosis of osteomyelitis is made from the typical picture of increased radionuclide uptake of the affected area on the bone scan in association with an appropriate clinical history. Adatepe *et al.*⁹ state that a normal bone scan excludes a diagnosis of osteomyelitis. We recommend that any patient in whom there is a reasonable suspicion of osteomyelitis should have a bone scan.

Prolonged treatment with antibiotics is needed to sterilize a bony focus, which may be a potential site for reinfection in a patient with an abnormal valve. Acute haematogenous osteomyelitis can be successfully treated with antibiotics alone unless a late diagnosis has been made and extensive bone necrosis has already occurred, in which case the dead bone must be surgically removed because it harbours microorganisms and is difficult to sterilize.⁷

Recommended antibiotic regimes range in total length from 6 weeks to 6 months. Waldvogel *et al.*⁷ suggest that at least 6 weeks of parenteral

antibiotics be given to cases of isolated osteomyelitis without endocarditis and even with this regime they experienced a relapse rate of one case in 20. They advocate surgical debridement where there is extensive destruction of the vertebral bodies with sequestra and abscess formation and, of course, if there are signs of spinal cord compression. Barham *et al.*¹¹ described a case of streptococcal endocarditis and osteomyelitis, which resolved after 5 weeks of intravenous antibiotics followed by 3 weeks of oral amoxycillin and erythromycin. A case of *S. epidermidis* endocarditis resulting in osteomyelitis at the level T9–T10 was cured after a course of 4 weeks of high-dose intravenous flucloxacillin followed by 5 months of oral amoxycillin.¹² In our experience of *S. epidermidis* endocarditis and osteomyelitis, successful cure can be achieved if treatment is continued for at least 3 months. For example, case 1 had a total of 8 weeks of intravenous therapy followed by 3 months of oral flucloxacillin and fusidic acid, and case 2 had 6 weeks of intravenous therapy and 2 months of oral flucloxacillin with probenecid. Case 3 had 10 weeks of intravenous antibiotics prior to discharge but no long-term treatment. Unfortunately, osteomyelitis was diagnosed late in case 3 and a recrudescence of endocarditis, most likely due to local reinfection although possibly from the bony focus, proved fatal.

In conclusion, we recommend that a diagnosis of osteomyelitis is considered in any patient with infective endocarditis and back pain, especially if the pain is persistent, severe or localized, and that physicians should have a high index of suspicion for this condition. These patients should be investigated with plain radiography and a bone scan, if the radiograph is normal. We also advocate that the treatment regime consists of at least 6 weeks of intravenous antibiotics, and 3 months or longer of outpatient oral therapy with close follow-up. Patients should be encouraged to keep a temperature chart at home and any recurrence of fever or back pain should, of course, be investigated.

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