

## LESSON OF THE MONTH

## Chronic recurrent multifocal osteomyelitis is a differential diagnosis of juvenile idiopathic arthritis

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### Case history

A 5 year old girl was referred to the paediatric rheumatology clinic in June 1999 for assessment of possible juvenile idiopathic arthritis (JIA). She had been well until seven months previously, when she began to limp and developed a swollen left ankle. At this time she appeared generally unwell and irritable but had no history of fever or rashes. There was no previous past medical history of note. She lived with her parents and twin brother, who were all well. A distant relative was believed to have rheumatoid arthritis. A full blood count was normal, C reactive protein and blood cultures were negative. A radiograph of the left ankle showed a lucency at the distal tibia with associated periosteal reaction (fig 1). A technetium-99m MDP bone scan showed increased uptake in the lower end of the left tibia (fig 2A) as well as the body of L5 and the left sternoclavicular joint (fig 2B). A biopsy of the lower end of the left tibia showed evidence of necrosis and new bone formation with much inflammation and fibrosis, but little suppuration (fig 3). No organisms were identified and culture of the biopsy was negative.

She appeared to improve after a course of flucloxacillin and fusidic acid that was prescribed empirically after the biopsy was carried out but before the result of the culture was known. These antibiotics were used because of their anti-staphylococcal action; *Staphylococcus aureus* is the commonest cause of osteomyelitis. In addition, fusidic acid is effective in penicillin resistant staphylococcal infection and achieves good bone penetration. However, in March 1999 she developed back pain and a swollen right knee, which settled with regular ibuprofen. In May 1999 the left ankle swelling recurred. A repeat <sup>99m</sup>Tc MDP bone scan showed less uptake in the distal left tibia but increased bony uptake in the left proximal tibial end plate and right distal femoral end plate. The uptake in L5 was unchanged.

On examination she appeared small for her age and was on the 9th centile for height and weight. There were no rashes or lymphadenopathy. Her joints appeared normal with no synovitis or tenderness. There was no spinal tenderness. The remainder of the examination was normal. Her parents had been keeping a

temperature chart for two months and this had been normal. Erythrocyte sedimentation rate and full blood counts were normal. C reactive protein, antinuclear antibody, rheumatoid factor, and HLA-B27 were all negative. Screening for neuroblastoma was also negative.

When reviewed one month later, she had been unwell again. Her parents reported several episodes of pyrexia of up to 38.9°C. There was some swelling proximal to the left ankle joint but a good range of movement and no evidence of active synovitis. Her symptoms



Figure 1 An x ray picture of the left ankle. Adjacent to the tibial epiphysal plate of the left ankle, there is an area of osteolysis of the tibial metaphysis (black arrows). This is associated with a periosteal reaction (white arrowhead).

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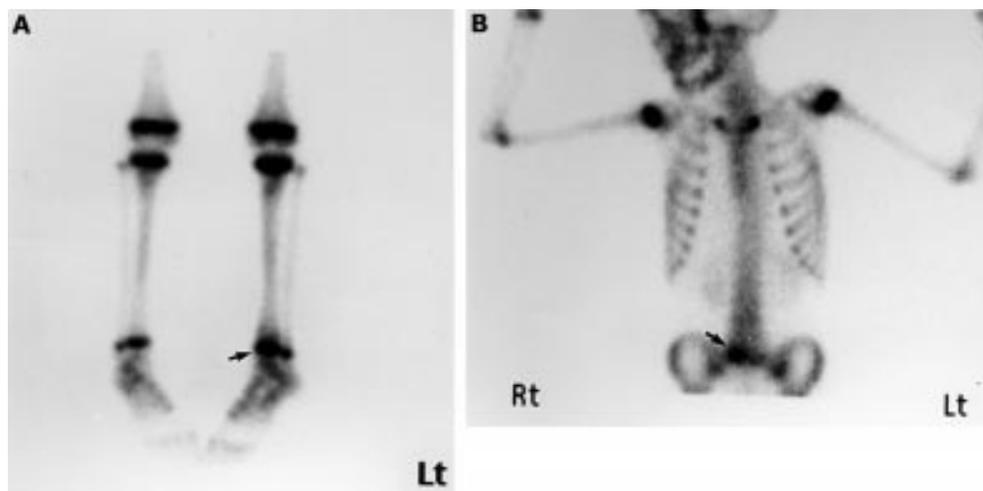


Figure 2 (A) Three phase  $^{99m}\text{Tc}$  MDP bone scan, static view shows increased uptake in the distal end of the left tibia (arrow). (B) Three phase  $^{99m}\text{Tc}$  MDP bone scan, static view also shows a small focus of increased uptake at the right aspect of L5 (arrow) and the left sternoclavicular joint.

were mainly controlled with naproxen, though on several occasions she had required opiates for pain relief. The acute phase response was again negative.

The lack of synovitis, persistent lack of a raised acute phase response, negative serology, and L5 and left sternoclavicular lesions on the bone scans were not typical of JIA. A magnetic resonance imaging scan (MRI) of her left ankle showed increased signal in the distal metaphysis of the left tibia (fig 4) and adjacent fibula and also in the proximal metaphysis of the right tibia. These appearances were consistent with a diagnosis of chronic recurrent multifocal osteomyelitis. She continued to be treated with regular non-steroidal anti-inflammatory drugs (NSAIDs), and her symptoms gradually improved over the following months. When last seen for review in February 2000 she was well and asymptomatic.

### Discussion

The diagnosis of chronic recurrent multifocal osteomyelitis (CRMO) is essentially one of exclusion. Rheumatic disease, infective osteomyelitis, and malignancy are the main differential diagnoses. For the single tibial lesion

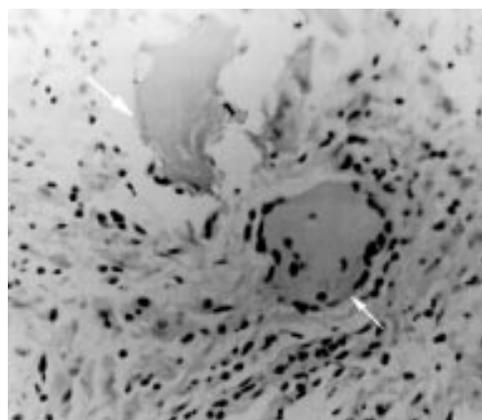


Figure 3 Biopsy of left tibial lesion showing an area of dead bone (large arrow), an osteoclast (small arrow), and a chronic inflammatory infiltrate which is mainly mononuclear with the occasional neutrophil.



Figure 4 MRI of the left ankle. There is increased signal in the distal metaphysis of the left tibia with surrounding periosteal oedema (arrow).

presents as a pure bone lesion. Cells of the reticuloendothelial system (histiocytes and eosinophils) form granulomatous collections. Bone containing marrow is resorbed and lytic lesions appear. The condition usually presents as a pathological fracture or an incidental finding and heals spontaneously. Multiple lesions may herald the onset of more systemic disease—for example, Hans-Schüller-Christian or Letterer-Siwe disease.

CRMO is a rare inflammatory disorder of the skeleton of unknown cause first described in 1972 by Giedion *et al.*<sup>1</sup> It occurs mainly in children and adolescents. It has recently been suggested that lack of diagnostic awareness and the diagnosis being made by exclusion after long term follow up may indicate it is more common than previously realised.<sup>2</sup> Clinically, CRMO is characterised by insidious onset of local swelling and pain in several metaphyses. A symmetrical recurrent multifocal pattern is usual and lesions are most often in the tubular bones. The spine and clavicle are the next commonest sites affected. Rib, sternal and pelvic lesions are rare. Systemic manifestations are common—for example, fever, malaise, weight loss. The characteristic course of the condition is prolonged with periods of exacerbation, sometimes involving new foci, interspersed with remissions. Most cases appear to remit in late childhood, but relapses in late teenage and early adulthood can occur. The long term prognosis is generally good, but resultant skeletal deformities may occur, particularly with the more protracted courses. Associations have been described with palmoplantar pustulosis, psoriasis, and Sweets' syndrome. It is considered to be related to the SAPHO syndrome.<sup>3</sup>

SAPHO is an acronym for Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis and describes an inflammatory condition where palmoplantar pustulosis, acne conglobata, acne fulminans, and hidradenitis suppurativa can occur with sterile multifocal osteomyelitis, sternoclavicular hyperostosis, hyperostosis of the spine, and (less commonly) a peripheral synovitis.<sup>4</sup> The anterior chest wall is most commonly affected and many components of this structure may be involved—namely, sternoclavicular, sternocostal, manubriosternal, costochondral, and costmanubrial joints.<sup>5</sup> The presence of the asymptomatic lesion at the left sternoclavicular joint in our patient is therefore of interest. The increased prevalence of HLA-B27, sacroiliitis, inflammatory bowel disease, and psoriasis in patients with the SAPHO syndrome has led it to be classed as a spondyloarthropathy. The role of *Propionibacterium acnes* is increasingly discussed in the SAPHO syndrome. In most patients, culture of the osteitic bone is sterile, but *P acnes* has been found in the affected area in a few cases.<sup>5,6</sup> However, it is a common skin commensal and contamination of microbiological samples is a possibility. In addition, there is little clinical response to antibiotic treatment in the SAPHO syndrome, but patients often improve with NSAIDs and corticosteroid administration. This has raised the possibility that *P acnes* antigen initiates an immunological reaction or acts

as a cofactor in such a reaction.<sup>6</sup> To our knowledge there have been no reports of *P acnes* in association with CRMO.

Histopathological confirmation by biopsy is necessary to rule out the above diagnoses. There are no specific histopathological criteria for CRMO, and histopathological features alone may not provide conclusive evidence of CRMO.<sup>7</sup> Therefore the definitive diagnosis is made by a combination of the clinical picture, radiological studies, microbiology, and histopathology. Radiological investigations have a role in assessing the extent of disease and the likelihood of the diagnosis, which is helpful before embarking on more invasive procedures.

Plain radiographs may be helpful in tubular bone lesions as appearances can be relatively specific.<sup>2</sup> Lytic destruction adjacent to the growth plate with a sclerotic rim demarcating it from normal bone with no periosteal new bone formation is typical. Radiographs at other sites—for example, clavicle and spine, are less specific and more difficult to distinguish from infection. Isotope bone scans are helpful to assess the extent of the lesions as some can be silent and asymptomatic. Recently, the value of MRI scanning in CRMO has been assessed.<sup>2</sup> The MRI features can be indistinguishable from classic septic osteomyelitis and the fact that the lesions are multifocal is absolutely crucial for the diagnosis. However, CRMO lesions of tubular bones and the spine can exhibit quite characteristic features. Abscess formation, sequestration, marrow infiltration or sinus tracts, features commonly seen in chronic infective osteomyelitis, can be excluded with MRI. In the spine, CRMO lesions are usually confined to one vertebra and do not cross intervertebral discs as can occur in infection. Malignant lytic lesions are, however, more difficult to differentiate. Early clavicular lesions on MRI are non-specific and can be indistinguishable from malignancy. Evaluation of the activity of CRMO lesions is possible using MRI—more active lesions have increased bone marrow signal intensity on T<sub>2</sub> weighted images and decreased signal intensity on T<sub>1</sub> images. MRI can also be used to indicate the most appropriate biopsy site for the highest potential diagnostic yield.

The addition of the MRI appearance to the clinical features and previous investigations greatly aided the attainment of a definitive diagnosis in this case. MRI is not diagnostic of CRMO and is not necessary for making a diagnosis. However, it is a welcome addition to the investigative techniques which can be applied to improve the specificity of a diagnosis of CRMO.

### The lessons

1 CRMO is a differential diagnosis of JIA, infective osteomyelitis, and malignancy. It is a diagnosis of exclusion.

2 CRMO should be considered if there is no evidence of a causative organism in a suspected case of osteomyelitis, and other asymptomatic lesions should be sought.

3 MRI scans are a useful addition to the available investigations for CRMO.

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