CASE REPORT

Whole body MRI in the diagnosis of chronic recurrent multifocal osteomyelitis

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Accepted: 22 February 2012

Summary Chronic recurrent multifocal osteomyelitis (CRMO) is a diagnosis of exclusion primarily in children and adolescents. As part of the essential criteria for the diagnosis of CRMO, multifocal lesions must be identified. We present the case of an 11-year-old boy with CRMO, whose diagnosis was facilitated by the use of whole body magnetic resonance imaging (WBMR), but not isotope bone scanning.

INTRODUCTION

Chronic recurrent multifocal osteomyelitis (CRMO) is a diagnosis of exclusion characterized by multiple areas of sterile osteomyelitis, which become symptomatic intermittently over time. Although principally a disease of children, it regularly continues to be symptomatic well into a person’s 20s, and has been reported in one patient of 55 years \cite{1,2}. CRMO is the most common disease process to involve the medial third of the clavicle in all age groups, and the most frequent non-oncological pathology to affect the clavicle in people under 20 years old \cite{3}. The most common areas affected are the tibia, femur, pelvis and spine \cite{4}.

The majority of patients present with disease at just one site, and occult multifocal lesions are discovered on subsequent imaging, or recurrent exacerbations. However, a significant minority of children with non-bacterial osteomyelitis may have only ever had a single lesion, for which the term “chronic nonbacterial osteomyelitis” rather than CRMO has been suggested \cite{5}. Therefore in order to identify CRMO, the key diagnostic criteria include identifying areas of sterile chronic osteomyelitis, which must be multifocal. Fritz et al. described basing their diagnosis of CRMO on the following criteria: multifocal osseous lesions; recurrence of signs and symptoms for at least 6 months; lack of an identifiable cause; lack of response to antimicrobial therapy for at least 1 month; and chronic, nonspecific inflammation consisting of lymphocytes, plasma cells, and histiocytes at histopathologic examination \cite{6}. Thus in order to find multiple clinically occult lesions one should consider either whole body magnetic resonance imaging (MRI), or whole body Tc-99m labelled methylene diphosphonate (MDP) bone scintigraphy. We present a case of CRMO where the diagnosis was facilitated by whole body MRI but not by bone scintigraphy.

CASE REPORT

An 11-year-old male was referred to our paediatric orthopaedic unit from a peripheral general hospital.
patient's main symptoms were that of a 6-week history of gradually increasing right medial clavicle discomfort, with a palpable firm swelling in that region (Fig. 1). There was a history of trauma, and a healing fracture was the initial working diagnosis in the peripheral hospital. The patient's clavicle continued to expand both clinically and on plain radiographs and he was referred to our unit for a second opinion. The patient had a mildly elevated erythrocyte sedimentation rate (ESR) of 18 at his initial presentation. After initial investigations were performed, including plain radiographs, computed tomography (CT) and routine bloods, the working diagnosis was that of an infective osteomyelitis, but non-bacterial osteomyelitis, CRMO, Langerhan's cell histiocytosis and unidentified neoplasm were included in the differential diagnosis. The patient had a bone biopsy, and the result indicated cell infiltrate consistent with chronic osteomyelitis, but no bacteria were grown. A diagnosis of nonbacterial osteomyelitis was regarded as probable, but since it is a diagnosis of exclusion the patient was commenced on a 6-week course of oral fluoxacinil and fusidic acid.

Despite these measures the patient's discomfort continued and he returned to our unit approximately four weeks after his antimicrobial therapy had started. A whole-body Tc-99m MDP bone scintigraphy was performed to help support a diagnosis of CRMO, but the only area of increased uptake was the right clavicle. The patient was commenced on a non-steroidal anti inflammatory (naproxen sodium) and his right clavicle discomfort began to settle. Three weeks later the patient re-attended to us as he had an exacerbation of his clavicle discomfort. Repeat plain radiographs indicated that the right clavicle lesion was continuing to expand. A whole-body MRI was performed. Coronal STIR sequences in five segments were obtained. In addition to the clavicular lesion, the MRI showed an unexpected area of increased signal intensity in the left acetabulum (Fig. 2). The patient had no symptoms in the left lower extremity, and had no history of injury or symptoms in this area. The finding allowed a diagnosis of CRMO to be made, given that the clinical criteria mentioned in the introduction had already been fulfilled [6]. The patient was given a 2-week course of an oral corticosteroid and long-term course of naproxen. At six month follow up, the patient's symptoms were well controlled, with mild short-lived intermittent episodes of clavicle discomfort. His left hip was never symptomatic. The nature of CRMO is such that his symptoms could recur sporadically.

**Discussion**

The diagnosis of CRMO is essentially one of exclusion. It is important however to establish a valid conclusion as soon as it is feasible, in order to prevent repeated courses of antibiotics and biopsies. At any time the number of lesions can vary from one to 18, with the majority being asymptomatic [7,8]. CRMO has been hypothesized to be an auto-inflammatory syndrome [9]. There have been reported associations with multiple autoimmune diseases, including peripheral arthritis, inflammatory bowel disease, psoriasis, sacro-ililitis and a juvenile form of seronegative spondyloarthropathy [10].

In 1989, Majeed et al. reported a consanguineous family with CRMO and Sweet syndrome, which contrasted with the usual sporadic nature of CRMO [11]. These Majeed syndrome families have demonstrated homozygous mutations of the LPIN2 gene present in chromosome 18p11, which may tentatively suggest a link between lipid metabolism and these inflammatory pathologies [12,13]. A condition similar to CRMO has been seen in mice, known as chronic multifocal osteomyelitis (CMO). Mouse CMO has been shown to be conveyed in an autosomal recessive manner. The PSTPIP2 gene on the mouse chromosome 18 has been recognized as the causative gene for CMO [14]. However, the PSTPIP2 gene resides on chromosome 18q12 in humans, while the responsible gene locus for sporadic CRMO cases is thought to dwell on chromosome 18q21-22, so it is unclear if the PSTPIP2 gene can be a causative agent in humans [15].

The differential diagnosis for CRMO includes infection, neoplastic lesions and occasionally trauma. Neoplastic type lesions, which CRMO mimic include Ewing sarcoma, neuroblastoma metastasis, osteosarcoma, leukemia, lymphoma, Langerhans cell histiocytosis, eosinophilic granuloma, osteoid osteoma, and osteoblastoma. Chronic osteomyelitis can also have a similar appearance to CRMO [10].

The standard approach when investigating possible osteomyelitis with bone scintigraphy, is to perform a three-phase scan using 99m Technetium-labeled methylene diphosphonate (MDP). The positive uptake on all three phases is sensitive for osteomyelitis (sensitivity 73% to 100%) [16]. The sensitivity of MRI for osteomyelitis has been commonly reported as being between 82% and 100%, and specificity between 75% and 96% [17,18]. El-Maghraby et al. argue that in the setting of CRMO, the imaging agent **67
Gallium-citrate\textsuperscript{14} can increase specificity when used in combination with Tc-99m MDP, but it is not clear if there is an increased sensitivity \cite{16}. Gallium is also associated with a significantly higher radiation dose and is thus used with caution in children. In this case, the new acetabular lesion was undetectable on the bone scan. Reasons for missing the second lesion here include the possibility that the normal physiological uptake in the acetabular physis masked the subtle marrow changes visible on the MRI. Bone scintigraphy relies on osteoblast activity, seen in infection, healing fractures and metastases but not in other conditions, such as myeloma. On the other hand, MR will detect "marrow" inflammation, with or without the presence of osteoblast activity. Fritz et al. argue that MR imaging has the advantage over bone scanning of better demonstrating lesions confined to the marrow \cite{6}. In this case the occult lesion was confined to the acetabular marrow. MR imaging is useful both for determining the extent of disease and for surveillance in CRMO. During the active phase of the disease, MR imaging shows typical findings of marrow edema, which appears hypointense on T1-weighted images and hyperintense on T2-weighted images. Whole-body MRI uses fat-saturated sequences to significantly reduce or null the signal coming from normal fatty marrow, thereby accentuating any high signal within the marrow. Associated periostitis, soft tissue inflammation, and transphyseal disease can also be visualized on MRI \cite{19,20}.

The advantages of whole body MRI (WBMR) over bone scintigraphy include the lack of any ionizing radiation, quicker completion time, ability to detect subtle lesions earlier and that associated soft tissue pathologies can be shown more readily, which would be otherwise missed by scintigraphy. MRI has become the established standard of reference for many diseases that involve bone marrow \cite{6}, although Khanna et al. caution against the expense of whole body MRI, particularly if a general anaesthetic is required in younger children \cite{4}.

Some disadvantages are that rib and skull lesions can be missed due to relatively large slice thickness. The lungs are also not well visualized due to motion artefact. Age-related paediatric bone marrow changes could also cause diagnostic difficulty to the untrained eye \cite{21,22}.

Because of the relative rarity of CRMO, there have been no randomized trials to elucidate the best treatment. NSAIDs have been reported to provide symptomatic relief in up 80% of patients \cite{5,23–25}, although up to 50% of patients continue to get symptoms or relapses despite NSAID medication \cite{5}. Corticosteroids have been used for short-term treatment of exacerbations \cite{5,23–25}, but side effects can preclude long-term use. Sulfasalazine and methotrexate have been used with successful resolution of symptoms \cite{5,25}. In children who don’t respond well to these treatment modalities, there have also been encouraging reports relating to TNF-\textalpha inhibitors and intravenous bisphosphonates \cite{24,26,27}. Surgical treatment is usually reserved to biopsy, although there are anecdotal accounts of symptom improvement following curettage. Prognosis is usually good in the long term. French and Canadian/Australian cohort reviews reported average disease duration of 5.3 and 5.6 years respectively \cite{25,28}. In the Canadian/Australian cohort as many as 50\% developed bony deformities they regarded as either cosmetically or functionally deleterious \cite{28}. A minority of sufferers continued to have chronic pain, which was usually associated with ongoing disease activity well beyond the average 5-year symptomatic period.

In relation to this case report and our difficulty diagnosing CRMO, we would recommend that whole-body MRI should considered when possible, as part of the diagnostic workup.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

**References**


