Chronic Recurrent Multifocal Osteomyelitis in Children: A Multidisciplinary Approach is needed to establish a Diagnosis

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Abstract

Chronic recurrent multifocal osteomyelitis (CRMO) is an inflammatory disease of unknown cause. In general, CRMO follows a characteristic clinical course and is regarded at present as a distinct entity. It affects bone and occurs predominantly in children and adolescents. The clinical, radiologic and pathologic findings are non-specific. The recognition of this rare entity is often delayed and difficulties in patient management sometimes emerge from its usual protracted course. We present a 6-year-old girl diagnosed with CRMO involving tibia and lumbar vertebra where a multidisciplinary approach was essential in making the diagnosis.

Keywords: Chronic recurrent multifocal osteomyelitis, non-pyogenic inflammatory bony lesions, Tc-99m Leucoscan and Tc-99m MDP bone scan

Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) or subacute symmetrical osteomyelitis was first described by Giedion *et al.* in 1972. It represents a rare condition, with an estimated incidence around 1:1000000 in children, characterized by an insidious onset of pain and signs of inflammation over affected bones which may last for months or years without responding to antibiotic therapy. Other organs such as the skin, gastrointestinal tract, lungs and the eyes may be affected and complicate the clinical picture. In almost all cases this condition is of unknown etiology and may be misdiagnosed as subacute or chronic osteomyelitis, arthritis or malignant or benign tumors. While the clinical course of the disease is usually benign, some patients may be predisposed to early degenerative arthritis.[1]

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Radiographic findings are similar to those seen in osteomyelitis, with lesions appearing predominately lytic early in the disease. In some cases a varying degree of sclerosis is evident consistent with healing as symptoms subside. The lesions are usually located at the metaphyseal region of long bones, but can occur at any site in the skeleton. Radioisotope bone scans assisted in establishing the diagnosis and in identifying lesions that were initially clinically silent. Furthermore, it helps in selecting and guiding the biopsy needed to establish the diagnosis. Whole body magnetic resonance imaging (MRI) can play a similar role however is currently unavailable in most institutions. Definite diagnosis relies on histopathology confirmation by biopsy. Biopsy can reveal a subperiosteal bone formation which indicates chronic inflammation in addition to granulocytes, lymphocytes, plasma cells and monocytes in later stages. However, the cultures of the biopsy will be negative.[2]

Case Report

This was a case of a 6-year-old girl presented in October 2007 with a history of pain in right leg for 4 weeks. On clinical examination, she was a febrile and her right leg was tender with mild diffuse swelling. Laboratory

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investigation at the time showed normal complete blood count (CBC), erythrocyte sedimentation rate (ESR) level was 25 and positive C-reactive protein. Ferritin level, antinuclear antibody level, rheumatoid factor status, concentration of complement components C3 and C4 and serum levels of IgG, IgA, IgM, IgE and IgD, were all unremarkable. Blood culture was also negative.

Plain X-rays showed wide periosteal reaction involving the whole diaphysis of right tibia [Figure 1]. Computed tomography (CT) scan showed sclerosis of the mid and distal third of right tibial medullary cavity, while proximal third showed increased density of the bone marrow. The anterior-medial aspect of right tibia showed periosteal reaction. No evidence of bone destruction or squestrum formation was noted. Differential diagnosis included Ewings and chronic osteomyelitis.

Three-phase 99mTc-methylendeiphosphonate (MDP) bone scan showed hyperemia and blood pooling of radiotracer over right leg and a focal area of increase tracer uptake over mid shaft of right tibia was noted on delayed images. Another focal area of increase tracer uptake was seen at L5 vertebra [Figure 2a-c]. Tc-99m Leucoscan of the corresponding side appeared unremarkable [Figure 2d]. This multifocal pattern of lesions was indistinguishable from Langerhans' cell histiocytosis, the other major differential diagnosis. Bone biopsy was therefore performed and the histopathology showed lymphocytic and plasmacellular infiltrate, in addition to peritrabecular fibrosis which excluded malignancy and the patient was treated accordingly.

In May 2008, the patient again presented with pain and tenderness over left leg. She was a febrile and her lab investigation showed normal CBC and ESR level was 23. CT scan showed diffuse cortical thickening at left tibia with increased bone marrow density [Figure 3]. Plain X-ray showed periosteal reaction at left tibia with no evidence of bone destruction [Figure 4a]. Three-phase 99mTc-MDP bone scan was requested and revealed hyperemia and blood pooling of radiotracer over the left leg. Delayed images showed focal area of increased tracer uptake over mid shaft of the left tibia [Figure 4b and c]. There was complete resolution of the lesion at right leg and L5 vertebra. Tc-99m Leucoscan showed mild diffuse increased tracer uptake at left leg with no delineated focus [Figure 4d]. Because the patient exhibited multiple bone lesions, a recurrent course, a biopsy consistent with choric inflammation and no cultivable bacteria on blood culture, the diagnosed of CRMO was reached.

Discussion

CRMO in children is a chronic non-suppurative inflammation involving multiple sites. It affects more commonly girls than boys. The peak age of incidence is around 10 years. It comprises periodic bone pain, fever and the appearance of multiple bone lesions that can occur in any skeletal site. The origin of this disease is unclear, but genetics appears to play a role. The clinical and radiological features on the disease are variable.[3] Clinical diagnosis can be difficult because the clinical picture and course of disease may vary significantly. The symptoms from the bone lesions are characterized by periodic exacerbation and remission.[3] The most common abnormal laboratory test is an elevated ESR. Neither anemia nor leukocytosis were observed in patients and serum calcium, phosphorus and alkaline phosphatase values are usually normal. Tissue and blood cultures are negative. Histologically, the lesions reflected

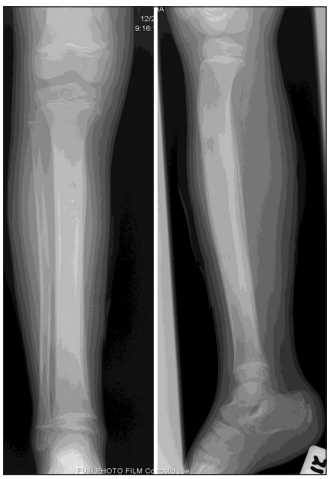

Figure 1: Plain X-rays showing wide periosteal reaction involving the whole diaphysis of right tibia and sclerosis of the mid and distal third of right tibial medullary cavity

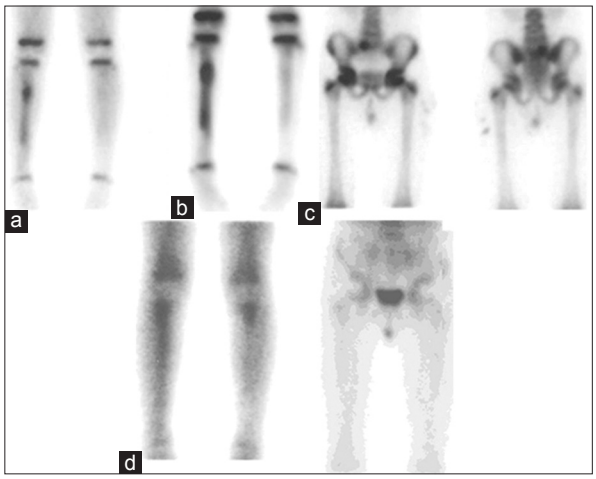

Figure 2: (a) Three-phase 99mTc-methylendeiphosphonate bone scan showing hyperemia and blood pooling of radiotracer over right leg. (b and c) Delayed images show focal area of increase tracer uptake over mid shaft of right tibia. Another focal area of increase tracer uptake is also seen at L5 vertebra. (d) Tc-99m Leucoscan of the corresponding side appears unremarkable

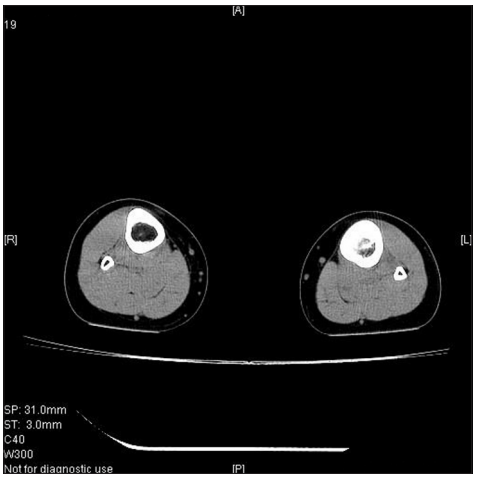

Figure 3: Computed tomography scan shows diffuse cortical thickening at left tibia with increased bone marrow density

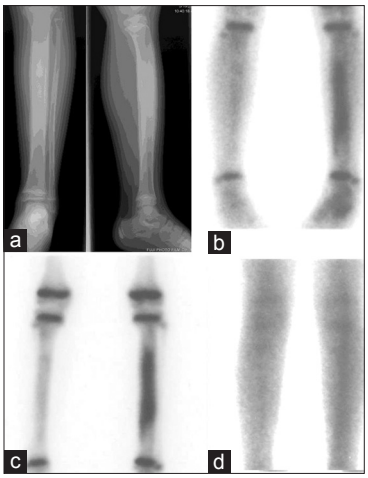

Figure 4: (a) Plain X-ray show periosteal reaction at left tibia. (b) Blood pool images of Tc99m methylendeiphosphonate bone scan showed blood pooling of radiotracer over left leg. (c) Delayed anterior images showed focal area of increase tracer uptake over mid shaft of left tibia. (d) Tc-99m Leucoscan with no corresponding abnormal uptake of radiotracer

different stages of chronic non-specific osteomyelitis. A quiescent inflammation with a small number of lymphocytes and plasma cells was the most common lesion. No frank necrosis, granulomas or specific patterns of inflammation are usually observed.[4]

In this case study, the patient started having right knee and leg pain; therefore the differential diagnosis initially included juvenile idiopathic arthritis. Clinical examination however provided no evidence for the presence of arthritis. Plain X-ray and CT scan showed periosteal reaction, sclerosis of mid shaft and distal third of right tibia and precluded the diagnosis of Ewings and chronic osteomyelitis. Skeletal manifestations include multiple synchronous or metachronous lesions apparent on plain radiographs. CT scans and MRIs were helpful to delineate the extent of the lesion, but the findings were non-specific. These modalities do not distinguish CRMO from acute bacterial osteomyelitis and biopsy and sampling of involved bone lesions are frequently necessary.[5]

Tc-99m-MDP bone scan showed multiple bone lesions at right tibia and L5 vertebra. This multifocal pattern of lesions raised the possibility of Langerhans' cell histiocytosis and neuroblastoma. Technetium whole body bone scan was also useful for identifying other sites of skeletal involvement. Girschick *et al*. demonstrated that, the lesions demonstrate increased uptake on technetium bone scans, even if they are clinically silent.[4]

Seven month later patient presented with left leg pain and bone scan showed bone lesion at left tibia and complete resolution of previous lesions at right tibia and L5 vertebra, indicating a sequential and relapsing onset.

At both occasions Tc-99m Leucoscan of the corresponding side appeared unremarkable. Tc-99m Leucoscan seems to be useful in excluding infection rather than confirming it in patients with suspected infection. In our experience, we found it very helpful especially in children due to its availability in kit form, easy preparation, *in-vivo* application and the absence of significant side-effects.[6,7] In this case, it was negative which may be explained by the fact it was not an acute case or it may be a false negative result. Further studies are required to confirm either possibilities.

Conclusion

This study clarifies the clinical and radiologic features of CRMO. The diagnosis of CRMO is a diagnosis of exclusion and should be included in the differential diagnosis of chronic inflammatory bone lesions in children. The definite diagnosis should be made by the collective analysis of the clinical picture, X-ray studies, bone scan, bacterial culture and histopathology in a multidisciplinary approach. This approach was necessary to cover the clinical variability of CRMO and to ensure that this syndrome is managed effectively. In our case, radionuclide Antigranulocytes images helped to exclude acute infection, however, further studies are required to establish its role. Diagnostic imaging played an important role in making the diagnosis and radiologists and nuclear physician should be aware of this disease.

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