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Chronic Recurrent Multifocal Osteomyelitis (CRMO): An Unusual Presentation of Limb Pain

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Abstract

Chronic recurrent multifocal osteomyelitis (CRMO), known as nonbacterial osteomyelitis, is an autoinflammatory disease with periodic exacerbations, also known as nonbacterial osteomyelitis. It is a rare, noninfectious inflammatory disorder characterized by multifocal bony lesions with pain. Conventional X-ray and CT imaging show multiple osteolytic and sclerotic lesions in the affected limbs. It is a great challenge for pediatricians to diagnose this disease for its rarity. Early diagnosis, regular follow-up and appropriate treatments are mandatory to reduce morbidity and prevent these disease complications. We report here two cases of CRMO who presented with pain, swelling and redness of multiple sites of lower limbs from the Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU). Clinical features, laboratory findings, and characteristic radiological findings were strongly suggestive of CRMO.

Keywords

Bone Pain, CRMO, Multifocal Osteomyelitis

1. Introduction

Chronic recurrent multifocal osteomyelitis (CRMO), also known as chronic nonbacterial osteomyelitis, is a rare, non-infectious autoinflammatory disorder of unknown origin. It has a unique character of periodic exacerbations and remissions in the course of the disease [1] [2]. Most commonly involved sites are the long bones characterized by multifocal lytic bone lesions. This condition affects children and adolescents with a female: male ratio of 4:1. In 1972, this disease was described by Giedion for the first time. Still, it is considered as a rare disease with a prevalence of 1 to 2 per million [3]. CRMO has varied presentations from asymptomatic single-bone involvement to chronic, recurrent, multi-

focal inflammation with systemic symptoms such as weakness, febrile states and weight loss [1]. Skeletal manifestations are unifocal or multifocal, any bone may be involved and most commonly involve the metaphyses and epiphysis of long bones (tibia, thigh), pelvic bones, spine, clavicle, or mandible [4]. CRMO remains a diagnosis of exclusion, based on the clinical, radiological, and histological evidence. Dramatic response to NSAIDs without antibiotics is a helpful clue to the underlying diagnosis [5]. The majority of cases showed leukocytosis with elevated inflammatory markers such as ESR and CRP. The biopsy is required to exclude infectious osteomyelitis or malignant bone tumor. Differential diagnosis of CRMO includes infectious osteomyelitis, leukaemia, bone tumour and histiocytosis [6] [7] [8]. These should be ruled out carefully before diagnosing a case of CRMO. So, the presentation of a child with bone pain and swelling having recurrent attacks is a diagnostic dilemma for the treating paediatrician. Most of the time, these conditions are wrongly diagnosed and treated as cases of chronic osteomyelitis without any significant clinical improvement. We are reporting here two cases of CRMO for a clear understanding of the approach to diagnosing and managing this disease for the general physicians and pediatricians.

2. Case Presentation

Case 1: A 6.5-year-old girl presented to the department of paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), with the complaints of pain and swelling in the lower part of her right leg and ankle joint for five months. She had history of generalized body ache including neck and shoulder pain along with low grade irregular fever during her initial presentation. For this illness she was diagnosed as growing pain and treated with non steroidal anti-inflammatory drugs (NSAIDs) with some improvement but due to persistence of symptoms she had to continue the analgesics regularly. She had no history of trauma, rash, eye involvement or any family history of bone or joint abnormalities. On examination, she was mildly pale, afebrile, vitally stable and well thriving. Her right ankle joint was swollen, tender with normal local temperature and no restriction of movement.

Laboratory results showed high ESR (48 mm), CRP (46.99 mg/l) with normal hematological and biochemical parameters (including vitamin D level). Blood and urine cultures were negative. Chest X-ray and X-ray of hip joint in frog leg position found sclerotic and lytic lesions with widening of anterior end of right 4^{th} rib (**Figure 1(a)**) and cortical widening in upper end of right femur (**Figure 1(b)**). X-ray of right leg including knee joint revealed sclerotic and lytic lesions with periosteal elevations in lower end of tibia (**Figure 1(c)** & **Figure 1(d)**). CT scan of right leg showed multiple lytic lesions with surrounding sclerosis at the lower metaphysis of right tibia. Cortical thickening and new bone formation associated with periosteal reaction at medial aspect of lower right tibia was also present (**Figure 1(e)**). Biopsy from right lower tibia showed chronic inflammatory cell and focal periosteal fibroblastic proliferation with no evidence of malignancy.

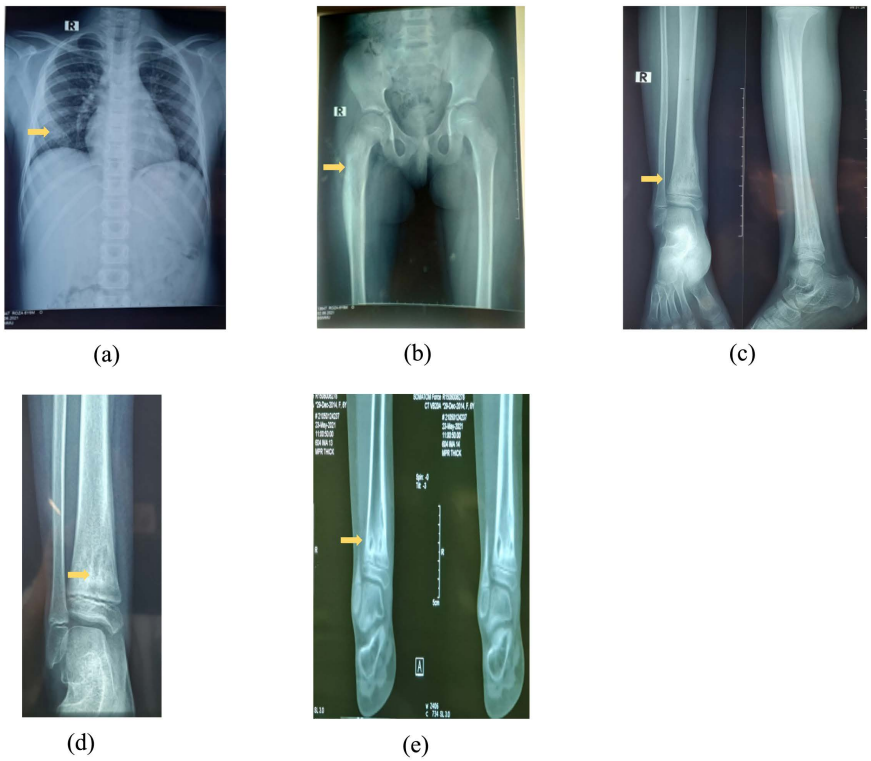

Figure 1. Radiological imagings of CRMO in our patient. (a): Osteolytic lesions with scerosis and widening of anterior end of 4th rib; (b): Sclerosis and osteolytic lesions with cortical widening in upper end of right femur; (c) & (d): Osteolytic lesions and sclerosis with periosteal elevations in lower end of right tibia; (e): CT scan of right ankle joint showing multiple lytic lesions with surrounding sclerosis at the lower metaphysis of right tibia adjacent to growth plate.

From history, clinical examinations and investigations, the girl was diagnosed as chronic recurrent multifocal osteomyelitis (CRMO). She was treated initially with antibiotics, oral NSAIDs—naproxen, calcium and folic acid. Subsequently, after confirmation of diagnosis, subcutaneous methotrexate (MTX) 15 mg/m^2 body surface area per week was added. The symptoms disappeared and the inflammation parameters returned to a normal range 2 months later. Anti-inflammatory treatment was discontinued after 3 months of therapy. Now, the girl is on our regular follow-up with normal inflammatory parameters and doing well with no symptom and sign.

Case 2: An 8.5-years-old girl was admitted in the department of paediatrics with pain, swelling and redness in the middle part of right leg for 3 months. She had no history of morning stiffness, fever, oral ulcer, trauma, rash or any family history of bone or joint abnormalities. She had history of similar illness at her 7 year of age and improved with NSAIDs and antibiotic therapy. On examination, the girl was mildly pale, febrile, vitally stable and moderately wasted (Z score: −2.5 SD). Mild tenderness was present on right leg, but local temperature was normal with no restriction of movement. X-ray of the right leg demonstrated an ill-defined sclerosis within the medullary cavity of the mid shaft of right tibia

with periosteal elevation. Her bone scan revealed a primary lesion in right mid-tibia. MRI of lower limbs demonstrated features of chronic osteomyelitis at mid-shaft of the right tibia. Histopathology was also suggestive of chronic osteomyelitis with no evidence of granuloma or malignancy. Subsequently, she had pain and swelling over the middle third of left leg. On examination, there was swelling and tenderness over the middle third of left leg. Her laboratory investigations showed normal haematological and biochemical findings except low vitamin D level (13.6 ng/ml) with elevated ESR and CRP. Bone scan was done which revealed features of active infection in the mid shaft of left tibia. She was treated with oral antibiotic (amoxicillin, cefuroxime) along with naproxen and vitamin D. initially symptoms were resolved, but subsequently, she again had similar type of problems. Finally, we concluded our diagnosis as chronic recurrent multifocal osteomyelitis (CRMO). Now she is on subcutaneous methotrexate (MTX), oral non steroidal anti inflammatory drug (NSAIDs), calcium, vitamin D and folic acid and is on regular follow-up with improvement of her symptoms and signs. Her inflammatory markers are within normal limit.

3. Discussion

CRMO is a diagnosis of exclusion based on clinical, laboratory and radiological findings. Sometimes CRMO is complicated with overlapping features of clinical and imaging findings. So, it remains a diagnosis of exclusions of malignancy and arthritis of infectious and inflammatory origin [8]. CRMO can be associated with peripheral arthritis, sacroileitis, inflammatory bowel diseases (in particular with Crohn's disease), psoriasis, pyoderma gangrenosum, Sweet syndrome, Wegener's granulomatosis or Takayasu's arteritis [9] [10] [11] [12]. Some pediatricians consider CRMO as the pediatric equivalent of SAPHO syndrome (Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis) characterized by association of osteoarticular and skin disorders [13]. Roderick *et al.* described 41 CRMO patients over 8 years from 2005 to 2012 and proposed the "Bristol diagnostic criteria for CRMO". According to criteria it may be suspected when there is bone pain with or without swelling and without significant features of infection, with the typical radiological findings (lytic areas, sclerosis, newbone formation). In case of multifocal involvment, with normal CRP level, and in single bone involvment with raised CRP (>30 g/l) and bone biopsy showing inflammatory changes without bacterial growth while not on antibiotic therapy [5]. Conventional X-ray is the first radiological approach and shows normal findings in the early stage of the disease. Early radiological findings are modifications of metaphysis close to the growth plates. Osteolytic and sclerotic lesions usually appear in the late stages of the disease [14]. MRI is very useful to identify bone lesions and tissue oedema. CRMO inflammatory lesions usually revealed hypointense in T1-weighted and hyperintense in T2-weighted images [15]. Histopathologic findings are not specific but it has significant role to exclude other causes of bone pain including infectious osteomyelitis, tumor like conditions or histocyto-

sis. Some authors suggested that biopsy may be avoided if a child has classical radiological findings of CRMO or comorbidities, such as Crohns disease [16] [17]. Clinical score and diagnostic criteria facilitate CRMO diagnosis and reduce the numbers of bone biopsies [5] [18].

We reported two young girls presented with pain and swelling of multiple sites of both lower limbs. Physical findings revealed joint swelling with mild tenderness and no restriction of movement. Conventional X-ray and CT scan of affected region found multiple sclerotic and lytic lesions suggestive of CRMO. Inflammatory markers are in a normal range in the majority of CRMO patients. However, Brown *et al.* and Catalano-pons *et al.* reported raised inflammatory markers in more than half of the examined patients [13]. In our case-CRP was elevated in case 1 and suggested infectious osteomyelitis. Since there was no response to antibiotic treatment, further investigations were done. Our cases fulfilled the diagnostic criteria proposed by Roderick *et al.* Gicchino *et al.* reported a case of 10 years old girl with one year shoulder pain. Shoulder joint involvement is rarely found in CRMO [19]. Our cases did not have any shoulder involvement. Bone biopsy is very important to exclude other differentials. In our cases, bone biopsy and histopathology were done which excluded malignancy.

There is no definite guideline to treat CRMO, so the treatment is still empiric. Non-Steroidal Anti-Inflammatory drugs (NSAIDs) are the first choice for CRMO treatment not only to keep pain under control but also to prevent bone damage [1]. Oral corticosteroids are used in patients with CRMO that do not respond to NSAIDs [20]. Methotrexate is a well-known treatment in rheumatologic conditions, and it represents a second line treatment in CRMO [21]. Sulfasalazine is usually used in patients with associated inflammatory bowel disease [22]. Bisphosphonates are indicated in patients with multifocal or spinal involvement [23]. TNF-alfa inhibitors may be added in patients who do not respond to conventional treatments. In some cases, CRMO leads to abnormal bone growth, bone deformity, and fractures [24]. Both the girls of this case report were initially treated with antibiotics, NSAIDS, calcium, folic acid. Subsequently, subcutaneous methotrexate was added and both the girls responded well and now they are much stable.

4. Conclusion

When a child presents with recurrent bone pain with raised inflammatory markers and imaging evaluation shows lytic or sclerotic bone lesions, CRMO should be considered as an important diagnosis. The majority of these patients are diagnosed very late, wrongly treated and develop complications. So early diagnosis and appropriate interventions are crucial in managing this disease and preventing complications.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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