

Case Report

Chronic Recurrent Multifocal Osteomyelitis: A Challenging Diagnosis in The Pediatric Age Group and The Role of Imaging: Sharing A Rare Clinical Experience from Ethiopia, East Africa

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Abstract:

Chronic recurrent multifocal osteomyelitis, which was originally described as chronic non-bacterial osteomyelitis is an autoinflammatory bone disorder of idiopathic origin affecting the metaphyseal portion of long bones at multiple sites. This disease entity, which was previously considered to be rare; is now showing a higher incidence according to recent studies. The disease affects children in the age range of 8-11 years and affects females more than males. It is characterized by clinical symptoms persisting more than six months with remissions and episodic exacerbations. Here we present a case of a 12- and half year-old girl who had multiple painful swellings with tenderness in her extremities and clavicle over a 4-year period which exacerbated over the last 18 months prior to diagnosis.

Keywords: recurrent osteomyelitis, autoinflammatory, idiopathic, multifocal, imaging.

Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory bone disorder of unknown origin and it was first described in 1972 by Giedion as an unusual form of multifocal bone lesions with subacute and chronic symmetrical osteomyelitis (1). This inflammatory condition is characterized by episodes of systemic autoinflammation (rather than autoimmune) including serological signs of inflammation (CRP, ESR, IL-6, TNF- α) occurring in the absence of autoantibodies, pathogens or antigen-specific T cells (2) The medical literature shows that there are about 400 case reports to date and states actual prevalence is very difficult to assess since there is very little known about this disorder with a very high probability of under-diagnosis (2). The disease primarily affects children and adolescents with a peak incidence in the age range of 8-11 years and a preponderance to females. The estimated incidence is 4/1,000,000. Diagnosis is often difficult and made by exclusion in almost all instances. A bone biopsy is often required. Imaging, particularly, whole-body MRI plays an important complimentary role (3,4,5). It is very challenging to differentiate this disease entity from other bone diseases like bacterial osteomyelitis, bone malignancies, or storage diseases often causing delay in instituting timely appropriate treatment (7,8,9).

Case Report

A twelve- and-a half-year-old girl was presented to orthopedic outpatient clinic in January, 2023 with intermittent pain in the right knee area which had been occurring on and off over the last 4 years, especially following physical exertion (sports, running, jumping). In the past 18 months, she had been having the pains in both legs (the upper parts of both her lower legs), along with a slowly increasing diffuse swellings on both upper legs, (just below the knees). These areas were somewhat tender to touch but with no pallor and limitation of movement. The pain eventually began to wax and wane even at rest. There were, however, no constitutional symptoms and signs like fever, loss of appetite, excessive sweating, or weight loss.

A lab work-up earlier in 2021 showed Vitamin D deficiency which was treated with a 6- month supplements. Except ESR which was 76, all other investigations including hormonal assays were all normal. Later in the same year, x-ray and MRI of both lower extremities were done and showed sclerotic metaphyseal lesions (figure 1) which were also detected as edema signals on MRI (Figure 2). Another similar lesion was also detected on MRI in the metaphysis of the right humerus (figure 3). The orthopedic surgeon in charge of the case eventually assumed treatment with a daily dose of doxycycline 100 mg for 3 months for bilateral subacute osteomyelitis (bilateral Brodie's abscess); The patient's condition, however,

did not improve and three successive ESR values obtained months apart remained high (90, 90 and 48). At this juncture, we had a virtual consultation with orthopedic surgeons in Cape Town, and the possibility of chronic recurrent multifocal osteomyelitis (CRMO) was entertained and biopsy to rule out this or other disorders was recommended.

In June 2022, she was referred to the Instituto Rizzoli (an orthopedic center) in Bologna, Italy where an open biopsy was done on her right upper leg, and a needle biopsy on her left upper leg. The multiple cultures they conducted did not grow any pathogens, and the histological exam was consistent with the diagnosis of CRMO. A whole-body bone scintigram (images could not be retrieved and hence not shown) was also done and it confirmed multiple other lesions (including one around her ankle, and another one on the right proximal humerus, and one single lesion on the right clavicle). There were no lesions on her vertebral bones. The ESR at the time) was 74 mm/hr. and the CRP was 16.8 mg/ liter.

Yet again, she was referred to an immunologist/ rheumatologist in Bologna, who agreed with the diagnosis of CRMO, and started her on Ibuprofen 400 mg TID along with daily lansoprazole 30 mg tablets daily, which she took for a month until the end of July.

Clinically, she had improved significantly, and was able to better tolerate walking, and overall had less pain than before, though she still complained of leg pain when she did some physical exercise at school, so we kept her off any jumping and running. She still had some pain (but much less) on her right shoulder region. The leg swelling had not increased in size any further.

The follow-up exams done on 18 August 2022 showed an ESR of 80 mm/hr and a CRP of 4.8 mg/liter. We noted that the CRP had come down to within normal range but the ESR remained high.

She was then put on celecoxib daily for 1 month, followed by an additional 3- week course of oral prednisone (in a tapered regimen). At the end of the course of prednisone (on 14 December, her ESR was still high at 90mm/hr., and her CRP was also high at 16.6 mg/l). Currently, as her status has not improved, she is on follow up for a possible cytotoxic drug therapy after eventual evaluation.



Figure 1: Frontal and lateral x-rays both legs showing sclerotic changes on the metaphyses of both tibiae proximally and distally.



Figure 2: MRI -Images A and B- are coronal and sagittal STIR images of the right tibia showing high signal intensity, and Images B, C, and D are sagittal T1 images of the distal and proximal tibial metaphyses with hypointense lesion respectively. Image F is a sagittal PD version of C with a hyperintense lesion distally in the same leg. These findings are consistent with edema on the metaphyseal ends of the tibia both proximally and distally.

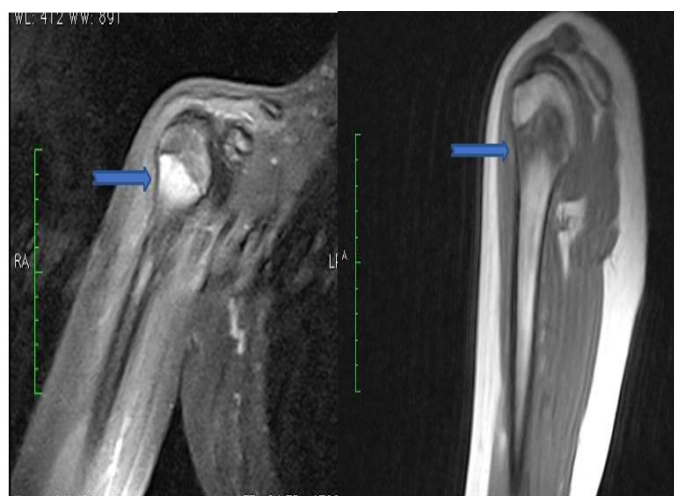


Figure 3: MRI STIR and T1W images of the right arm showing STIR hyperintensity and T1 hypointensity signals consistent with edema of the metaphysis of the humerus.

Discussion

Chronic recurrent multifocal osteomyelitis, which was originally described as chronic non-bacterial osteomyelitis is an autoinflammatory bone disorder of idiopathic origin affecting the metaphyseal portion of long bones at multiple sites (1). The typical feature of CRMO is insidious onset of pain with swelling and tenderness localized over the affected bones. Involvement of the clavicle is a characteristic picture (this was also seen in our patient on bone scintigraphy done for her); Typically, the metaphyses and epiphyses of the femur, tibia or humerus are usually affected. Lesions may occur in any bone,

including the vertebrae. This disease entity, which was previously considered to be rare; is now showing a higher incidence according to recent studies (2). The disease affects children in the age range of 8-11 years and affects females more than males. It is characterized by clinical symptoms persisting for more than six months with remissions and episodic exacerbations. (3,4).

This disease entity is often a challenge to clinicians as the search for the diagnosis is often very late and will only be initiated by way of exclusion when treatment for known causes fails. As an effort to mitigate this, Jansson and his colleagues proposed diagnostic criteria with major and minor components as mentioned below (5,6).

Major criteria-

Osteolytic/sclerotic lesions, multifocal bone lesions on imaging, presence of palmoplantar pustulosis or psoriasis; sterile bone biopsies with signs of inflammation and/or sclerosis.

Minor criteria-

Normal CBC, Good general health; moderate elevation of ESR and CRP, disease course greater than 6 months, hyperostosis, association with other autoimmune diseases, first or second degree relative with autoimmune or autoimmune disease

Jansson proposed the diagnosis of CRMO if if two major or one major and three minor criteria are met (5,6).

The main purpose of this case report is to emphasize the complimentary but vital role of imaging for diagnosis which is evidently delayed for up to 2 years from the time of onset of symptoms (3).

Conventional x-rays have low sensitivity, although sclerotic lesions may be picked up on metaphyseal regions symmetrically. Asymmetrical lesions are also possible. Lytic lesions suggest early stage of the disease while sclerotic lesions appear in the late stage of the disease (7)

Whole body scintigraphy, particularly PET may help in differentiating acute from chronic conditions. CT for assessing sterno-clavicular joint involvement in older patients is useful. Whole body MRI, in particular, has a much higher sensitivity and specificity in picking up bone changes in asymptomatic patients quite early through the detection of marrow edema, periostitis, soft tissue edema, and extension to the physis usually depicted on T2w, STIR and T1w contrast sequence protocols.

A study by Roderick et al published in 2016 from Bristol, UK, came up with a rather simpler criteria to assist clinicians and shorten the time between initial onset of symptoms and final diagnosis as shown below known as the Bristol diagnostic criteria for CRMO (2).

Bristol diagnostic criteria for CRMO (2)

The presence of typical clinical findings (bone pain +/- localized swelling without significant local or systemic features of inflammation or infection)

AND

The presence of typical radiological findings (plain x-ray:

showing combination of lytic areas, sclerosis and new bone formation or preferably STIR MRI: showing bone marrow oedema +/- bone expansion, lytic areas and periosteal reaction

AND EITHER

Criterion 1: more than one bone (or clavicle alone) without significantly raised CRP (CRP < 30 g/L).

OR

Criterion 2: if unifocal disease (other than clavicle), or CRP >30 g/L, with bone biopsy showing inflammatory changes (plasma cells, osteoclasts, fibrosis or sclerosis) with no bacterial growth whilst not on antibiotic therapy (2)

This disease is known to masquerade other disease entities such as infectious osteomyelitis, SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis syndrome), Langerhans cell histiocytosis (LCH), and Ewing's sarcoma, leukemia, and storage diseases like Gaucher's disease (7,8, 9).

Treatment of CRMO is usually with nonsteroidal anti-inflammatory drugs, where up-to 80% of cases show good response; In those cases that show poor response with the frontline regimen mentioned above; corticoids, interferon, calcitonin, azithromycin, sulfasalazine and bisphosphonates are administered a second line of treatment. Tumor necrosis factor (TNF) blockers may be used in a few severe cases (4,5). Our patient has shown no response with the first and second -line treatment regimens, we are, therefore, considering the third option after re-evaluation.

Conclusion

CRMO is a rare disease and quite unknown in our local medical practice. We believe our case will help clinicians develop a high index of suspicion when dealing with cases where treatment for known cases have shown no response. We would also like to stress the complimentary role imaging and urge its appropriate and timely utilization.

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