Chronic Recurrent Multifocal Osteomyelitis (CRMO): The Deceptive Disease That Mimics Sarcoma Radiologically but Promises a Complete Recovery

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ABSTRACT: Chronic recurrent multifocal osteomyelitis (CRMO) is a rare and distinct form of chronic non-bacterial osteomyelitis with an unknown etiology. This 11-year-old Asian girl presented with a painful swelling in her right arm, which was suspected to be a Ewing's sarcoma based on radiological findings. The lesion appeared as a unifocal destructive bone lesion in the proximal diaphyseal region of the right humerus, accompanied by periosteal reaction and soft tissue involvement. She was otherwise clinically well, except for the elevated C-reactive protein, erythrocyte sedimentation rate and alkaline phosphatase. Due to the clinical and radiological suspicion of sarcoma, repeated bone biopsies were performed. All the biopsies revealed mature lamellar bone, normocellular marrow with moderate mixed inflammation, and fibrosis, indicative of a chronic inflammatory process. Given the discordance between the clinical, radiological, and pathological findings, surgical management was withheld and the patient was closely monitored. Over the course of several months, her symptoms gradually improved without any medical or surgical interventions. A follow-up X-ray taken 3 years after the initial diagnosis showed that the lesion had significantly reduced in size, nearly returning to a normal bone contour.

KEYWORDS: osteomyelitis, Ewing sarcoma, humerus, inflammation, bone tumour, multifocal

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Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare and distinct form of chronic non-bacterial osteomyelitis, predominantly reported in young Caucasian females.[1-3] It is a disease of unknown aetiology, with rare genetic and autoimmune associations.[1] Although the name suggests multifocal and recurrent inflammatory flare-ups in long bones, unifocal presentations are also observed.[4] Diagnosing chronic osteomyelitis can be complexed and is often not straightforward, even with detailed clinical assessment and advanced imaging techniques. In many cases, it may take several months or even years from the onset of symptoms to reach a definitive diagnosis. The challenge becomes even harder when radiology is inconclusive. CRMO is a diagnosis of exclusion and often mimics sarcomas on radiology. Therefore, accurate clinical judgment and histological assessment are paramount in making the correct diagnosis. Here, we report a case of CRMO in a young Asian girl initially diagnosed radiologically as Ewing sarcoma. This case underscores the importance of correlating clinical judgment with histological findings to arrive at an accurate diagnosis in complex situations.

Case Report

An 11-year-old Asian girl presented to a local hospital with a one-month history of gradually worsening pain in the right upper arm. She had been previously healthy with an unremarkable birth and developmental history. The pain was constant throughout the day and exacerbated by hand movements and writing. Her daily activities, including school performances, were affected due to severe pain and resulting movement restriction. Neither she nor her parents could relate the onset of symptoms with any specific event, such as trauma or febrile illness.

The initial assessment revealed a slightly swollen and tender upper arm with restricted active and passive shoulder movements. She was hemodynamically stable, with no joint swelling or neurological deficits. Aside from elevated C-reactive protein, erythrocyte sedimentation rate, and alkaline phosphatase levels, all other basic hematological, biochemical and microbiological investigations were normal (Table 1).

The initial X-ray showed a destructive diaphyseal lesion in the right upper humerus with cortical breach and soft tissue involvement (Figure 1), which was further confirmed by the subsequent Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). The CT scan showed a 9 cm large destructive bone lesion in the proximal diaphysis, located 2 cm distal to the growth plate, extending into the mid-diaphysis. There was lamellated periosteal reaction and cortical breach. The MRI additionally revealed metaphyseal involvement and soft tissue extension in the diaphyseal area. These findings were highly suggestive of Ewing's sarcoma.

The patient was referred to a specialized paediatric orthopedic unit for an urgent incisional biopsy. Extensive imaging studies did not reveal similar lesions elsewhere, and there was no evidence of pulmonary metastasis.

The biopsy findings were inconsistent with the clinical and imaging suspicion of a sarcoma, prompting a re-biopsy.

Table 1. Results of basic hematological, biochemical and microbiological investigations.

INVESTIGATION	RESULTS	REFERENCE RANGE
Full blood count		
White blood cells	10.9×	5.0-13.0 × 10^9/L
Neutrophils	64%	
Lymphocytes	29%	
Hemoglobin	13.2 g/dL	
Platelets	351 × 10^9/L	170-450 × 10^9/L
Erythrocyte sedimentation rate	65 mm/1st hour	<20 mm/1st hour
C Reactive protein	16 mg/L	< 5 mg/L
Alkaline phosphatase	454 U/L	60-275 U/L
ALT	13 U/L	10-40 U/L
AST	25 U/L	13-31 U/L
Total bilirubin	3.4 µmol/L	5-21 µmol/L
Blood urea	3.2 mmol/L	2.2-8.2 mmol/L
Serum creatinine	56 µmol/L	60-115 µmol/L
Serum LDH	194.8 U/L	< 450 U/L
Blood culture	No growth	

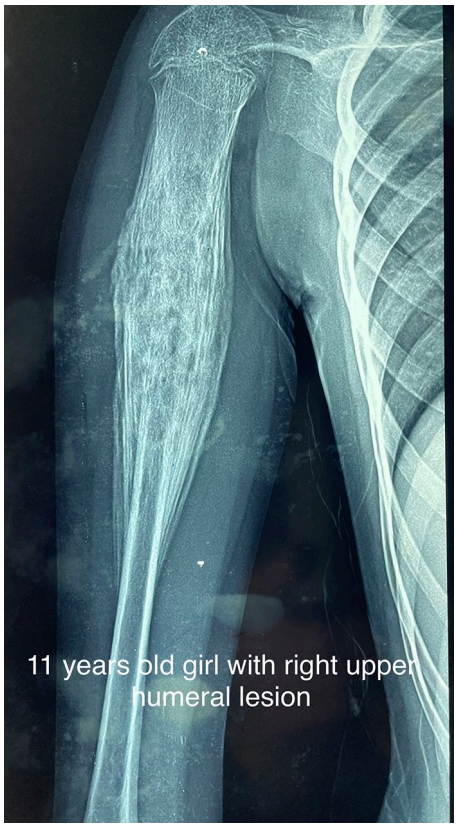

Figure 1. X ray (PA) of right arm taken in 2018 – the X ray shows a large destructive lesion in the upper diaphyseal region extending into the metaphysis. There is periosteal reaction and soft tissue oedema around the lesion.

Histology of the repeated biopsies revealed arcades of cortical bone trabeculae and normocellular marrow. Some areas showed spindly stromal tissue with scattered mixed inflammatory cells. There were no atypical cells or malignant osteoids (Figure 2A and B). Due to the high clinical and radiological suspicion of a sarcoma, a deep incisional biopsy was performed again. However, all three biopsies displayed similar morphology, indicating a benign inflammatory process.

The discordance between the clinical, radiological and pathological findings led to the decision to withhold any medical or surgical intervention. She was closely assessed through regular clinic visits. Over the next 3 years, her symptoms significantly improved, with no substantial pain or deformity. A repeat X-ray taken 3 years after the initial diagnosis showed that the lesion had drastically reduced in size, nearly returning to a normal bone contour (Figure 3).

Considering the histological appearance of a chronic inflammatory process and the overall clinical behaviour, this case is consistent with chronic recurrent multifocal osteomyelitis.

Discussion

Chronic recurrent multifocal osteomyelitis is a rare form of non-bacterial osteomyelitis with an unknown aetiology.[1] It was first described five decades ago by Giedion et al[5] as 'subacute and chronic symmetrical osteomyelitis'.

It is generally considered as a disease of childhood and adolescents although adult presentations are reported.[4] Children and adolescents of first two decades are at a higher risk of developing CRMO. There is a female predominance with female to male ratio of 5:1.[3]

Although the exact aetiology is not known, an autoimmune process is suggested owing to its frequent association with other autoimmune diseases such as inflammatory bowel diseases, psoriasis, sweet syndrome and vasculitis.[3] A genetic basis to the disease is suggested by the fact that there are cases affected in families and in twins.[3]

Typical clinical presentation includes unifocal or multifocal destructive bone lesions which are mainly located in long bones, clavicles, spine, pelvis, scapula and small bones of hands and feet. One study showed 24% of unifocal disease following extensive radiological assessment.[6] Recurrent exacerbations with synchronous or metachronous lesions are common.[7] Extra skeletal manifestations including skin and gastrointestinal symptoms are not uncommon and some of these symptoms are related to co-existing systemic diseases such as ulcerative colitis, Crohn's disease or SAPHO (synovitis, acne, pustulosis, hyperkeratosis and osteitis) syndrome.[2]

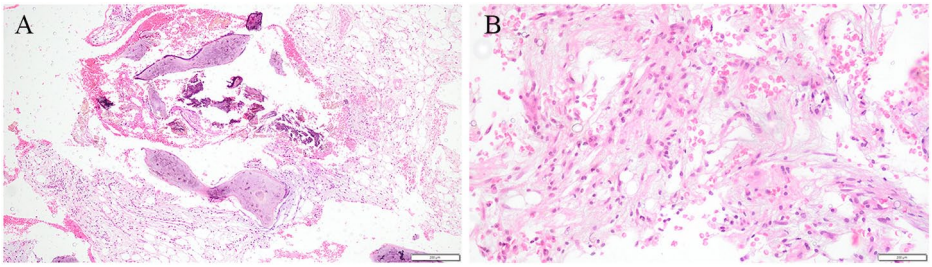

Figure 2. (A) Microscopy of bone biopsy (x40 H&E) – there are destructed mature cortical bone trabeculae surrounded by fibrotic tissue. (B) Microscopy of bone biopsy (x100 H&E) – the tissue is infiltrated by a moderate chronic inflammatory infiltrate with fibroblastic reaction. The appearance is compatible with a chronic inflammatory process.

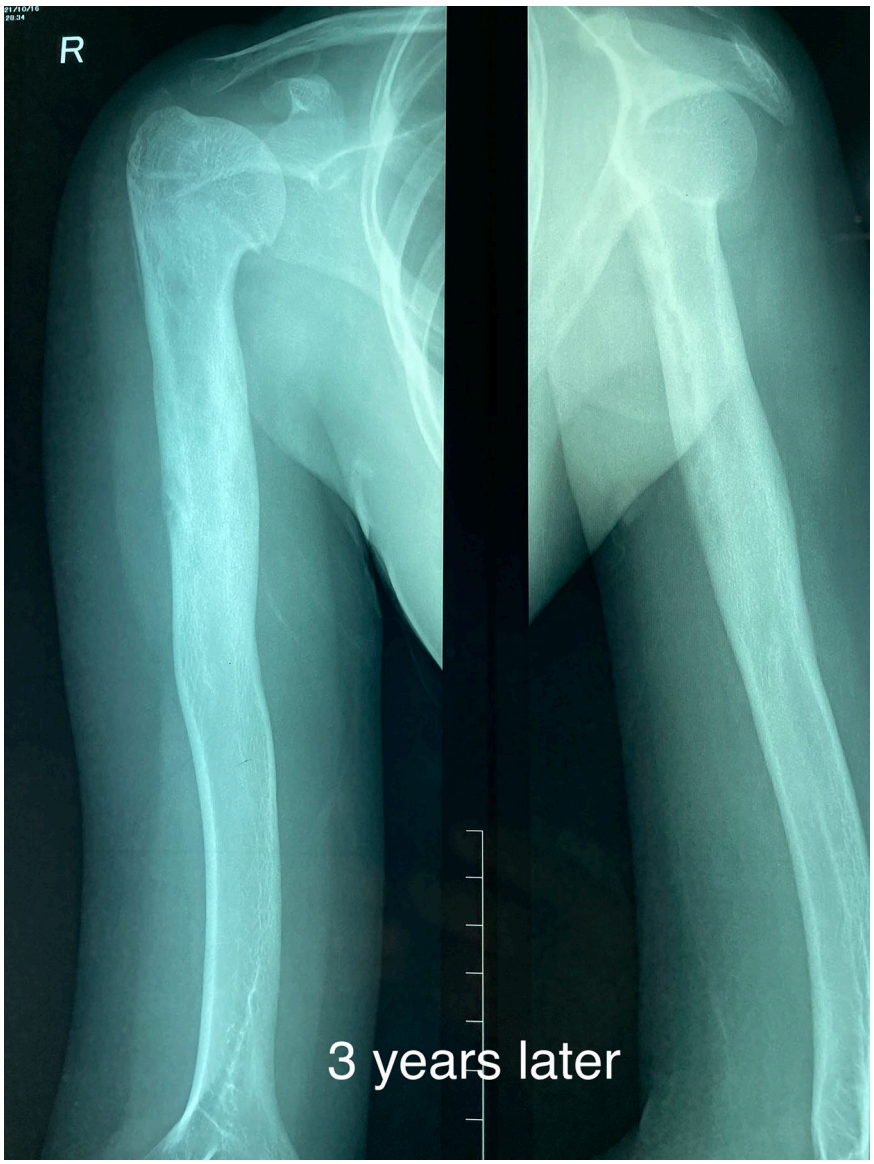

Figure 3. Repeat X ray of right upper arm taken in 2021 – the size of the lesion is drastically reduced. The bone contour has come to an almost normal level.

Typical clinical symptoms of CRMO tend to be intermittent with periodic flare-ups and remissions. However, some patients, like ours, can experience constant pain exacerbated with movements. This atypical presentation can raise diagnostic challenge, as it mimics non-inflammatory process such as Ewing sarcoma, complicating differentiation.

Radiological appearance is usually characteristic. Most of the long bone lesions are in the metaphysis and can

occasionally extends to diaphysis and metaphysis. Early active lesions are mostly lytic with a sclerotic rim. These heal with sclerosis. Lesions may exhibit periosteal reactions, soft tissue oedema and bone destruction which makes it difficult to differentiate osteomyelitis from neoplastic lesion. CRMO can mimic osteosarcoma, Ewing sarcoma, osteoblastoma, osteoid osteoma and Langerhans cell histiocytosis on plane radiograph. CT, MRI and bone scintigraphy are important in difficult cases.[3,8,9] The presence of multifocality and spontaneous resolution are key distinguishing features of CRMO compared to Ewing sarcoma. This case is particularly unique as it mimicked Ewing sarcoma while presenting as a solitary lesion, despite comprehensive radiological evaluation.[10]

Histological assessment is important in differentiating CRMO from neoplastic lesions. A range of histological findings including acute, chronic or mixed inflammatory reaction, resorption of cortical lamellar bone, reactive woven bone formation and variable degree of fibrosis are reported.[11] However, peritumoral tissue from an unsampled neoplastic lesion can demonstrate these features, making an unequivocal diagnosis difficult.

Different diagnostic criteria are developed to incorporate different aspect of the disease into consideration. Roderick et al[6] formulated a diagnostic criteria to be used for CRMO diagnosis which incorporate clinical, radiological, serological and pathological findings. The presence of typical clinical findings including bone pain and localized swelling with no evidence of inflammation or infections; and radiological finings including lytic lesions, sclerosis, new bone formation, bone marrow oedema or expansion and periosteal reaction; either with multifocal disease or unifocal lesion with high C- reactive protein or histological evidence of inflammation in bone biopsy are characteristic. Jansson et al[12] proposed an alternative diagnostic criteria for CRMO, which includes four major criteria and six minor criteria. The major criteria are radiological evidence of sclerotic or lytic bone lesions, multifocality, skin manifestations and a sterile bone biopsy showing evidence of inflammation. The minor criteria include normal blood counts, elevated C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), a history of symptoms lasting over 6 months, hyperostosis, association with autoimmune diseases and a positive family history of similar conditions. Presence of two major criteria or one major criteria with three minor criteria favours CRMO.[4,12] According to Bristol diagnostic criteria introduced by Roderick et al,[6] our patient presented with typical clinical features, including bone pain and localized swelling with radiological evidence and inflammatory changes identified in the bone biopsy. Similarly, based on the diagnostic criteria proposed by Jansson et al,[12] our patient met two major criteria including the radiologically proven bone lesion and a sterile bone biopsy showing inflammatory changes; and three minor criteria, including normal blood counts, mildly to moderately elevated CRP levels and disease duration exceeding 6 months. Thus, our patient fulfils the diagnostic criteria for CRMO as defined by both systems.

The clinical course of CRMO is typically benign and self-limiting, though multiple relapses are common, necessitating long-term follow-up. Generally radiological resolution starts within 6 to 12 months, while complete radiological resolution can take 3 years or more depending on the nature of the lesion.[1] Various treatment modalities have shown benefits, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, bisphosphonates, interferon, indomethacin and methotrexate. Since CRMO is widely regarded as a non-bacterial inflammatory condition, antibiotic treatment is generally not recommended.[1] However, the exact role of micro-organisms in pathogenesis of CRMO remains uncertain, warranting further investigation.

Conclusion

The diagnosis of CRMO should be based on a combination of clinical, radiological and histological findings. Arriving at an accurate diagnosis can be extremely challenging in cases where there is discordance among clinical, radiological and pathological findings, often necessitating repeat biopsies and resulting in delays in diagnosis. However, it is crucial to correlate all these aspects to avoid unnecessary antibiotic treatments and inadvertent surgical interventions.

Author Contributions

LD – Pathological diagnosis, literature review, preparation of manuscript. SW – Clinical management and collection of relevant clinical details, CS – Pathological diagnosis and overall supervision of the process.

Data Availability Statement

All data generated during the assessment and publication of this case are available upon request from the corresponding author.

Ethical Approval

Our institution does not mandate ethical approval for the reporting of individual cases or case series, provided that no identifiable personal information is included.

Informed Consent

Informed written consent was obtained from the parents for the publication of this article.

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