Original Article

Chronic Recurrent Multifocal Osteomyelitis - A Case Series from India

Abstract

Background: Chronic recurrent multifocal osteomyelitis (CRMO) is a rare auto-inflammatory disease of the bone. It tends to be multifocal and usually the symptoms tend to run for months and years before diagnosis is usually made. The objective of our study was to understand the clinical presentation and short-term response to treatment of CRMO patients. **Materials and Methods:** A retrospective analysis of patients diagnosed with CRMO between 2011 and 2016 was done. Case records of these were retrospectively reviewed for clinical features, investigations and treatment received. **Results:** Six patients were diagnosed with CRMO. The median age of onset and time to diagnosis from onset of symptoms was 8 and 3.5 years respectively. Lower limb bones were the most commonly involved. **Conclusions:** There is significant delay in diagnosis of CRMO and this could be because of a lack of awareness of this condition amongst clinicians. Our case series with only male affection is rather unique as compared to other case series reported in medical literature which tend to have more female predilection. Pain with or without swelling was the most common symptom. Most of patients responded to combination therapy.

Keywords: *Chronic recurrent multifocal osteomyelitis, etanercept, majeed syndrome, nonsteroidal anti-inflammatory drugs, pamidronate*

MeSH terms: *Osteomyelitis, chronic disease, analgesics*

Anand Prahalad Rao, Pooja Prakash Mallya[1], Shashi Ranjani[2], Jyothi Raghuram[3]

Pediatric Rheumatology Clinic, Manipal Hospital and Vijaya Children's Clinic, Indira Gandhi Institute of Child Health, [1]Department of Pediatric Hemato-Oncology, Mazumdar Shaw Cancer Center, [2]Department of Pediatric Hemato-Oncology, Healthcare Global Enterprises, [3]Pediatric Rheumatology Clinic, Indira Gandhi Institute of Child Health and Columbia Asia Hospital, Bengaluru, Karnataka, India

Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare auto-inflammatory bone disease occurring primarily in children and adolescents. Auto-inflammatory diseases are disorders of innate immunity characterized by absence of autoantibodies in high titres and autoreactive lymphocytes. CRMO is also known more recently as chronic nonbacterial osteomyelitis and was first described in 1972 by Giedion *et al*.[1]

The clinical presentation of CRMO can vary from asymptomatic or mild inflammation of single site (metaphysis of the bone) which tends to be time limited to CRMO. Patients present with insidious onset of pain, swelling, localised skin redness and tenderness of the involved bones. It is typically seen in the metaphysis of long bones, clavicle, and vertebral bodies.[2] Rarely other sites, including mandible, pelvis and small bones of the hands and feet can be involved. A subset of patients with CRMO may present with psoriasis, inflammatory bowel disease and acne. There is no widely accepted diagnostic criterion and hence, CRMO remains a diagnosis of exclusion. Blood investigations reveal nonspecific evidence of inflammation. Whole body magnetic resonance imaging (MRI) is the imaging of choice for diagnosis of CRMO. CRMO is a diagnosis of exclusion with a caveat that infection and malignancy (especially Langerhan's cell histiocytosis) be ruled out.[3]

CRMO can have a monogenic inheritance or can be sporadic. Majeed syndrome is an autosomal recessive condition caused by mutation of LPIN2 gene associated with CRMO, neutrophilic dermatosis and dyserythropoietic anemia. It has been described predominantly in patients from West Asia. The authors have described 2 patients from the same family who were genetically proven to be Majeed syndrome, first time to be ever described from the Indian subcontinent.[4]

CRMO is considered the pediatric equivalent of synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome. SAPHO syndrome is characterized by a combination of osteoarticular and dermatological manifestations.[5]

The objective of our study was to understand the clinical presentation and

How to cite this article: Rao AP, Mallya PP, Ranjani S, Raghuram J. Chronic recurrent multifocal osteomyelitis - A case series from India. Indian J Orthop 2018;52:672-7.

Address for correspondence:
Dr. Pooja Prakash Mallya, 46, 2nd Cross, Panduranga Nagar, Bannerghatta Road, Bengaluru - 560 076, Karnataka, India.
E-mail: poojamallya71@yahoo.com

Access this article online

Website: www.ijoonline.com

DOI: 10.4103/ortho.IJOrtho_464_17

Quick Response Code:

short-term outcome of treatment of CRMO patients. This study reiterates the fact that this condition is not so uncommon and has a significant delay in diagnosis as a result of ignorance amongst the orthopedic surgeons and pediatricians.

Materials and Methods

6 patients were diagnosed and treated as CRMO between 2011 and 2016, at our institute. Case records were retrospectively reviewed for clinical features, investigations and treatment of these children. The diagnosis of CRMO was based on the history of insidious onset of bone pain and/or swelling and presence of radiologic evidence of multiple osteolytic lesions in the long bones/bone biopsies showing sterile chronic inflammation. Informed written consent from all the patients was obtained. Ethics approval was not required in accordance with the policy of the institution and verbal informed consent from all the patients/parents was obtained.

Results

Over a 4 year period, 6 patients were diagnosed as CRMO and all were boys [Table 1]. The median age of onset of symptoms was 8 years (range 2–10 years) and the median age of diagnosis was 13 years (range 10–16 years). The median time from onset of symptoms to diagnosis was 3.5 years (range 2–13 years). Pain with or without swelling was the most common symptom. Two out of 6 patients presented with low grade fever. Tibia and fibula were involved in all the patients. Femur, tarsals and metatarsals were involved in 4 out of 6 patients (66.7%). Mandibular, clavicular, pelvic, rib and vertebral body involvement were seen in one out of 6 (not in the same patient). One patient with anemia with leucopenia and was subjected to a bone marrow examination, which revealed congenital dyserythropoietic anemia (later diagnosed as Majeed syndrome). Erythrocyte sedimentation rate (ESR) was elevated in all patients except one, with a median ESR of 61.5 mm/h (range 8–70 mm/h).

Two children underwent bone biopsy, which showed chronic inflammatory changes with presence of sclerotic bone. The cultures of the bone biopsy were sterile in both these patients. All patients except one underwent MRI of the affected region. This patient being the cousin of the proband with Majeed syndrome had clinical features and radioisotope bone scan which were suggestive of CRMO and his genetic analysis revealed that he shared the same LPIN2 mutation. MRI was done in 5 out of 6 patients and was suggestive of CRMO in all the five patients [Figure 1]. Two patients underwent genetic studies and were found to have LPIN2 mutation [Table 2]. Both these patients were cousins who were diagnosed to have Majeed syndrome.

All patients were initially treated with on nonsteroidal anti-inflammatory drugs (NSAIDs) and methotrexate. Three

Table 1: The clinical details and blood investigations at the time of diagnosis

Case	1	2	3	4	5	6
Age at onset (years)	8	8	10	2	10	8
Sex	Male	Male	Male	Male	Male	Male
Age at diagnosis (years)	10	11	13	15	14	16
Delay to diagnosis (years)	2	3	3	13	4	8
Pain	+	+	+	+	+	+
Swelling	+	+	-	+	-	+
Fever	+	-	-	-	+	-
Involved bones						
Femur	-	+	+	+	-	+
Tibia/fibula	+	+	+	+	+	+
Humerus	-	+	-	+	-	-
Radius/ulna	-	+	-	+	-	-
Vertebra	-	-	+	-	-	-
Mandible	-	-	-	-	+	-
Tarsal bones	Talus, calcenaus, cuboid	Talus, calcaneus, cuboid	Calcaneus	-	-	Calcaneus, talus, navicular, cuneiform
Others	3rd rib		Metatarsals, pelvis, clavicle	-	-	Metatarsals
Laboratory tests						
Hb (g/dl)	11.4	11.2	12.1	8.5	12.8	11.9
WBC (cells/cumm)	11490	7610	10200	5500	9540	3690
ESR (mm/hr)	67	58	51	65	8	70
CRP (MG/DL)	Elevated	ND	ND	ND	ND	Elevated

WBC=White blood cells, ESR=Erythrocyte sedimentation rate, CRP=C-reactive protein, ND=Not done

out of 6 patients responded to this combination treatment. The remaining three patients were given the option of either bisphosphonates (pamidronate) or tumour necrosis factor α (TNF α) blockers. Two patients out of the three, who were given this choice preferred pamidronate infusion, given for 3 days every 3 monthly once at 0.5 mg/kg on day 1 and 1 mg/kg on day 2 and 3 [Table 2], because of lower cost of treatment and less frequent administration. The index case diagnosed to have Majeed syndrome responded partially to a combination of 3 monthly pamidronate with methotrexate and required intermittent NSAIDs for control of symptoms with frequent flares. TNF α blocker (etanercept biosimilar) was used intermittently (due to financial constraints) to control the flare on a weekly basis on 2 occasions a year apart. The second patient did well on 3 monthly pamidronate. The third patient was started on weekly etanercept (TNF α blocker) and has done very well with significant reduction in the intensity and frequency of symptoms.

The median duration of followup was 31.5 months.

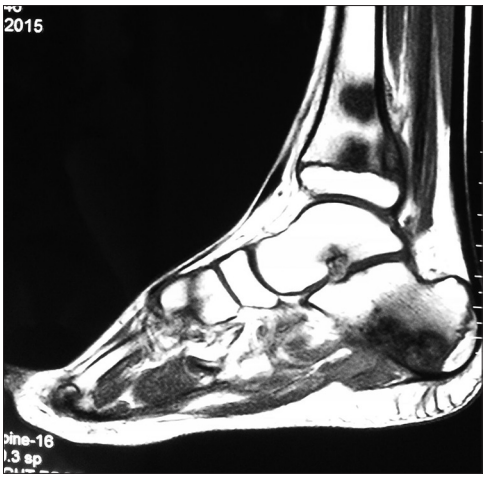

Figure 1: MRI T2W sagittal image showing multiple osteolytic lesions in tibia, calcaneum and talus

Discussion

CRMO is a rare autoinflammatory bone disorder, commonly found in the long bones of children. This is the first case series from the Indian subcontinent. The mean age of onset reported in literature is 10 years (range 4–17 years) which is very similar to our study. There was a significant delay in diagnosis (median duration of time from onset to diagnosis-3.5 years) which is mostly related to the fact that there is lack of awareness about this condition amongst the care providers in this part of the world. All the affected patients in our series were male in contrast to other studies which have reported female preponderance.[6] This could just have been a result of referral bias.

The pathophysiology of CRMO remains unknown. Recent studies have found an imbalance between pro-(interleukin-6 [IL-6], TNF-α) and anti-inflammatory (IL-10) cytokines may be centrally involved in the molecular pathology of CRMO.[7]

The most common symptom is insidious onset bone pain.[8] The pain usually is dull aching, which can be interspersed with a shooting pain in a few patients. Swelling, warmth and tenderness of the affected bone can also be present. Intermittent episodes of exacerbation and remission can be seen in many of these patients. Other organs like the eyes, skin, gastrointestinal system and lungs can also be involved.

Only one patient (Index case of Majeed syndrome) had presence of extra osseous manifestation in the form of congenital dyserythropoietic anemia. Rest of the patients had isolated bone disease. Remission of the disease can be natural or therapeutically induced.

The lower limb bones were the most commonly involved which was similar to other studies.[9,10] Clavicle was not a commonly involved site in the patients in our series unlike other case series.

Table 2: The imaging, biopsy, genetic studies and treatment of all six patients

Case	1	2	3	4	5	6
MRI	CRMO	ND	CRMO	CRMO	CRMO	CRMO
Biopsy	Sterile	ND	ND	ND	Sterile	ND
Genetic studies	ND	LPIN2	ND	LPIN2	ND	ND
NSAIDS	+	+	+	+	+	+
Methotrexate	+	+	+	+	+	+
Pamidronate	-	-	+	+	+	-
Etanercept	-	-	+	+ (intermittent)	-	-
Duration of follow up (months)	18	66	35	82	28	8
Response to treatment	Good response to methotrexate	Good response to methotrexate and is off therapy and doing well	Good response to etanercept, partial response to Methotrexate	Partial response to Intermittent NSAIDs and Etanercept	Good response to methotrexate and Pamidronate	Lost to Follow up

MRI=Magnetic resonance imaging, CRMO=Chronic recurrent multifocal osteomyelitis, ND=Not done NSAIDs=Non-steroidal anti-inflammatory drugs

Laboratory investigations like total leucocyte count, ESR and C-reactive protein may be normal or reveal only minor alterations.[11] Almost all our patients except one had an elevated ESR (83.3%) and this is slightly different from other similar studies.[3]

Plain radiographs reveal osteolytic lesions surrounded by sclerosis. MRI is the imaging modality of choice. MRI was confirmatory in 5 out of 6 patients. Whole body MRI was done in only one patient because of cost constraints. Bone biopsy is done to rule out infection or neoplasm.[12] Two of our patients underwent bone biopsy, which revealed chronic inflammatory cells with sclerotic bone. A diagnostic criteria for CRMO was framed by Roderick *et al* [Table 3].

There is a significant genetic contribution to CRMO disease susceptibility. Two monogenic syndromic forms of CRMO include deficiency of IL-1 receptor antagonist (DIRA) due to mutations in IL1RN and Majeed syndrome due to mutations in LPIN2.[10] Recently there is some evidence that sporadic or nonsyndromic CRMO might have a genetic basis. Majeed Syndrome presents with CRMO, dyserythropoietic anemia and neutrophilic dermatosis. Two of the patients in our series were diagnosed as Majeed syndrome with LPIN2 mutation in our study.[4] DIRA is an

Table 3: Bristol diagnostic criteria for chronic recurrent multifocal osteomyelitis

The presence of typical clinical findings AND	Bone pain+/- localised swelling without significant local or systemic features of inflammation or infection
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 <30g/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	

Table 4: Other studies on chronic recurrent multifocal osteomyelitis

Study	Number of patients	Mean age at diagnosis (years)	Male/female	Location	Treatment	Mean follow up period
Anja Schnabel, *et al*., (2017) Retrospective study	56	11	33/23	44: Multifocal 26: Unifocal	1st line NSAID'S (55) 50% relapsed Second line: Steroids Bisphosphonates and TNF blockers	2 years
Roderick *et al*., (2016) Retrospective study	41	9	10/31	19: Multifocal 22:Unifocal	1st line NSAID'S 2nd line: Bisphosphonates Methotrexate, sand steroids	8 years
Pavla Walsh *et al*., (2015) Retrospective study	34	10.9	13/21	6: Unifocal 28: Multifocal	1st line NSAID'S 2nd line: Steroids Methotrexate, Adalimumab	Ranged from 0.3 to 7.9 years
Christine Beck *et al*., (2010) Prospective study	37	11	24/13	29: Multifocal 8: Unifocal	1st line Naproxen 2nd line: Sulfasalazine and steroids	6 months
Catalano Pons (2008) *et al*., Retrospective study	40	11.5	6/34	15: Unifocal 25: Multifocal	1st line NSAID'S 2nd line: Bisphosphonates methotrexate, etanercept	5 years
Anand P. Rao *et al*., (present study)	6	13	All males	6: Multifocal	1st line: NSAID'S and Methotrexate 2nd line: Bisphosphonates/ TNF-blockers	31.5 months

TNF=Tumour necrosis factor, NSAIDs=Non-steroidal anti-inflammatory drugs

autoinflammatory disorder that presents in the neonatal period with generalized pustulosis, osteitis, periostitis, and systemic inflammation due to mutations in IL1RN.[11,13] It is a life threatening disorder that presents in the neonatal period and has an autosomal recessive inheritance.

The optimal treatment strategy of CRMO is still not known.[14] NSAIDs are the first line of treatment for CRMO.[15,16] In this series, methotrexate was added at the time of diagnosis in view of literature showing that it may be helpful when the response to NSAIDs has been suboptimal.[17-19] It may also help to reduce the prolonged NSAID use in many of these patients. Barral Mena *et al.* reported that 6 of the 7 patients with CRMO did not respond to naproxen and required other drugs to control the disease better.[20]

Recently bisphosphonates (pamidronate) and biological agents like TNF α blockers have been increasingly used in patients who fail standard therapy.[21,22] The treatment is mostly affordable and long term followup is required as in any chronic disease.

The repeat imaging MRI in the patients treated with etanercept hasn't been done as yet as the duration of treatment has been short and due to financial implications. There are various other studies on CRMO worldwide [Table 4] and ours is the first case series from India.

The limitations of the study were a small sample size, short duration of followup and lack of information of other occult bone involvement since whole body MRI was not done in all patients.

Clinical relevance

There is significant delay in diagnosis of CRMO and this could be because of a lack of awareness of this condition amongst the physicians (orthopedic surgeons and pediatricians). This study was to create the awareness and highlight the fact that CRMO does exist in the community and is amenable to treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgement

Dr Polly Ferguson for identification of *LPIN2* mutation analysis in 2 patients diagnosed as Majeed Syndrome.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Giedion A, Holthusen W, Masel LF, Vischer D. Subacute and chronic "symmetrical" osteomyelitis. Ann Radiol (Paris) 1972;15:329-42.
2. Khanna G, Sato TS, Ferguson P. Imaging of chronic recurrent multifocal osteomyelitis. Radiographics 2009;29:1159-77.
3. Roderick MR, Shah R, Rogers V, Finn A, Ramanan AV. Chronic recurrent multifocal osteomyelitis (CRMO) – Advancing the diagnosis. Pediatr Rheumatol Online J 2016;14:47.
4. Rao AP, Gopalakrishna DB, Bing X, Ferguson PJ. Phenotypic variability in majeed syndrome. J Rheumatol 2016;43:1258-9.
5. Tlougan BE, Podjasek JO, O'Haver J, Cordova KB, Nguyen XH, Tee R, *et al.* Chronic recurrent multifocal osteomyelitis (CRMO) and synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome with associated neutrophilic dermatoses: A report of seven cases and review of the literature. Pediatr Dermatol 2009;26:497-505.
6. Catalano-Pons C, Comte A, Wipff J, Quartier P, Faye A, Gendrel D, *et al.* Clinical outcome in children with chronic recurrent multifocal osteomyelitis. Rheumatology (Oxford) 2008;47:1397-9.
7. Hedrich CM, Hofmann SR, Pablik J, Morbach H, Girschick HJ. Autoinflammatory bone disorders with special focus on chronic recurrent multifocal osteomyelitis (CRMO). Pediatr Rheumatol Online J 2013;11:47.
8. Oberc A, Sułko J. Chronic recurrent multifocal osteomyelitis (CRMO) in children-single-centre clinical observations and experience. Ortop Traumatol Rehabil 2014;16:297-305.
9. Falip C, Alison M, Boutry N, Job-Deslandre C, Cotten A, Azoulay R, *et al.* Chronic recurrent multifocal osteomyelitis (CRMO): A longitudinal case series review. Pediatr Radiol 2013;43:355-75.
10. Holden W, David J. Chronic recurrent multifocal osteomyelitis: Two cases of sacral disease responsive to corticosteroids. Clin Infect Dis 2005;40:616-9.
11. Ferguson PJ, Sandu M. Current understanding of the pathogenesis and management of chronic recurrent multifocal osteomyelitis. Curr Rheumatol Rep 2012;14:130-41.
12. Bracamonte JD, Roberts CC. Chronic recurrent multifocal osteomyelitis mimicking osteosarcoma. Radiol Case Rep 2006;1:42-6.
13. Hofmann SR, Kapplusch F, Girschick HJ, Morbach H, Pablik J, Ferguson PJ, *et al.* Chronic recurrent multifocal osteomyelitis (CRMO): Presentation, pathogenesis, and treatment. Curr Osteoporos Rep 2017;15:542-54.
14. Girschick HJ, Zimmer C, Klaus G, Darge K, Dick A, Morbach H, *et al.* Chronic recurrent multifocal osteomyelitis: What is it and how should it be treated? Nat Clin Pract Rheumatol 2007;3:733-8.
15. Girschick HJ, Raab P, Surbaum S, Trusen A, Kirschner S, Schneider P, *et al.* Chronic non-bacterial osteomyelitis in children. Ann Rheum Dis 2005;64:279-85.
16. Job-Deslandre C, Krebs S, Kahan A. Chronic recurrent multifocal osteomyelitis: Five-year outcomes in 14 pediatric cases. Joint Bone Spine 2001;68:245-51.
17. Beck C, Morbach H, Beer M, Stenzel M, Tappe D, Gattenlöhner S, *et al.* Chronic nonbacterial osteomyelitis in childhood: Prospective followup during the first year of anti-inflammatory treatment. Arthritis Res Ther 2010;12:R74.
18. Borzutzky A, Stern S, Reiff A, Zurakowski D, Steinberg EA,

Dedeoglu F, *et al.* Pediatric chronic nonbacterial osteomyelitis. Pediatrics 2012;130:e1190-7.
19. Twilt M, Laxer RM. Clinical care of children with sterile bone inflammation. Curr Opin Rheumatol 2011;23:424-31.
20. Barral Mena E, Freire Gómez X, Enríquez Merayo E, Casado Picón R, Bello Gutierrez P, de Inocencio Arocena J, *et al.* Non-bacterial chronic osteomyelitis: Experience in a tertiary hospital. An Pediatr (Barc) 2016;85:18-25.
21. Hospach T, Langendoerfer M, von Kalle T, Maier J, Dannecker GE. Spinal involvement in chronic recurrent multifocal osteomyelitis (CRMO) in childhood and effect of pamidronate. Eur J Pediatr 2010;169:1105-11.
22. Eleftheriou D, Gerschman T, Sebire N, Woo P, Pilkington CA, Brogan PA, *et al.* Biologic therapy in refractory chronic non-bacterial osteomyelitis of childhood. Rheumatology (Oxford) 2010;49:1505-12.