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Case Report

Chronic recurrent multifocal osteomyelitis presenting with prolonged multifocal bone pain: a case report

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ABSTRACT

Chronic Recurrent Multifocal Osteomyelitis (CRMO) is an autoinflammatory bone disorder affecting primarily children and adolescents, characterized by sterile, recurrent bone pain and multifocal skeletal lesions. Diagnosis is based on clinical criteria and imaging, particularly MRI, to exclude infection or malignancy and to detect both symptomatic and clinically silent lesions. The pathogenesis involves dysregulation of the innate immune system and cytokine imbalance, contributing to chronic inflammation. We report a 13-year-old Indian girl with a prolonged 7-year history of intermittent multifocal bone pain and recurrent low-grade fever. Laboratory evaluation revealed elevated inflammatory markers with negative autoimmune and infective workup. MRI demonstrated multifocal medullary bone lesions consistent with non-infective osteitis. Based on clinical, laboratory, and radiological findings, a diagnosis of CRMO was established. The patient showed significant clinical improvement following treatment with NSAIDs and intravenous pamidronate.[10,11] Early diagnosis and individualized treatment strategies are crucial in CRMO to improve outcomes and prevent long-term complications.

Keywords: ERA, CRMO, Autoinflammatory bone disorder

INTRODUCTION

Chronic Recurrent Multifocal Osteomyelitis (CRMO) is a rare, non-infectious autoinflammatory bone disorder seen predominantly in children and adolescents. First described by Giedion et al in 1972, CRMO belongs to the broader spectrum of Chronic Nonbacterial Osteomyelitis (CNO).[1] It is characterized by recurrent episodes of sterile bone inflammation, most commonly involving the metaphysis of long bones, pelvis, clavicle, and vertebrae, in the absence of identifiable bacterial infection or malignancy.[2] The pathophysiology of CRMO is believed to involve dysregulated innate immunity, particularly imbalances in cytokines such as IL-1β, IL-6, TNF-α, and IL-10.[3] Although most cases occur sporadically, familial clustering suggests a genetic predisposition in certain patients. CRMO shows a female predominance and is frequently misdiagnosed or diagnosed late due to its indolent course and clinical overlap with infectious osteomyelitis, juvenile idiopathic arthritis (JIA), and malignancy.[4] Early and accurate diagnosis is essential to prevent complications such as growth retardation, bone deformity, and psychosocial morbidity. MRI plays a central role in early detection and disease monitoring, while laboratory markers remain nonspecific. Management includes NSAIDs, corticosteroids, bisphosphonates, and biologic agents in refractory cases.[5-7] India lacks large national prevalence or incidence studies on CRMO due to its rarity. Globally, prevalence estimates range from 1-9 cases per 1,000,000 individuals

(0.0001%-0.0009%), with older reports suggesting an incidence between 1 in 160,000 and 1 in 2,000,000 individuals. We present a case of CRMO in a 13-year-old Indian girl with a prolonged disease course and delayed diagnosis, managed successfully with bisphosphonate therapy.

CASE REPORT

A 13-year-7-month-old girl, born of a third-degree consanguineous marriage, presented with a 7-year history of intermittent, dull aching pain involving the lower limbs and spine. The pain began in the hip region at 7 years of age and progressively involved the entire lower limbs and axial skeleton. It was aggravated at night and with physical activity and partially relieved with analgesics and local massage. The chronic pain significantly interfered with her daily activities. She also experienced recurrent low-grade febrile episodes since the onset of symptoms, initially occurring once or twice per month and lasting 3-5 days. Over time, the fever became more frequent and persistent, occurring daily over the preceding two months. There were no associated chills, rigors, or diurnal variation, and response to medications was partial. There were no features suggestive of systemic autoimmune disease, including joint swelling, rash, oral ulcers, weight loss, or night sweats.

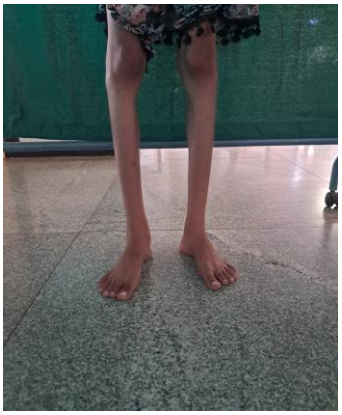

Figure 1: Clinical photograph of the wasting of lower limbs.

The patient reported occasional tingling sensations in both upper and lower limbs along with reduced appetite. There were no complaints of gait disturbance, muscle weakness, bladder or bowel dysfunction, or sensory loss. Neurological examination consistently revealed normal tone, power, and reflexes. Her past history was significant for an episode of myositis in 2019, with persistent but nonspecific EMG changes suggestive of a chronic inflammatory musculoskeletal disorder. Infective evaluation, including CBNAAT and Mantoux testing, was negative. She had also experienced self-resolving calf swellings in 2017 and 2021, with imaging showing osteolytic and osteosclerotic changes. Additional history included Ludwig's angina, a medial epicondyle chip fracture, and imaging evidence of mesenteric lymphadenopathy. Autoimmune disorders such as systemic lupus erythematosus and JIA had been ruled out previously.

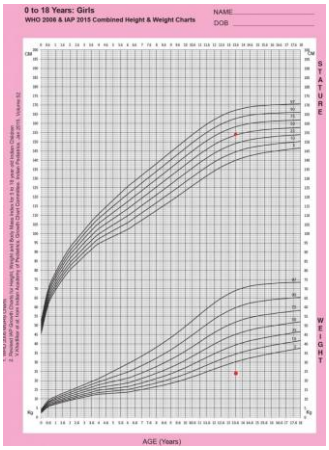

Figure 2: Height and weight assessment using IAP growth charts.

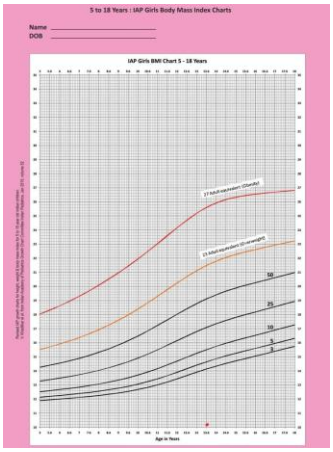

Figure 3: Body mass index (BMI) assessment using IAP BMI chart.

On examination, her height was appropriate for age (154 cm; 50th-75th centile), while her weight was significantly low (24 kg; <3rd centile), with a BMI of 10.11 kg/m², suggestive of chronic undernutrition. Pallor was present, with no icterus, cyanosis, clubbing, or lymphadenopathy. She was alert and interactive, with no joint swelling, deformity, or hypermobility. Tenderness was noted over the calf muscles and spine. Neurological and systemic examinations were otherwise unremarkable. Laboratory investigations revealed mild anemia (hemoglobin 10.1 g/dL), normal leukocyte count, and elevated inflammatory markers (ESR 65 mm/hr, CRP 12 mg/l). Muscle enzymes, liver and renal function tests were within normal limits. Autoimmune markers including ANA and rheumatoid factor were negative. MRI of the pelvis and lower limbs revealed multifocal, ill-defined hyperintensities in the medullary regions of multiple long bones and pelvic bones, consistent with non-infective osteitis. No cortical erosions or soft tissue masses were

seen. A CT aortogram incidentally demonstrated reduced aortomesenteric angle and distance suggestive of vascular compression syndrome, which was clinically insignificant. Based on clinical features, exclusion of infective and autoimmune etiologies, and characteristic MRI findings, a diagnosis of CRMO was established in consultation with pediatric rheumatology. The patient was initiated on intravenous pamidronate and oral naproxen, with significant improvement in pain and systemic symptoms. She remains on regular follow-up with pediatric rheumatology and endocrinology, with plans to monitor pubertal development and reassess hormonal parameters once inflammatory activity is controlled.

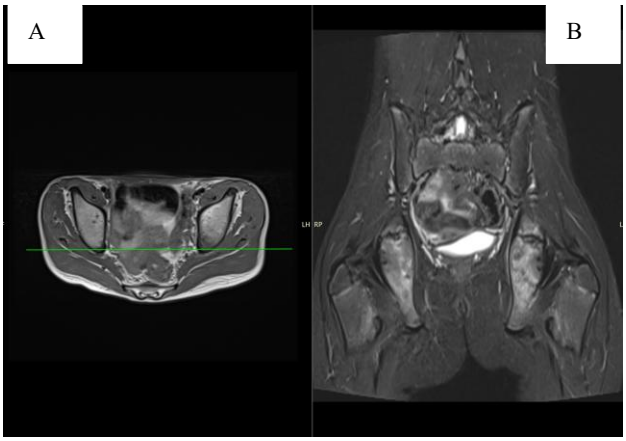

Figure 4 (A and B): MRI pelvis showing multifocal non-infective osteitis.

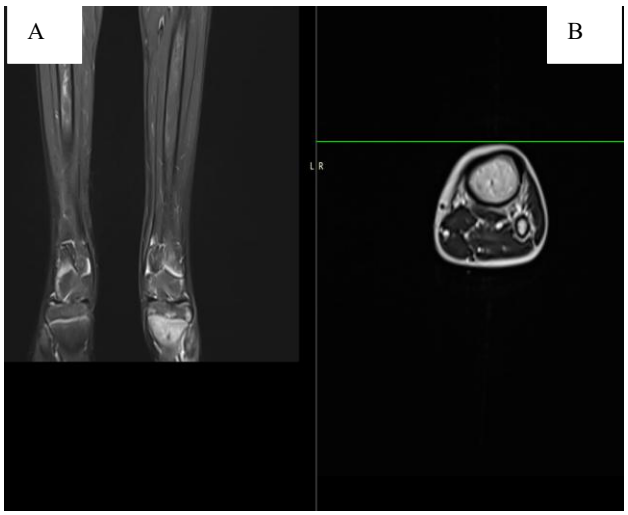

Figure 5 (A and B): MRI of bilateral lower limbs showing multifocal non-infective osteitis.

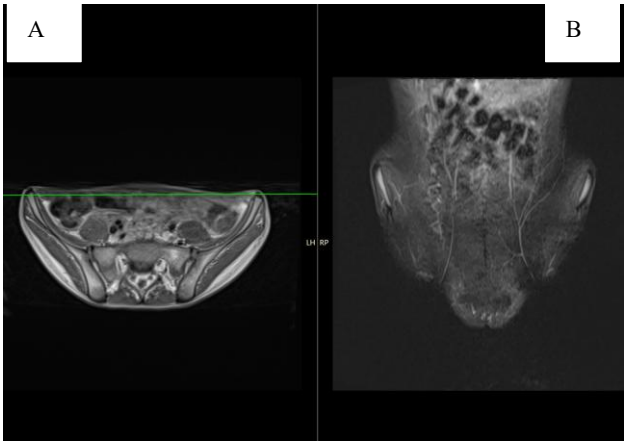

Figure 6 (A and B): MRI pelvis showing bilateral pelvic bone involvement.

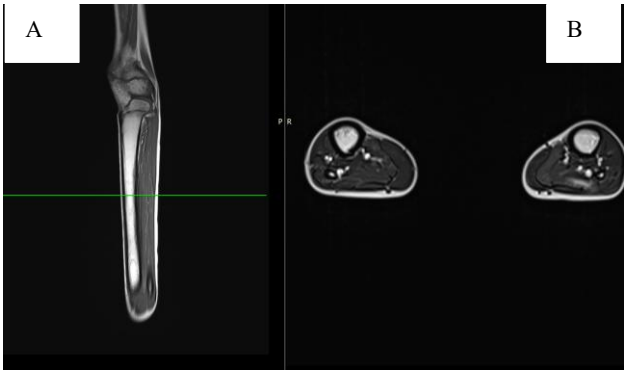

Figure 7: MRI of the lower leg showing intramedullary inflammatory changes.

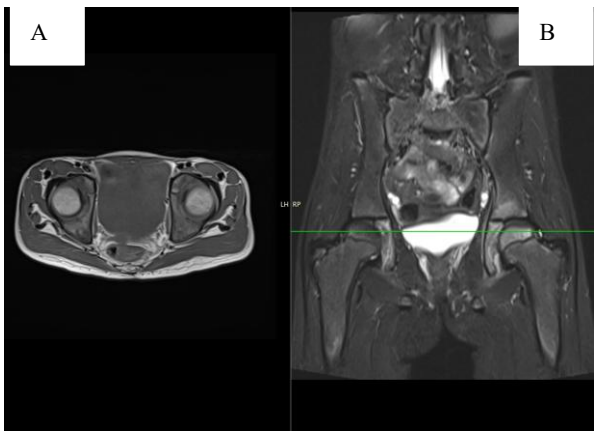

Figure 8 (A and B): MRI pelvis demonstrating bilateral iliac bone marrow edema.

Table 1: Chronological summary of relevant investigations.

Year / date	Investigation	Result	Remarks
2017	Hemoglobin	10.3 g/dl	Mild anemia
	X-ray right knee joint	Osteolytic / osteosclerotic lesion	—
	MRI right femur	Hyperintensities and hypointensities in vastus medialis with	Reported as

Continued.

Year / date	Investigation	Result	Remarks
		areas of liquefaction and subcutaneous tissue edema	infective etiology
	ESR	24 mm/hr	Mildly elevated
	CPK	86 u/l	Normal
	ASO titre	Negative	—
	ANA	Negative	—
2019	MRI pelvis/hip	Myositis involving left iliacus and iliopsoas with mild left hip joint effusion	—
	ESR	40 mm/hr	Elevated
	CRP	10.8 mg/l	Elevated
2020	Clinical diagnosis	Ludwig's angina with right sternocleidomastoid swelling	Treated with amoxiclav×5 days
2020	NCV	Myopathic pattern involving bilateral tibial and peroneal nerves	—
	EMG (rectus femoris)	Interference pattern	—
	CPK	82 u/l	Normal
	CRP	83 mg/l	Markedly elevated
	Vitamin D	31 ng/ml	Insufficient
	T3	2.23	Normal
	T4	104.9	Normal
	TSH	1.34 µiu/ml	Normal
	ESR	24 mm/hr	Mildly elevated
	Mantoux test	Negative	—
2022	EMG and NCS	Normal	—
	CBNAAT (gastric lavage)	Negative	—
	USG iliopsoas	Diffuse edema	Infective
	MRI	Likely myositis	—
2023	USG abdomen	Mesenteric lymphadenopathy (largest 1.06×0.55 cm)	—
	FSH	2.73	Normal
	Estradiol	<10 pg/ml	Normal
	ALP	302 u/l	Liver enzymes normal
	Total bilirubin	0.25 mg/dl	Normal
	Albumin	4 g/dl	Normal
2024	NCCT elbow	Chip fracture of medial epicondyle of humerus	History of fall
	ESR	28 mm/hr	Elevated
	NCS and EMG (all 4 limbs)	Normal	—
	ANA	Negative	—
	CRP	8 mg/l	Elevated
	Serology for HIV, HEPB, HEPC	Negative	—
Present	Hemoglobin	10.1 g/dl	Mild anemia
	Total leukocyte count	8500 /mm³	Normal
	Differential count	N 50.3%, L 39.3%, M 7.9%, E 2.1%, B 0.4%	Normal distribution
	CPK	0.23 u/l	Low
	Phosphorus	4.50 mg/dl	Normal
	ESR	65 mm/hr	Markedly elevated
	CRP	12 mg/l	Elevated

DISCUSSION

CRMO is a rare autoinflammatory disorder characterized by sterile bone inflammation with a relapsing–remitting course. As described by Hofmann et al, the disease predominantly affects school-aged children and adolescents, with a female preponderance and insidious onset of symptoms.[1] Our patient fits this epidemiological

profile, with symptom onset at 7 years of age and a prolonged disease course extending over eight years. Bone pain is the most consistent presenting feature in CRMO. Large cohorts have shown preferential involvement of the metaphysis of long bones, pelvis, and spine.[3] Rao et al, in an Indian cohort, reported lower limb and pelvic involvement as the most frequent sites, similar to the extensive femoral, tibial, pelvic, and sacral involvement seen in our patient.[4] However, the degree of multifocality and axial skeleton involvement in our case was more extensive, which likely contributed to symptom severity and diagnostic delay.

Systemic features such as fever are variably reported in CRMO. While Gupta et al observed fever in only a subset of patients, our patient had intermittent low-grade fever for several years, progressing to daily episodes in the months preceding diagnosis.[5] This atypical persistence of fever mimicked chronic infection and contributed to repeated evaluations and empirical antibiotic use, a diagnostic challenge also highlighted in Indian case series by Rao et al and Gupta et al.[4,5]

MRI plays a pivotal role in diagnosis and disease monitoring. Roig-Abraham et al emphasized that typical MRI findings include multifocal T2/STIR hyperintense lesions with corresponding T1 isointensity or hypointensity in the medullary cavity, without abscess formation or cortical destruction.[8] The MRI findings in our patient closely mirrored these descriptions, demonstrating widespread medullary involvement of long bones and pelvic bones with preservation of cortical integrity and absence of soft-tissue masses. Importantly, early radiographs in our patient showed osteolytic and osteosclerotic changes, which retrospectively align with chronic stages of CRMO described in prior literature.[3-8]

The long history of recurrent inflammatory episodes, including myositis-like presentations and calf swellings, represents an uncommon but important diagnostic pitfall. Singhal et al highlighted the broad clinical spectrum of CRMO and its overlap with infectious, autoimmune, and neuromuscular disorders.[9] In our case, repeated normal electrophysiological studies and sterile inflammatory episodes over several years underscore how CRMO can masquerade as isolated myositis or recurrent infection before characteristic skeletal lesions become evident.[9]

Growth failure and delayed puberty, as observed in our patient, have been recognized consequences of chronic uncontrolled inflammation. Hofmann et al noted that prolonged disease activity may adversely affect nutritional status and pubertal progression, particularly in patients with delayed diagnosis.[1] In our patient, delayed puberty was attributed to chronic systemic inflammation rather than primary endocrine pathology. Therapeutically, NSAIDs remain first-line treatment; however, bisphosphonates are increasingly used in patients with extensive or refractory disease.[1-3] The marked clinical improvement following pamidronate therapy in our patient is consistent with outcomes reported in Indian and international study supporting its role in moderate-to-severe CRMO.[6-10] Overall, this case highlights the heterogeneous presentation of CRMO and reinforces the need for early MRI-based evaluation and multidisciplinary management, particularly in children with chronic, unexplained musculoskeletal pain.[1,3,8]

CONCLUSION

CRMO is a rare but important cause of chronic bone pain in children and adolescents. Its nonspecific clinical presentation, intermittent fever, and fluctuating inflammatory markers often lead to delayed diagnosis, as illustrated by the prolonged disease course in this patient.

This case emphasizes the need for a high index of suspicion for CRMO in children with recurrent, sterile inflammatory bone lesions and negative infective and autoimmune workup. MRI is indispensable for early diagnosis and detection of multifocal involvement. Timely initiation of appropriate therapy, including bisphosphonates in selected cases, can significantly improve symptoms and prevent long-term complications such as growth failure and delayed puberty. Increased awareness and reporting of such cases are essential to improve early recognition and outcomes in this underdiagnosed autoinflammatory disorder.

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