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# Orthopaedic Perspectives Of Chronic Non-Bacterial Osteomyelitis.

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**Abstract**

Chronic non-bacterial osteomyelitis (CNO) is an inflammatory osteitis often unifocal or Chronic recurrent multifocal (CRMO) in children. Pain and swelling of the long bones with or without fever spikes can present periodically in different sites including vertebrae. CNO can present with other inflammatory conditions such as Juvenile idiopathic inflammatory arthritis, Inflammatory bowel disease, Psoriasis, and Pustulosis. Histo pathologically CNO mimics bacterial osteomyelitis. The diagnosis of CNO is by exclusion and can be challenging, hence an average of 4-6 months delay is noted before its definitive treatment. The orthopedic instinct of empirical antibiotics can raise the risk of antibiotic resistance. X-rays in CNO show lytic or sclerotic metadiaphyseal lesions. Advanced imaging such as CT scans and MRI are mandatory but may not be conclusive. The bone biopsy which has negative bacteriological cultures with a clinical correlation of the radiological pictures and blood inflammatory parameters is mandatory for the diagnosis of CNO. NSAIDS suffice for simple cases but Bisphosphonates, Methotrexate, and TNF alpha agents are needed for refractory cases. We report 2 cases of CNO for its Orthopedic challenges in the diagnosis and treatment.

**Keywords**: Chronic non-bacterial osteomyelitis, (CNO), Chronic recurrent multifocal osteomyelitis, (CRMO), Inflammatory osteitis., Transient Inflammatory bone disease

## Introduction

Chronic non-bacterial osteomyelitis (CNO) is an immunological disorder. Common between 8-13 years with an incidence of 0.4 -10 / 1,00,000 population (1, 2). The extended-spectrum (2) includes Chronic Recurrent Multifocal Osteomyelitis (CRMO) and other systemic involvement. Pain is consistent in clinical presentation (5). Femur, tibia, pelvis, and vertebrae in order of frequency were commonly affected in CNO with the majority being multifocal rather than a monofocal disease (1,5). Fever spikes with extraosseous involvement of the eyes, lungs, skin, and gastrointestinal system could be seen in 40% of cases (4).

The diagnosis of CNO should exclude osteomyelitis and bone tumors. Invariably ESR and CRP will be raised in 60 % of CNO cases (5.). The bacteriological cultures remain negative including PCR techniques for various bacteriological testing (1). Chemokines elevation differenciates CNO from bacterial Osteomyelitis.

Whole-body MRI with a coronal STIR is the gold standard and detects silent lesions in CNO (2, 8). Bone biopsy excludes infections, fibrous dysplasia, malignancy or Langerhans cell histiocytosis (1).

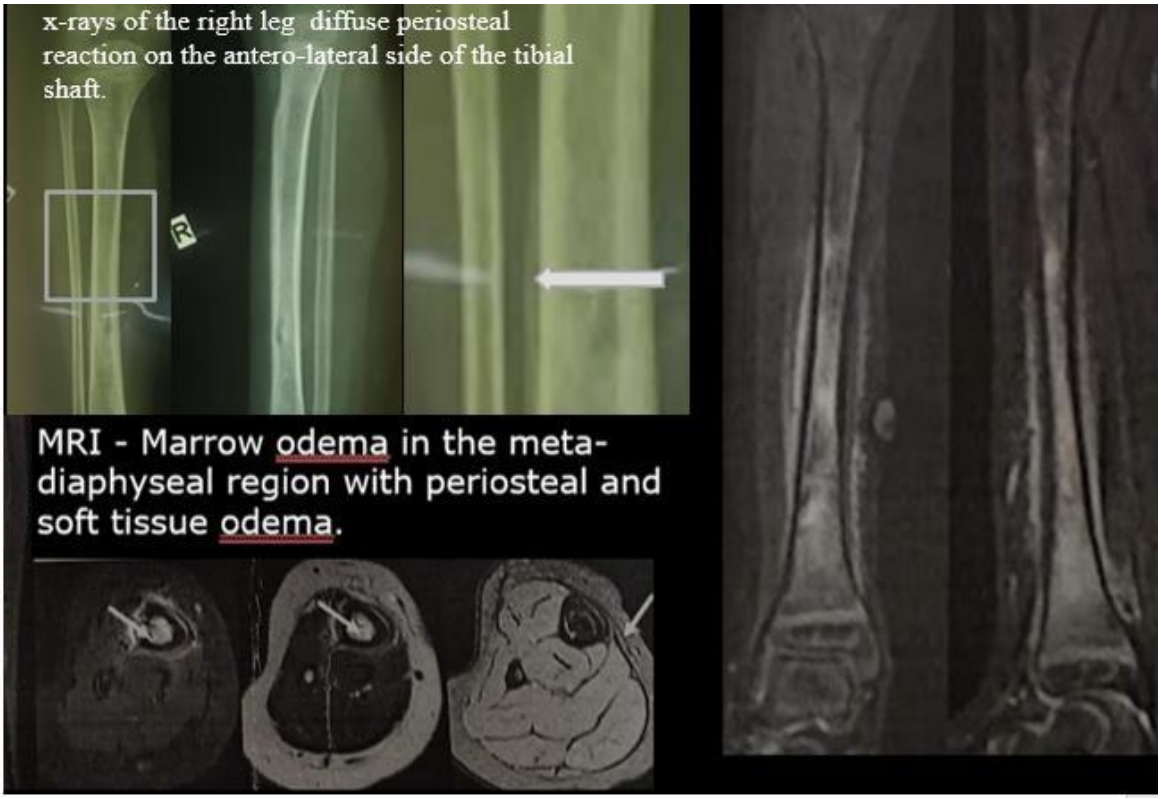
The Ped-CNO prognostic score for CNO includes ESR, the severity of disease, and the Childhood health assessment questionnaire (CHAQ). Jansson et al proposed diagnostic criteria (7) with major and minor criteria in the diagnosis of CNO.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the first line of treatment. In the treatment of CRMO, for refractory cases of CNO and spinal involvement second-line agents play a crucial role in the disease remission.

**Case Report 1:** A 3 years old male child presented with complaints of isolated right leg pain over 10 months duration without a history of trauma. With normal motor and mental milestones, he was able to weight bear and walk without any history of fever or such episodes of complaints in the past.

Examination revealed mild diffuse tenderness over the right midshaft tibial region with normal hip and knee range of movements (ROM) without any regional lymph nodes. Blood investigations showed Hb of 12.0 gms/dl, with normal CRP and ESR of 14 mm/ hr. His Xrays could not exclude bacterial osteomyelitis, and Ewings sarcoma.

**Fig 1**




Open bone biopsy was done for diagnostic exclusion. The bacterial cultures were negative for any organism. He was on a protective cast to prevent stress fracture and intra-venous empirical antibiotics as he spiked 100 degree F twice on the 3rd and 5th post-operative days. In the absence of evidence for bacterial pathology, his antibiotics were stopped and was treated with anti-inflammatory drugs along with steroids for 4 weeks. He responded well. His vitals and inflammatory markers were normal before discharge. With periodic follow-up for 12 months, he had no episode of relapse.

Case 2) An 8-year-old girl presented with pain over multiple sites in her extremities (left arm, Right thigh, and right leg over 35 days. There was no history of trauma but two episodes of fever spikes 15 days prior to her admission. She could weight bear and walk but

with generalized reluctance. Her bladder and bowel habits were normal. Past history of left leg pain 12



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months prior and was diagnosed as a case of sub-acute osteomyelitis of the left tibia but that was in another

hospital where she had extensive bone curettage.

Samples sent for histopathology and culture sensitivity had features of chronic OM but no organism grew. The same was treated with empirical antibiotics and analgesia that resolved her past symptoms. General examination revealed no signs of associated systemic inflammatory disorders. Local examination showed warmth and mild diffuse tenderness in left upper limb and right lower limb. The adjacent elbow and shoulder movements in the left upper limb were normal. The right hip and knee movements were also full and free. Blood markers for infection showed WBC 9180., ESR 48mm/hr and CRP value of 1.2.

**Fig 2: Left humerus, Right Femur Xrays- showing the periosteal reaction. Additional soft tissue elevation over the region of periosteal thickening.**

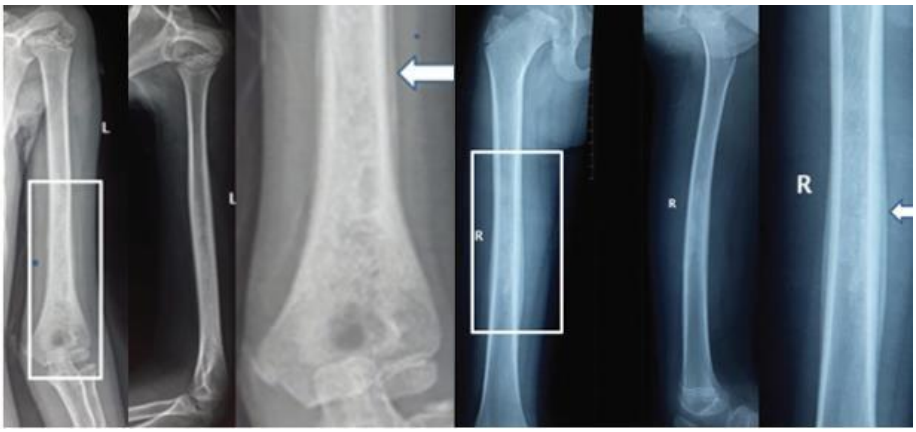


**Fig 3: MRI studies confirmed marrow signal changes with extensive periosteal and soft tissue signal changes suggestive of inflammatory edema.**

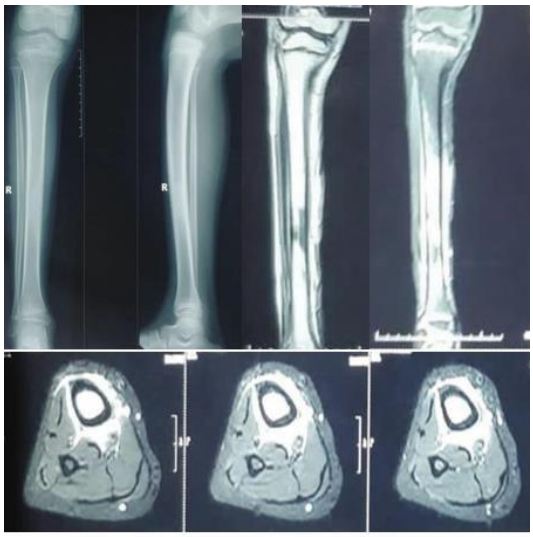



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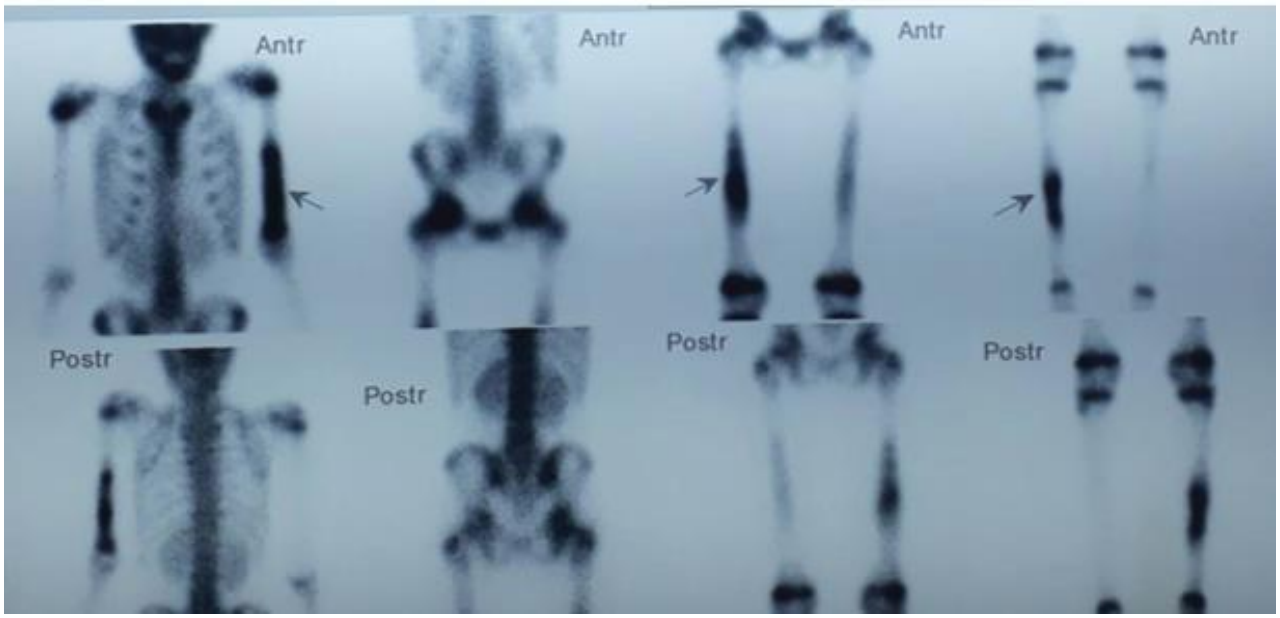
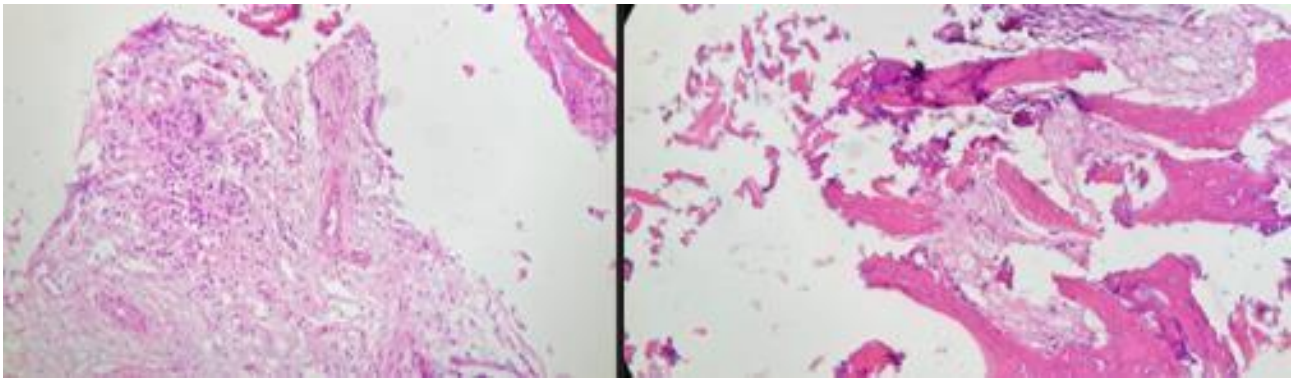
**Fig 4: High uptake of the isotope in the left humerus, Right femur, and Right Tibia indicates the hyperactive lesions.**




To exclude infective cause, bone biopsy was performed from the left humerus, Right femur and Right tibia. The core specimens were sent for histopathological assessment and bacteriological cultures. While awaiting tissue cultures she had temperature spikes and hence initiated the empirical antibiotics. When the cultures were all negative she had NSAIDs in addition to Methotrexate but the antibiotics for her was stopped.



**Discussion:**

The CNO is a misnomer, an "Osteitis" rather than an 'osteomyelitis'. The immunological disorder has an incidence of 4 per million (2) common in the age group between 8- 13 years but not below 3 years of age. Inadequate awareness among the general orthopedic surgeons and lack of wholebody MRI adds to the under-reporting on this entity.

Symptoms could be insidious onset of non-specific bone pain, waxing and waning pattern, night pain, and non-compliance with school activities (1). The extended-spectrum of CNO (2) includes Chronic Recurrent Multi focal Osteomyelitis (CRMO), early-onset Non-infectious osteomyelitis (Majeed Syndrome), Pyoderma gangrenosum with Acne or palmoplantar pustulosis (PAPA syndrome), Synovitis, Hyperostosis, Osteitis, referred as (SAPHO syndrome) in adults and deficiency of Interleukin1 alpha receptor as (DIRA syndrome) Syndromic involvement of Inflammatory bowel diseases and spondylitis can be seen in 20% of cases.

In acute onset symptoms Osteomyelitis needs to be excluded. CNO has waxing and waning pattern as against infective cause which progressively deteriorates.Nocturnal pains in CNO mimics "growth pains" and osteoid osteoma. The nonspecific pattern with chronic pains and poor school performance should exclude other endocrine disorders.



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Signs of localized tenderness over the metaphyseal regions of lower extremities around the knee and ankle are commonly reported. Symmetrical lesions are seen in 20% of cases and Sacro- pelvic acetabular involvement in 20-30 % of cases. Although monofocal lesions are reported in CNO multifocal lesions are underreported.

The descriptive classification (8) is based on site-specific upper or lower limb domination. The 'Tibio-appendicular multifocal' type has 66% involvement of the tibia in addition to its symmetrical lesions. The 'Claviculo–spinal pauci focal' type has 22% clavicular lesion. It is essential for its diagnostic purposes although the treatment strategy may not change.

The localizing tenderness along with focal bony thickening and diffuse periosteal reaction should exclude bone tumor-like Ewings sarcoma. Although the ESR, and CRP are high in 80% of cases, More than 3 to 4-fold elevation should favour bacterial osteomyelitis. Some show elevated anti-nuclear antibodies and positive HLA B27 (1).

Tests of exclusion include LDH and Uric acid (Malignancies), WBC count (Leukemia), Alkaline phosphatase (Hypophosphatasia), and Vitamin C levels (Scurvy) all of which remains normal in CNO. Specific cytokine elevations are yet to get validated as a diagnostic tool in CNO cases.

X-rays may show metaphyseal sclerotic lesions, lytic areas, hyperostosis, and periosteal reactions with thickening. Isotope bone scan detects silent and spine lesions, but now obsolete due to the radiation hazards and easy access to MR modalities. CT scan could be a choice to exclude Osteoid osteoma. MRI remains the gold standard with higher sensitivity in detecting silent, soft tissue and vertebral lesions without radiation hazards also valuable in the follow-up assessment and in exclusion of Neuroblastoma that has multi-organ involvement.

The diagnosis of CNO hence is by exclusion. Despite the symptoms over 4-6 months, with radiological changes in otherwise healthy looking children, after a detailed history and systematic examination, essential regional xrays inluding CT and MRI are needed and still the diagnosis may not be complete without open biopsy and bacteriological exclusion.

**Treatment of CNO & CRMO:**

The first-line drug NSAIDs inhibits the cyclooxygenase that is responsible for osteoclastic resorption and hence the pain regress in the majority of cases.

Refractory cases need corticosteroids, DMARD (Sulfasalazine, Methotrexate), Bisphosphonates, and Anti -TNF agents.

Histopathology include dense cellular infiltrate and non specific pattern in CNO and CRMO but are useful in the elimination (7) of other differential diagnoses such as Osteomyelitis, Non ossifying fibroma, Langerhans histiocytosis.

**Conclusion**

A varied spectrum of presentations can be challenging for orthopedic surgeons in its diagnosis. A high index of suspicion is needed in cases of recurrent multifocal osteomyelitis and cases with negative bacterial cultures in the diagnosis of CRMO and CNO. A team approach involving the Pediatrician, Rheumatologist, Radiologist, and Pathologist at an early stage of diagnosis could avoid unwanted delay and abuse of antibiotics.

**Consent for publication:** Obtained from all authors, including the patient consent as appropriate

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