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CASE REPORT

Nocturnal bone pain revealing chronic nonbacterial osteomyelitis: a case report

Joana Baptista de Lima[1], Liliana Teixeira[2], Tânia Lopes[3], Carla Zilhão[1,4], and Sérgio Alves[1,4]

[1]Department of Pediatrics, Centro Materno-Infantil do Norte (CMIN), Unidade Local de Saúde de Santo António (ULSSA), Portugal, [2]Department of Neonatology, Centro Materno-Infantil do Norte (CMIN), Unidade Local de Saúde de Santo António (ULSSA), Portugal, [3]Department of Pediatrics, Unidade Local de Saúde do Alto Minho (ULSAM), Portugal, [4]Pediatric Rheumatology Unit, Centro Materno-Infantil do Norte (CMIN), Unidade Local de Saúde de Santo António (ULSSA), Portugal

Abstract

Introduction: Chronic nonbacterial osteomyelitis (CNO) is a rare autoinflammatory disorder characterized by sterile bone inflammation, mainly affecting children. Diagnosis is challenging and delays may lead to permanent skeletal damage. **Case report**: An eight-year-old girl presented with a six-week history of right ankle pain, associated with nocturnal worsening, which initially improved with non-steroidal anti-inflammatory drugs but subsequently progressed to involve the left wrist. She had elevated inflammatory markers, X-rays revealed lytic bone lesions, and MRI showed a lesion suggestive of a Brodie abscess. Bone scintigraphy revealed increased uptake in the distal right tibia, left radius, and right costovertebral joint. Surgical exploration found no purulent material. Histopathology revealed subacute/chronic inflammation, and microbiological tests were negative. A diagnosis of CNO was established. **Discussion**: CNO should be considered in children presenting with insidious multifocal bone pain and characteristic imaging findings. Early recognition is essential to avoid unnecessary antibiotic treatments, invasive procedures, and potential long-term complications.

Resumo

Introdução: A osteomielite crónica não bacteriana (OCN) é uma doença auto-inflamatória óssea não infeciosa rara. O diagnóstico pode ser desafiante e o atraso pode levar a danos permanentes. **Caso Clínico**: Criança de 8 anos com quadro de dor no tornozelo direito com seis semanas de evolução, associada a despertar noturno. Melhoria inicial após tratamento com anti-inflamatórios, mas posteriormente com progressão para o punho esquerdo. Apresentava parâmetros inflamatórios elevados, radiografias com lesões líticas e ressonância magnética evidenciando lesão sugestiva de abcesso de Brodie. A cintigrafia óssea revelou captação na tíbia direita distal, rádio esquerdo e articulação costovertebral direita. A exploração cirúrgica não revelou conteúdo purulento. A histologia mostrou inflamação subaguda/crónica e os estudos microbiológicos foram negativos. Estabelecido diagnóstico de OCN. **Discussão**: A OCN deve ser considerada em crianças com dor óssea multifocal insidiosa e achados imagiológicos característicos. O reconhecimento precoce é fundamental para evitar terapêuticas antibióticas desnecessárias, procedimentos invasivos e complicações a longo prazo.

Keywords: Bone pain. Lytic lesions. Chronic nonbacterial osteomyelitis.

***Correspondence:**
Joana Baptista de Lima
E-mail: joana.bap.lima@gmail.com

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What is known:
- Chronic nonbacterial osteomyelitis is a rare autoinflammatory disorder, typically affecting children and adolescents.
- CNO is a diagnosis of exclusion, requiring careful differentiation from infectious osteomyelitis, malignancies, metabolic bone diseases, and amplified pain syndromes.
- Magnetic resonance imaging is the preferred method for detecting early bone changes.

What is new:
- Early diagnosis of CNO prevents unnecessary antibiotic exposure and surgical interventions.
- Non-steroidal anti-inflammatory drugs remain the first-line therapy, but escalation to biologics or bisphosphonates may be necessary.
- Increased awareness of CNO leads to improved clinical outcomes through timely diagnosis and appropriate treatment strategies.

Introduction

Chronic nonbacterial osteomyelitis (CNO) is an autoinflammatory bone disorder presenting with sterile bone pain, mainly in children, although it can persist into or manifest during adulthood[1,2]. Its diagnosis is challenging, often mistaken for infection or malignancy, and delays can cause permanent skeletal damage. Immune dysregulation underlies the disease, which may also affect the skin, joints, and gastrointestinal tract[1].

Case report

An eight-year-old girl, with no relevant past medical history, was seen at the Emergency Department, with a six-week history of right external malleolus pain, worsened mainly with exertion but also causing occasional nocturnal awakenings. No morning stiffness or consistent circadian pattern were reported. Two weeks after the onset of pain, an X-ray and ultrasound were performed showing signs of tenosynovitis of the flexor tendons of the foot. Treatment with ibuprofen 5 mg/Kg/dose every 12 hours was initiated, with clinical improvement after one week. Shortly after suspending non-steroidal anti-inflammatory drugs (NSAIDs), she began to complain again about the same site, as well as new pain in the left wrist, accompanied by swelling and warmth. She reported progressive worsening in the four days before admission, with daily night-time awakenings, a constant need for analgesia, and low-grade fever the day prior. She said there was no history of trauma or cutaneous entry, asthenia, anorexia, weight loss, or night sweats. On physical examination, she was feverish (38.4°C) and presented with focal tenderness, swelling, and warmth in the right external malleolus and left forearm (radial aspect). The active and passive motion range of the tibiotarsal and radiocarpal joints were normal. Initial blood testing revealed increased inflammatory markers [c-reactive protein (CRP) 118.3 mg/L; erythrocyte sedimentation rate (ESR) 43 mm/h] with normal hematological (including peripheral blood smear) and biochemical parameters (including lactate dehydrogenase, alkaline phosphatase, and uric acid). X-rays of the right ankle and left forearm were performed, showing lytic lesions (Fig. 1). Further testing with magnetic resonance imaging (MRI) of the right ankle was performed (Fig. 2), revealing an ovoid lesion with an irregular, wavy contour. It showed increased signal intensity on T1-weighted images and marked enhancement after contrast was administered, outlining four concentric layers with a central area suggestive of fluid content (Brodie abscess). Given the history of multifocal insidious bone pain, a diagnosis of CNO was considered and she was started on ibuprofen 10 mg/Kg/dose every eight hours. Since we could not exclude osteoarticular infection, we empirically started clindamycin 40 mg/Kg/day every 8 hours. Bone scintigraphy revealed increased uptake in the distal extremities of the right tibia and left radius, and the fourth right-sided costovertebral joint.

In view of the MRI findings supporting the hypothesis of a Brodie abscess, surgical intervention was carried out for drainage and a bone biopsy. Nevertheless, no purulent content was found during the operative approach. Bone histology revealed subacute/chronic inflammation, allowing us to rule out malignancy and Langerhans cell histiocytosis. Blood and bone cultures were negative (including the mycobacterial culture) as was bacterial DNA detection with universal 16s ribosomal RNA primers. There was clinical and analytical improvement. The antibiotic was stopped after we had the results of the microbiology tests.

She underwent six months of NSAIDs with no side effects. She is currently in remission with partial normalization of the radiographic lytic lesions.

Discussion

CNO, also known as chronic recurrent multifocal osteomyelitis (CRMO), is an autoinflammatory disease that causes bone pain arising from sterile osteomyelitis. It is primarily a pediatric condition but can persist into adulthood[1,3]. The average age of onset is nine to

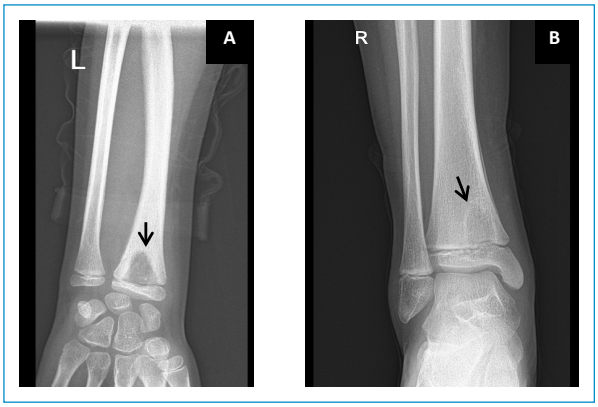

Figure 1. A: anteroposterior X-ray of the left forearm, showing a lytic lesion of the distal radio metaphysis (black arrow). **B:** anteroposterior X-ray of the right ankle, showing a lytic lesion of the distal tibia metaphysis with a sclerotic halo (black arrow) and periosteal reaction (white arrowhead).

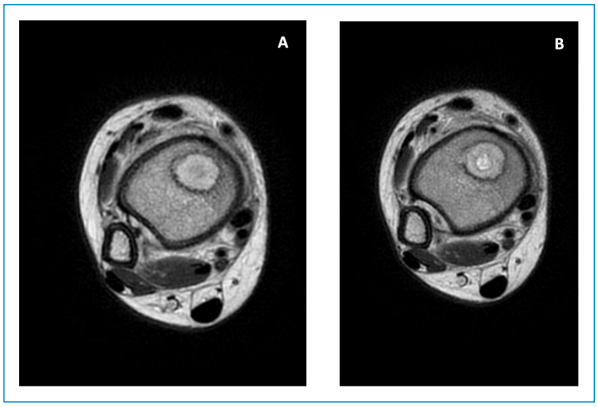

Figure 2. A: ovoid formation on the right ankle surrounded by an irregular wavy contour, with an increased signal on T1-weighted images (and low T2 — penumbra sign). **B:** accentuated enhancement after administering the contrast, defining four concentric layers, with the central area suggestive of a fluid component.

10 years old, and girls are more likely to be affected (female to male ratio of 2:1)[1]. Although CNO is still considered a rare disorder, its incidence is probably underestimated[3]. It is likely underdiagnosed and underreported due to a lack of awareness of CNO in the general population and medical community[1,2].

Clinical manifestations of CNO are highly variable and should be considered in a child with intermittent or persistent focal bone or joint pain, particularly in the lower limbs (metaphyseal region), clavicle, spine, and/or mandible[1,3]. Pain is typically worse at night, may interfere with sleep, and is associated with tenderness at the affected site[1]. Constitutional symptoms such as fever (in around 20%) and weight loss can occur, but most patients appear otherwise well[1,3].

In our patient, the insidious bone pain of the right ankle, partially relieved with NSAIDs but recurring after withdrawal, together with multifocal involvement and nocturnal worsening, raised the suspicion of CNO. However, as CNO is a diagnosis of exclusion, differential diagnosis initially included osteoarticular infection, malignancy, benign bone neoplasms, metabolic bone disease, amplified pain syndromes, and nutritional deficiencies[1,3].

In this context, a fever and markedly elevated inflammatory markers in our patient reinforced the concern for infection, leading to the initiation of antibiotics and the decision to perform surgical drainage and a bone biopsy.

In CNO, laboratory investigations may reveal a mild elevation in the white blood cell count and inflammatory markers (CRP and ESR)[3]. Other parameters are important to exclude alternative diagnoses. Lactate dehydrogenase and uric acid are useful to screen for increased cell turnover in children with leukemia and lymphoid malignancies. Alkaline phosphatase and serum phosphorus are helpful to screen for hypophosphatemiax[1]. Blood and bone cultures should be obtained to exclude infection[3]. Children with a classic presentation that includes looking well, normal laboratory findings, and symmetrical lesions in typical sites such as the metaphysis of long bones, may be spared from a bone biopsy prior to treatment[4].

In our case, however, a biopsy was unavoidable given the radiologic suspicion of a Brodie abscess and the elevated inflammatory markers.

Imaging evaluations should begin with X-rays of the symptomatic sites. When X-rays are normal despite significant clinical symptoms, further evaluation with MRI should be considered[5]. In the early stages, plain X-rays typically demonstrate an osteolytic lesion located adjacent to the growth plate in the metaphysis. Over time, progressive sclerosis develops around the lytic lesion[5]. This was observed in the right ankle of our patient, supporting the subacute course. MRI is particularly valuable in defining the extent of the disease and for follow-up. During active disease, MRI shows typical findings of bone marrow edema, which appears hypointense on T1-weighted images and hyperintense on T2-weighted images[5].

In our patient, MRI revealed an ovoid lesion of the right ankle, surrounded by an irregular wavy contour, with increased signal intensity on T1-weighted images and low signal on T2-weighted images (penumbra sign), features compatible with a Brodie abscess. This

reflects another diagnostic challenge, as an imaging overlap between CNO and bacterial osteomyelitis is common[3]. Another relevant feature in this case was the multifocal distribution of lesions (tibia, radius, and costovertebral joint), confirmed by bone scintigraphy, further supporting the diagnosis of CNO. Bone scintigraphy may provide additional diagnostic information in CNO, particularly when symptoms are multifocal or when clinically silent lesions are suspected. It can reveal increased radionuclide uptake in active lesions, often at multiple skeletal sites, even in the absence of local symptoms[3,4].

First-line treatment consists of NSAIDs, which have been proven useful for pain control and inducing remission in a percentage of patients varying from 43 to 83%[1,3]. For those who respond, there is no clear guideline on the total treatment duration. Our patient responded favorably to NSAIDs, remaining in remission after six months, with partial regression of lytic lesions on X-rays. The initial relapse after early withdrawal was likely related to the short treatment course, as prolonged therapy is often necessary in CNO.

In refractory or severe cases, second-line treatment may include tumor necrosis factor (anti-TNF) inhibitors, bisphosphonates, or disease-modifying antirheumatic drugs such as methotrexate[1,3].

With this case, we seek to highlight the fact that the clinical picture of insidious multifocal bone pain with nocturnal worsening should always raise the suspicion of CNO, even in the presence of systemic inflammation. Besides that, MRI features can be misleading, as seen in our patient where a presumed Brodie abscess prompted unnecessary surgical drainage. Finally, a favorable and sustained response to NSAIDs reinforced the diagnosis and prevented unnecessarily prolonged antibiotic therapy. As in other published cases, the combination of multifocal lesions, sterile cultures, and histological findings was key to reaching the final diagnosis and avoiding long-term skeletal complications associated with delayed recognition.

Authors contributions

All authors contributed equally to the idea behind, as well as the writing and revision of the manuscript. All authors have read and approved the final version of the manuscript.

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Conflicts of interest

None declared

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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