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Radiological Case Report / Caso Clínico

Chronic Recurrent Multifocal Osteomyelitis: A Rare Pediatric Disease

Osteomielite Multifocal Crónica Recorrente: Uma Doença Pediátrica Rara

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Abstract

Chronic recurrent multifocal osteomyelitis is a rare inflammatory disease of the bone with unknown cause, affecting primarily children and adolescents. It is typically characterized by multifocal and symmetric inflammatory bone lesions, with exacerbations and remissions along the disease course. We present a case of a fourteen-month-old girl with the diagnosis of chronic recurrent multifocal osteomyelitis. The girl was initially misdiagnosed as chronic infectious osteomyelitis, and treated with prolonged antibiotic therapy. Despite antibiotic treatment, new multifocal sites of disease emerged, making chronic recurrent multifocal osteomyelitis the most likely diagnosis. Antibiotics were stopped, and the patient was treated with immunosuppressants and pamidronate with good recovery.

Keywords

Children; Chronic recurrent multifocal osteomyelitis; Hyperostosis; Extremities; Ribs.

Resumo

A osteomielite multifocal crónica recorrente é uma doença inflamatória rara do osso de etiologia desconhecida, acometendo principalmente crianças e adolescentes. Caracteriza-se tipicamente por envolvimento ósseo multifocal e simétrico, com exacerbações e remissões ao longo do curso da doença. Apresentamos um caso de uma menina de catorze meses com o diagnóstico de osteomielite multifocal crónica recorrente. Inicialmente foi diagnosticada como osteomielite crónica de etiologia infeciosa, sendo tratada com antibioterapia prolongada. Apesar do tratamento antibiótico, novos locais de atingimento da doença foram surgindo ao longo do seguimento clínico, impondo a hipótese de osteomielite multifocal crónica recorrente como o diagnóstico mais provável. Os antibióticos foram então interrompidos e a criança iniciou tratamento imunossupressor e pamidronato, com boa recuperação.

Palavras-chave

Crianças; Osteomielite multifocal crónica recorrente; Hiperostose; Membros; Costelas.

Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare inflammatory disease of the bone with unknown cause, affecting primarily children and adolescents (most frequently between 9 and 14 years of age), with girls being affected twice as often as boys.[1] Autoimmune and genetic origins have been linked with the triggering of the disease, which explains its association with dermatologic disorders (such as psoriasis, palmoplantar pustulosis, acne fulminans, pyoderma gangrenosum and Sweet syndrome), inflammatory bowel diseases, recognized family-based associations due to a susceptibility locus at 18q21.3-22 and also mutations of some genes, such as *LPIN2* gene in Majeed syndrome, *PSTPIP1/CD2BP1* gene in pyogenic arthritis-pyoderma gangrenosum-acne (PAPA) syndrome, and deficiency of interleukin-1 receptor antagonist (DIRA).[2,3] The condition has no association with infectious pathogens and initial related reports were probably due to contamination of the biopsy samples.[3]

CRMO has an insidious onset with ambiguous symptoms. It is typically characterized by multifocal and symmetric inflammatory bone lesions, with exacerbations and remissions along the course of the disease.[1] CRMO is a diagnosis of exclusion, and, as a consequence, the true prevalence may be higher than reported (less than 1:1.000.000).[4]

We present a case of a fourteen-month-old girl with the diagnosis of CRMO. The girl was initially misdiagnosed as chronic infectious osteomyelitis and treated with prolonged antibiotic therapy.

Case Report

A fourteen-month-old girl was admitted with a history of fever (up to 39ºC), limping, swelling, hot and redness in both ankles and feet in the previous three weeks. She was very tearful and refused to walk. She did not have other skeletal or joint abnormalities on physical examination. Her appetite and weight were normal for her age. There was no history of significant medical problems or previous trauma. Skin and neurological exams were normal. There was no family history of skeletal or autoimmune diseases. Laboratory findings showed elevation of the white blood cell count (17,68x10^9/L, neutrophils 65.4%, lymphocytes 22.7%), erythrocyte sedimentation rate (125 mm/h) and slight elevation of the C-reactive protein (39.2 mg/L). Blood culture was negative for pathogenic organisms. Radiographs of the legs revealed soft tissue swelling with

marked sclerosis, hyperostosis and periosteal reaction in the distal metadiaphyseal region of both tibia and right fibula, and also in both calcaneus (image A in Fig. 1). Magnetic resonance imaging (MRI) showed bone marrow edema, periostitis and soft tissue inflammation in the same locations as the radiographic findings, with no signs of transphyseal disease or joint effusion (images B and C in Fig. 1). There was no evidence of fluid collections or abscesses, fistulous tracts, sequestra, cortical disruption or associated soft tissue masses. Empiric antibiotic therapy was started, and a biopsy was performed. The bone samples revealed mixed acute and chronic inflammation, with no evidence of responsible infectious organisms or neoplasia. Over several weeks, the clinical signs and symptoms gradually improved. She was regularly followed as a case of chronic osteomyelitis and treated with multiple and prolonged antibiotic courses.

Five months later, the girl suffered a deterioration of her clinical condition and was readmitted. She presented generalized malaise and fever, with bilateral swelling and tenderness of the ankles, feet, thighs, left arm, forearms and right hand. Laboratory findings showed again elevation of the white blood cell count, erythrocyte sedimentation rate and of the C-reactive protein. Blood cultures persisted negative and additional bone biopsies revealed no infectious organisms. Radiographs were performed showing multifocal changes, with bone expansion, sclerosis, hyperostosis and periosteal reaction (images A, B, and C in Fig. 2). MRI of the extremities revealed bone marrow edema, periostitis and soft tissue inflammation, with no evidence of abscesses, fistulous tracts, sequestra, or soft tissue masses (image D in Fig. 2). Whole-body evaluation with Technetium 99m (^{99m}Tc) bone scintigraphy confirmed its multifocal nature, also revealing additional sites of disease (image E in Fig. 2).

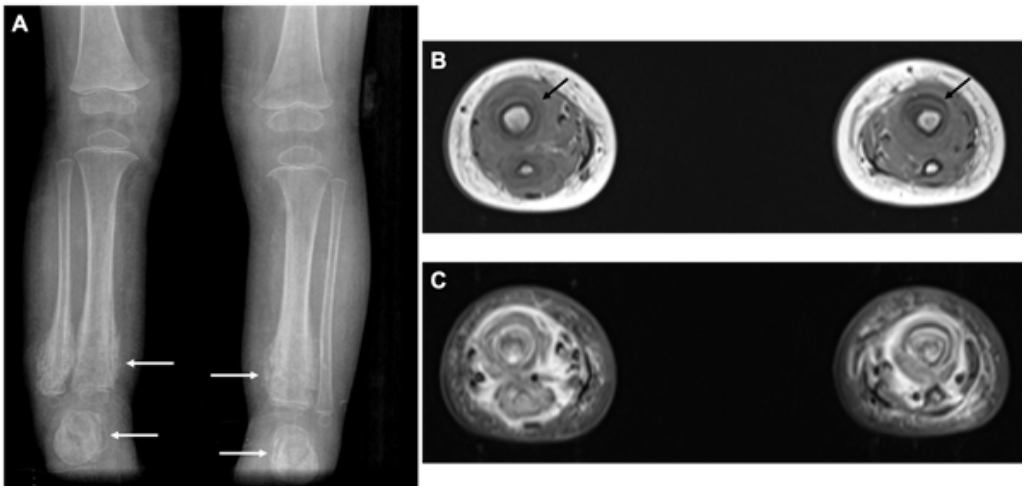

Figure 1 – First admission of a fourteen-month-old girl with CRMO. (A) Anteroposterior (AP) Radiograph of the legs shows symmetric alterations, with soft tissue swelling, sclerosis, hyperostosis and periosteal reaction in the distal metadiaphyseal region of both tibia and right fibula, and also in both calcaneus (white arrows). (B) Axial T1-weighted and (C) short tau inversion recovery (STIR) images depict bilateral bone marrow edema, periosteal reaction (black arrows), and soft tissue inflammation. There is no evidence of abscesses, fistulous tracts, sequestra, cortical disruption or associated soft tissue masses.

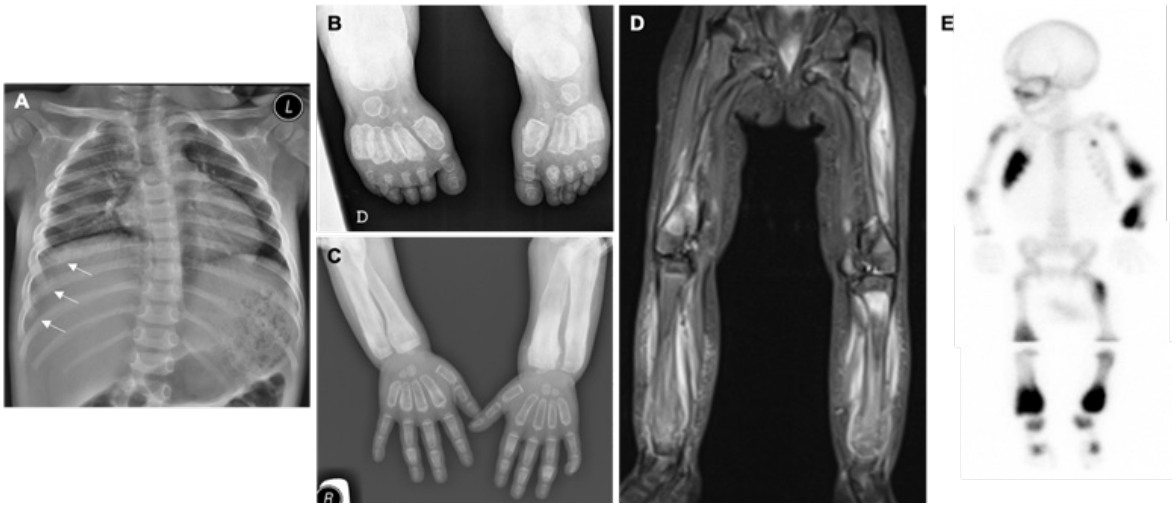

Figure 2 – Second admission of a young girl with CRMO. (A) AP radiograph shows sclerosis and periosteal reaction from the sixth to the eighth right ribs (arrows). There is no evidence of disease in both clavicles and vertebrae. (B) AP radiograph of the feet shows soft tissue edema, accompanied by bone expansion, sclerosis and hyperostosis of the metatarsals and some phalanges. (C) AP radiograph of the hands and forearms depicts soft tissue edema specially on the left, accompanied by sclerosis and hyperostosis of both ulnas, left radius, and some metacarpals and phalanges. (D) Coronal STIR image shows soft tissue edema, accompanied by marrow edema in the tibias, proximal left femur, and distal right femur. There is no evidence of abscesses, fistulous tracts, sequestra, cortical disruption or associated soft tissue masses. (E) Anterior projection 99mTc bone scan shows multifocal and symmetric lesions: radionuclide-avid lesions in the right rib cage, a focal uptake in a left rib, right and left distal tibia/fibula, distal left humerus, distal left radius/ulna, left proximal femur, right distal femur, calcaneus, and metatarsals. Mild increased uptake is also seen in the proximal left tibia/fibula, proximal right humerus, and proximal radius/ulna. Uptake is also evident in the paranasal sinuses due to acute sinusitis.

The patient was then diagnosed as a case of CRMO and antibiotics were stopped. Due to the severity of the case, the girl was initially treated with prednisolone 2 mg/kg oral daily, interferon-gamma 10 μg subcutaneous 3x/week, and pamidronate 3mg/kg (when needed). Then treatment was changed to recombinant interleukin-1 (IL-1) receptor antagonist anakinra 3,3 mg/kg subcutaneous daily and pamidronate 3mg/kg (when needed), because the patient did not achieve a complete remission with the first treatment. During the last treatment, white blood cell count normalized ($8{,}56x10^9$/L); erythrocyte sedimentation rate and C-reactive protein dropped, but remained slightly elevated (60 mm/h and 11,2 mg/L, respectively). She demonstrated good recovery, with no major functional sequels during the follow-up (around 4 years) (Fig. 3). Genetic studies were negative, including Majeed and PAPA syndromes, and DIRA.

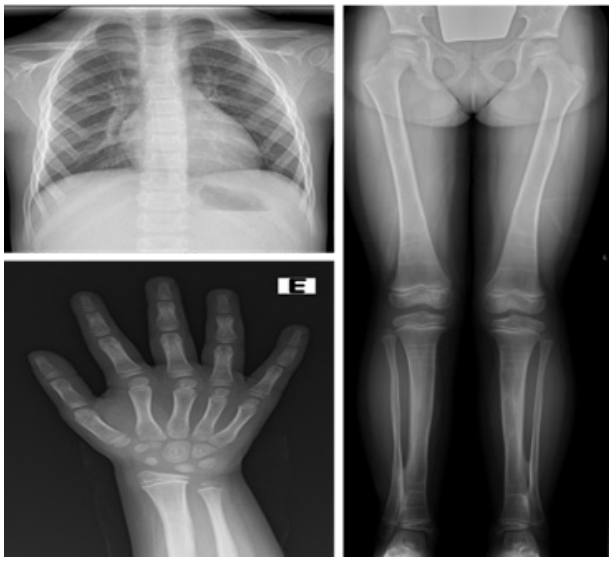

Figure 3 – Resolution of the imagiological alterations 4 years after treatment with anakinra and pamidronate.

Discussion

CRMO is characterized clinically by the onset of insidious swelling and pain at the involved bones. Patients may experience concomitant systemic symptoms such as generalized malaise and fever. Skin disorders, most commonly pustulosis palmoplantaris, may also be present and accompany disease recurrences. Laboratory findings are nonspecific, and may show mild elevation of the white blood cell count, erythrocyte sedimentation rate, and C-reactive protein. However, the inflammatory parameters are often normal. Cultures of blood and bone are always negative.[1,4,5]

Involvement of the clavicle is the typical picture. However, bone lesions are frequently localized in the metaphysis of the tubular bones and spine. The tubular bones of the lower extremities are most frequently affected (distal femur, tibia, and distal fibula). Less commonly, the disease involves the pelvis, ribs, and sternum. Multifocality is the characteristic finding, and symmetric involvement is frequent.[5]

The imaging assessment usually starts with radiographic evaluation of the symptomatic regions. MRI further permits evaluation of the bone marrow, complications of chronic infections (abscesses, fistulous tracts, and sequestra), and evidence of signs suggestive of aggressive lesions, such as soft tissue masses and cortical disruption. When considering CRMO as a possible diagnosis, whole-body MRI or the less expensive ^{99m}Tc bone scintigraphy are essential to confirm the multifocal nature of the disease and also to clinically identify asymptomatic lesions.[1,6]

Radiography initially shows osteolytic lesions in the metaphysis of the tubular bones adjacent to the growth plate, and lined by a thin sclerotic rim. Chronic lesions are predominantly sclerotic, with associated hyperostosis, periosteal reaction and bone expansion. MRI depicts bone marrow edema, which has hyperintensity on T2-weighted images and hypointensity on T1-weighted images. Associated findings include periostitis, transphyseal involvement, and soft tissue inflammation. The evidence of abscesses, sequestra, or fistulous tracts imposes the diagnosis of infectious osteomyelitis. MRI is also very useful in the follow-up of patients, for evaluation of disease recurrence or resolution.[5]

CRMO has no specific imaging findings, making this condition a diagnosis of exclusion. Differential diagnosis includes infectious osteomyelitis, Langerhans cell histiocytosis, and malignancies, such as bone sarcomas, metastasis, neuroblastoma, lymphoma, and leukemia.[1,5]

The disease is self-limited in most cases, resolving without significant sequelae, but some patients may suffer from premature closure of the growth plates, kyphosis, and bone deformities.[7,8,9] Non-steroidal anti-inflammatory drugs (NSAIDs) are considered the first line therapy. Other therapies (specially in nonresponders) include: corticosteroids, disease modifying anti-rheumatic drugs (DMARDs, usually sulfasalazine or methotrexate), tumor necrosis factor-alpha (TNF-alpha), interferon (alpha and gamma), bisphosphonates (pamidronate) or IL-1 receptor antagonist (anakinra).[2,3,10]

Imaging plays a key role in the assessment of this disease. Familiarity and recognition of the manifestations of CRMO enable the Radiologist to be the first to suggest the diagnosis, avoiding unnecessary invasive diagnostic procedures and antibiotic therapies, with initiation of an appropriate treatment. Criteria for the diagnosis of CRMO include: prolonged and fluctuating course with recurrent episodes of pain and localized swelling; combination of bone lesions suggesting subacute and chronic osteomyelitis; lack of fistula, sequestra and abscess formation; unusual locations of lesions such as the clavicle; multifocal (3 bony lesions) and/or symmetric lesions; inflammatory changes on bone biopsies with lack of a causative organism; absence of response to antibiotics; associated skin conditions (most frequently pustulosis palmoplantaris) or auto-immune/inflammatory disorders; mild elevation of the inflammatory parameters.

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Protection of human and animal subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).
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