Clinical Case Reports

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Chronic recurrent multifocal osteomyelitis: A challenging diagnosis

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Introduction. Chronic recurrent multifocal osteomyelitis (CRMO) is a pediatric autoinflammatory disorder that is characterized by multiple sterile inflammatory bone lesions with a relapsing and remitting course. CRMO belongs to the autoinflammatory family of rheumatologic disorders based on absence of significant titers of autoantibodies and autoreactive T-lymphocytes. In absence of pathognomonic clinical, radiographic or pathological features, diagnosis can be challenging.

Case presentation. We report an unusual case of a 3-year-old girl presenting back pain, neurogenic bladder and syringomyelia. A tethered cord was diagnosed and treated, improving urinary function. Despite the surgical treatment, back pain was persistent. A whole body MRI showed multiple lesions compatible with chronic recurrent multifocal osteomyelitis.

Conclusion. CRMO shares imaging features with other diseases. It is important for neurosurgeons and radiologists to be able to differentiate other diseases from CRMO because prognosis varies from completely benign to frankly malignant.

Keywords: chronic recurrent multifocal osteomyelitis, chronic nonbacterial osteomyelitis, tethered cord, back pain, syringomyelia

INTRODUCTION

Chronic recurrent multifocal osteomyelitis (CRMO) was first described in 1972 by Giedion as “an unusual form of multifocal bone lesions with subacute and chronic symmetrical osteomyelitis” (Roderick et al. 2016).

Different from acute bacterial osteomyelitis, CRMO is considered an idiopathic, non-infectious inflammatory bone disorder. It covers a wide clinical spectrum with unifocal and timely limited courses at the one end, being called chronic nonbacterial osteomyelitis (CNO), and prolonged, multifocal, recurrent, sometimes destructive courses at the other end, which is usually referred to as chronic recurrent multifocal osteomyelitis (CRMO) (Schnabel et al. 2016).

Despite intense study, the exact pathophysiology of CRMO remains unknown. Recently, a dysregulation of innate immune mechanisms was demonstrated, potentially contributing to the infiltration of innate immune cells in affected bones (Kostik et al. 2020).

Clinical signs are related to local bone disorder, and spinal involvement can lead to low back pain, which can sometimes be confused with symptoms of neurosurgical diseases.

Considering the aforementioned, CRMO is a heterogeneous disorder and not all symptoms may occur at the same time which can make diagnosis challenging. The authors present here an unusual case of tethered cord, syringomyelia and CRMO.

CASE REPORT

A 3-year-old girl, presenting with intermittent and A 3-year-old girl, presenting with intermittent and recurrent low back pain, with relief when sitting or bending down. After 8 months, recurrent urinary losses began.

During this period, the patient underwent rheumatological and orthopedic consultations, but without improvement or without initial clinical suspicion.

There was no history of fever or infections. The laboratory rheumatological investigation was negative, as well as the C-reactive protein (CRP) titers were low.

An MRI of the lumbosacral spine was performed, and the diagnosis of thocarolumbar syringomyelia and edema in thoracolumbar transition vertebrae was made. The medullary conus was normopositioned, but the filum terminale was thick (Figure 1). PPD reaction was negative and she had no family history of tuberculosis.

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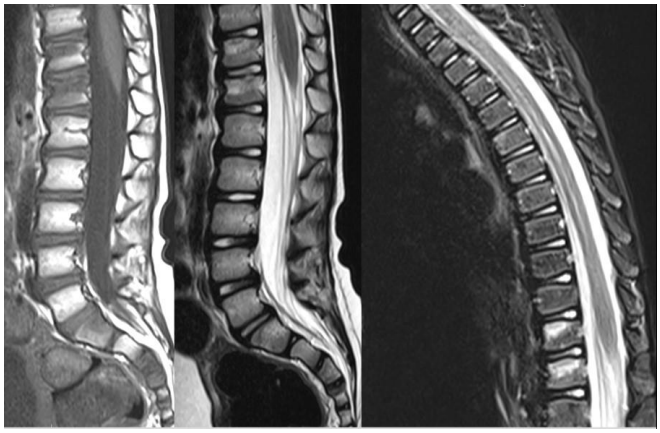

Figure 1- Spine MRI showing normal positioned conus and syringomyelia. Signal changes in D11-D12 vertebral bodies

The patient was then referred to a neurosurgical consultation. As the child presented frequent urinary losses, we decided to perform an urodynamic study, which revealed detrusor hyperactivity (Fig 2). Thus, a tethered spinal cord with a normal positioned conus was diagnosed and the section of the filum terminale was performed, uneventfully. At 3 months after the operation, the patient showed improvement in bladder control and the urodynamic study was better.

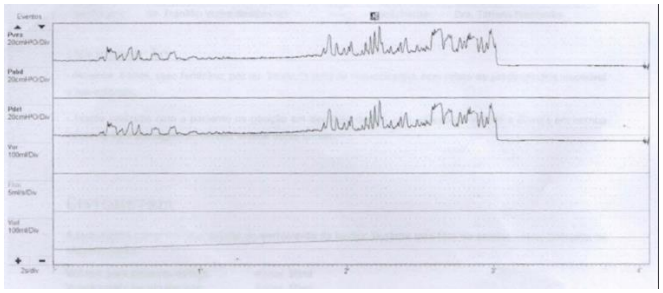

Figure 2- Urodynamic exam showing detrusor hyperactivity

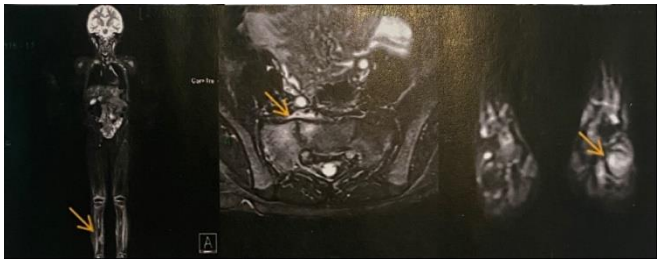

Figure 3- Whole body MRI confirming edema in sacral vertebrae, dyaphisis of the right tibia and in the left foot (orange arrows)

Four months after surgery, she had an episode of back pain again, needing to squat to improve. The rheumatological investigation was repeated, which remained normal. Only an increased erythrocyte sedimentation rate (ESR) was found.

Blood culture was negative for bacterial infection.

Therefore, a total body MRI was performed, identifying multicentric edema/inflammatory process in the thoracic and sacral vertebrae, in the diaphysis of the right tibia and in the left cuboidal bone, corroborating the diagnosis of chronic recurrent multifocal osteomyelitis (Fig 3). Biphosphonate therapy was initiated, with clinical control of the disease.

DISCUSSION

Sporadic CNO covers a wide clinical spectrum from rather mild, time-limited, monofocal bone inflammation to severe chronically active or recurrent multifocal bone inflammation. These most severe presentations are referred to as chronic recurrent multifocal osteomyelitis (CRMO), as presented in our case.

CRMO is an autoinflammatory bone disorder mostly affecting children and adolescents (Hofmann et al. 2017). Autoinflammatory disorders are characterized by an activation of the innate immune system in the absence of high-titer autoantibodies.

Other names have been used for CNO which include SAPHO (Synovitis, Acne, Pustulosis, Hyperostosis, and Osteomyelitis) and may represent the same disease entity. Technically, however, SAPHO should only be used for patients with cutaneous features, including acne and pustulosis(Hofmann et al. 2017).

Clinical signs of bone inflammation include localized skin redness, swelling, and pain. Of these symptoms, our patient only presented low back pain, which was initially associated with thickened filum, syringomyelia and neurogenic bladder, indicating that the presence of local vertebral edema could occur in the progressive phase of the tethered cord syndrome.

Additional symptoms have been reported in the literature, caused by paraosseous inflammation, involving peripheral nerves, vessels, skin, bowel inflammation and synovitis. Some patients exhibit inflammatory organ involvement, including psoriasis and palmoplantar pustulosis (~ 8%), inflammatory bowel disease (~ 10%), and severe acne (~ 10%). Other CNO patients develop sacroiliitis, and some patients may progress from childhood CNO to spondylarthropathies in later life stages (Hofmann et al. 2017). In our case, it was only possible to visualize sacroiliitis on the total body MRI, months after the surgery, with progression of the disease as shown in figure 3.

Routine laboratory tests deliver unspecific results but can help to exclude differential diagnoses. Usually, mildly elevated CRP and ESR are present, with frequencies ranging from 49 to 80% in large cohorts (Jansson et al. 2007; Wipff et al. 2015; Girschick et al. 2018). Although not specific and not

excluding CNO, highly elevated CRP and ESR in a suspected case should warrant further investigation for alternative causes(CARRA SVARD CRMO/CNO workgroup et al. 2018). Antinuclear antibodies and HLA-B27 are found to be positive in 8-38% and 2_25%, respectively (Zhao et al. 2021). Our case only presented ESR elevation and antibodies titers were normal.

Regarding radiological investigation, spinal radiography can be non-specific, despite always being the initial examination. Historically, bone scintigraphy was used to diagnose CRMO (Zhao et al. 2021), however, due to the known consequences of using irradiation in children, both scintigraphy and computed tomography should be avoided. The advent of magnetic resonance imaging, with greater sensitivity and without the risks of irradiation, has made it the exam of choice in relation to the exams mentioned above. Another form of diagnosis is bone biopsy. In reality, in CNO/CRMO the findings are non-specific and may include dense infiltrates of immune cells, lysis of bone, fibrosis and/or normal bone(Jansson et al. 2007). The role of the biopsy is to exclude other possible diseases, such as bone tumors, infections and histiocytosis.

Currently, CRMO remains a diagnosis of exclusion as no widely accepted diagnostic criteria are available.

Three papers suggested diagnostic criteria for CNO (Jansson et al. 2007; Roderick et al. 2016; Zhao et al. 2018) which all include overall stable or good clinical appearance of patients, disease duration of 6 months or more, the presence of multifocal bone lesions with “typical” appearance on imaging (in which biopsies are not always necessary) or unifocal lesion with no evidence of infection and malignancy.

In accordance with these authors, in the presented case a biopsy was not necessary, since the total body resonance showed multiple lesions and other rheumatological and infectious diseases were excluded.

Regarding syringomyelia, there is no report in the literature of CRMO related to syringomyelia or neurogenic bladder. This leads us to believe that our patient actually had two concomitant diseases. The presence of a thick filum terminale with a normal positioned conus and related to neurogenic bladder is already well known and established in the literature(Warder and Oakes 1993; Steinbok et al. 2007; Stamates et al. 2018). The fact that the patient's urinary condition improved shows us that there was indeed a tethered spinal cord, but the pain and vertebral edema were related to the autoimmune disease, initially subclinical.

Untreated CRMO has the potential to cause debilitating skeletal deformities, arthritis, and chronic pain; hence early recognition and treatment are paramount (CARRA SVARD CRMO/CNO workgroup et al. 2018). Treatment consists of various antiinflammatory medications and may also include bisphosphonates if vulnerable skeletal sites are involved, as in the presented case. Even when treated, the disease may have a relapsing course lasting years.

Therefore, pediatric neurosurgeons must be aware of this condition, which, despite being rare, predominates among children and adolescents and the symptoms can be confused with those of other neurosurgical conditions.

CONCLUSION

CMRO is an autoimmune bone disease, characterized by inflammatory bone involvement, which can lead to low back pain when there is spinal involvement. Left untreated, this condition can lead to chronic pain, progressive deformity and poor quality of life. Recognition of this disease by pediatric neurosurgeons is mandatory, as symptoms may be associated with other concomitant neurosurgical diseases and, despite being rare, the disease is more common in children and adolescents.

DISCLOSURES

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local Ethics Committee, number: not applicable

Consent to participate

The patients gave consent to use their information and images for research purposes. *Consent for publication*

The patient gave consent to use his information and images for publication.

Conflict of interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper."

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Artificial intelligence

No.

CONTRIBUTIONS

-**Tatiana Protzenko**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

-**Clara Magalhães Paiva**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources
-**Marcelo Pousa**: Conceptualization, Data curation, Investigation, Methodology, Resources
-Antônio Bellas: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Supervision

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