

# Chronic recurrent multifocal osteomyelitis: what is it and how should it be treated?

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## SUMMARY

**Background** Chronic recurrent multifocal osteomyelitis (CRMO) is the most severe form of chronic nonbacterial osteomyelitis. In children and adolescents, chronic nonbacterial osteomyelitis predominantly affects the metaphyses of the long bones, but lesions can occur at any site in the skeleton. Other organs (the skin, eyes, gastrointestinal tract and lungs) can also be affected. Clinical diagnosis is often difficult because the symptoms and course of disease vary significantly. We present a 10-year-old girl diagnosed with CRMO involving several vertebrae, the femur and the metatarsus.

**Investigations** Physical examination, abdominal ultrasonography, conventional X-ray, MRI, technetium bone scan, esophagogastroduodenoscopy, colonoscopy, tests for HLA-B27 and thiopurine methyltransferase, polymerase chain reaction and thoracic vertebral bone biopsies.

**Diagnosis** CRMO and Crohn's disease.

**Management** The patient's condition improved whilst being treated with NSAIDs for 3 months; however, the patient had an allergic skin reaction to this therapy. Treatment was switched to sulfasalazine, accompanied by 3 weeks of therapy using oral prednisone, but sulfasalazine was discontinued 2 months later because the patient exhibited a minor elevation in the levels of liver enzymes. The patient was free of musculoskeletal symptoms for 6 months, at which time she started to complain again about pain in her back and bowel. Multimodal therapy, consisting of mesasalazine, corticosteroids (budesonide) and azathioprine, induced clinical remission of Crohn's disease.

**KEYWORDS** chronic inflammatory bowel disease, chronic nonbacterial osteomyelitis, chronic recurrent multifocal osteomyelitis, Crohn's disease, SAPHO syndrome

## CME

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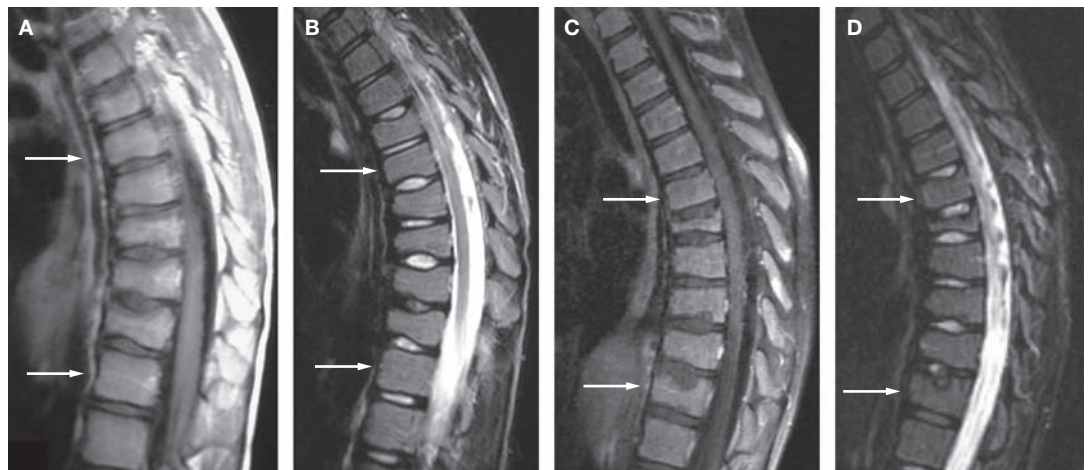
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### THE CASE

The patient complained about pain in her spine at the age of 9 years. Her left knee, left hip and both feet were also painful. These symptoms were not constant, so it was 4 months before the patient was referred to a pediatrician. Examination revealed nothing remarkable, except dorsal back pain. Laboratory parameters, including C-reactive protein level, erythrocyte sedimentation rate, level of peripheral leukocytes, ferritin level, antinuclear antibody level, rheumatoid factor status, concentration of complement components C3 and C4, and serum levels of IgG, IgA, IgM, IgE and IgD, were all unremarkable. HLA-B27 was absent. Radiographs of the spine and chest were normal; however, MRI of the spine and pelvis revealed multiple inflammatory lesions of thoracic vertebrae numbers 6–11 and sacral vertebrae numbers 2 and 3. The patient was, therefore, referred to our institution.

In most cases, MRI of patients with chronic nonbacterial osteomyelitis (CNO) cannot completely rule out malignancy. The possibility of neuroblastoma was excluded using further diagnostic tests, including measurement of the urinary levels of homovanillic acid and vanillylmandelic acid and the serum level of neuron-specific enolase. A technetium bone scan showed the lesions already defined by MRI, in addition to a right metatarsal lesion and an epiphyseal lesion in the left distal femur. This multifocal pattern of lesions was indistinguishable from Langerhans' cell histiocytosis, another major differential diagnosis. A bone biopsy of the thoracic spine was, therefore, performed. The histological work-up revealed a lymphocytic and plasmacellular infiltrate, in addition to peritrabecular fibrosis. The immunohistology results showed that T lymphocytes, monocytes and plasma cells were present, which excluded malignancy from the diagnosis.



**Figure 1** Osseous damage by CNO in a 10-year-old girl. MRI 6 months after diagnosis showed partial vertebral compressions, particularly of thoracic vertebrae numbers 8–10. (A) Despite anti-inflammatory treatment, T1-weighted imaging after intravenous gadolinium-DTPA revealed contrast enhancement of thoracic vertebrae numbers 8–11. (B) The strongly T2-weighted images, with fat-suppression (TIRM), no longer showed edematous changes of the bone marrow. MRI 1 year after the diagnosis of CNO revealed multiple compressions of thoracic vertebrae numbers 6–11 (C and D; arrows). (C) T1-weighted imaging after intravenous gadolinium-DTPA did not reveal contrast enhancement. (D) The TIRM images did not show bone edema. Arrows mark thoracic vertebrae numbers 6 and 11 in all images. Abbreviations: CNO, chronic nonbacterial osteomyelitis; DTPA, diethylene triamine penta-acetic acid; TIRM, turbo inversion recovery magnitude.

Standard microbial and mycobacterial cultures and universal polymerase chain reaction, to amplify eubacterial and mycobacterial genes, showed no sign of bacterial infection.

Because the patient exhibited multiple bone lesions, a recurrent course, a biopsy consistent with chronic inflammation and no cultivable bacteria, chronic recurrent multifocal osteomyelitis (CRMO) was diagnosed.

The patient was administered naproxen (15 mg/kg/day); however, treatment had to be discontinued after 3 months because of the appearance of a putative allergic skin reaction. Ibuprofen was tried as an alternative therapy but was also not well tolerated and caused stomach pain. Sulfasalazine, a disease-modifying antirheumatic drug (DMARD), was then administered at a dose of 40 mg/kg/day. Sulfasalazine therapy was initially accompanied by a 3-week course of oral glucocorticoid treatment (prednisone 2 mg/kg/day for 1 week and then discontinued stepwise by 25% every 5 days). Significant clinical improvement was noted after 1 week; however, follow-up imaging studies, conducted 4 weeks after the initiation of sulfasalazine therapy, showed partial vertebral compressions of thoracic vertebrae numbers 8–10 (Figure 1A, B). MRI of the spine and extremities,

performed after another 8 weeks of sulfasalazine treatment, showed a significant reduction of signal intensity in the T2-weighted images. The lesion in the epiphysis of the distal left femur, previously shown by the technetium bone scan, was also visualized, and thus confirmed, by this MRI. Therapy was discontinued at this time because the patient exhibited a minor elevation in the levels of liver enzymes.

Significant pain recurred 6 months later in the right knee and back. Arthritis was present in the right knee, which showed joint effusion. Since MRI revealed another fracture of the seventh thoracic vertebra, as shown by a local increase in signal intensity in the T2-weighted images, the symptoms were interpreted as a clinical flair. Another short-term glucocorticoid treatment period (prednisone 2 mg/kg/day for 1 week and then discontinued stepwise by 25% every 5 days) was successful in completely alleviating pain and arthritis. Low-dose prednisone treatment (0.1 mg/kg/day) was subsequently continued and a corset was applied to the trunk. Neither naproxen nor sulfasalazine treatment could be reintroduced because of the adverse effects previously experienced by the patient.

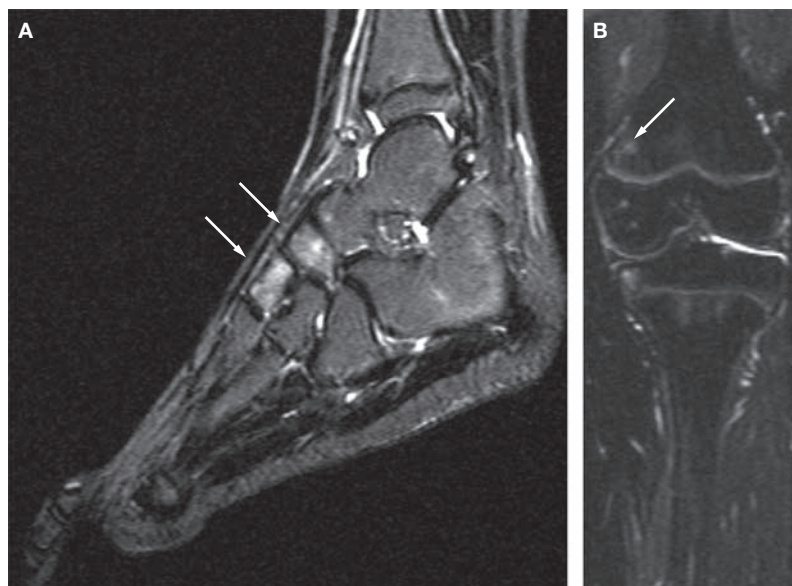
Concomitantly, the patient started to complain about chronic stomach pain. Gastroduodenoscopy

showed mild mucosal inflammation. An infection by *Helicobacter pylori* was ruled out by microbial culture of the gastric mucosal biopsies and a C13 exhalation test; thus, omeprazole therapy was started. Another MRI 3 months later showed a stable situation, without further vertebral compression. Abdominal pain, however, persisted. A colonoscopy was performed (15 months after the diagnosis of CNO was made); considerable inflammation of the colon and terminal ileum was demonstrated. Crohn's disease was confirmed histologically by the presence of mucosal ulcers, fistulas and granulomas. The symptoms of Crohn's disease worsened significantly during the following weeks. A multimodal anti-inflammatory therapy, using local and systemic steroids (budesonide), local and systemic mesasalazine and azathioprine, was initiated after 1 week, when the histological work-up was received. The patient also complained of minor pain (2 on a scale of 0–10) in her feet. MRI was repeated another 1 week later and, as expected, significant compression of thoracic vertebrae (numbers 6–11) was still visible, without signs of active inflammation (Figure 1C, D). There was, however, inflammation of the metatarsal bones (os naviculare and cuneiforme mediale on the right side and os cuneiforme mediale on the left side) and a minor lesion in the left distal metaphysis of the femur (Figure 2). The patient was in clinical remission 4 months later.

### DISCUSSION OF DIAGNOSIS

CNO and, therefore, CRMO are diagnoses of exclusion (Box 1). The patient had repeatedly complained of hip pain; therefore, the differential diagnosis initially included juvenile idiopathic arthritis.<sup>1</sup> Clinical examination, however, provided no evidence for the presence of arthritis.

The laboratory parameters are neither consistent nor predictive in CNO. For example, skin-related disorders, such as palmoplantar pustulosis, psoriasis and acne conglobata, occur in up to 30% of pediatric and adolescent patients with CNO.<sup>2</sup> Radiography of bone lesions in early CNO often does not reveal characteristic changes although, later in the course of the disease, osteoplastic and sclerotic changes of long bones in the extremities and clavicle can be suggestive of CNO. Vertebral compression is also a rather late radiographic sign, but further differential diagnoses of malignancy



**Figure 2** CNO lesions of the extremities. MRI still revealed inflammatory lesions in the tarsal bones and femur 1 year after the diagnosis of CNO was made. T2-weighted images, with TIRM fat suppression, show bone marrow lesions or edema in the navicular and cuboid bones (**A**; arrows), including a small effusion in the ankle joint and minor lesion in the distal left femur metaphysis (**B**; arrow). T1-weighted images after intravenous gadolinium-DTPA administration revealed a signal enhancement of the lesions (not shown). Abbreviations: CNO, chronic nonbacterial osteomyelitis; DTPA, diethylene triamine penta-acetic acid; TIRM, turbo inversion recovery magnitude.

#### Box 1 Differential diagnosis of chronic nonbacterial osteomyelitis and chronic recurrent multifocal osteomyelitis.

##### Juvenile idiopathic arthritis

- Enthesitis-related arthritis or psoriatic arthritis

##### Malignancy

- Osteosarcoma
- Ewing's sarcoma
- Neuroblastoma
- Rhabdomyosarcoma
- Leukemia
- Lymphoma
- Langerhans' cell histiocytosis

##### Benign tumorous bone lesions

- Osteoid osteoma
- Osteoblastoma

##### Bacterial subacute or chronic osteomyelitis

##### Bone bruise or fracture

##### Osteonecrosis or osteoporosis

##### Hypophosphatasia

and osteoporosis must be considered on presentation of this finding. The diagnosis of

CNO must, therefore, rely on the clinical picture, in addition to imaging studies.

T2-weighted MRI sequences with fat-suppression techniques (e.g. turbo inversion recovery magnitude and short-inversion-time inversion recovery) are useful at the initial and follow-up examinations. In addition, enhancement with gadolinium-diethylene triamine penta-acetic acid provides further insights into the inflammatory activity of the lesions.<sup>3</sup> Technetium bone scans are helpful in the initial diagnostic setting because clinically silent CNO lesions are often present. Total-body MRI and technetium bone scans seem to be equally useful for defining the overall presence of lesions. MRI is somewhat more sensitive for showing bone marrow edema; however, whole-body MRI is currently unavailable in most institutions.

In a considerable number of patients, diagnostic imaging alone does not rule out malignancy; therefore, biopsy should be considered, especially because it is often difficult to make a definite distinction between oncologic bone lesions and lesions associated with CNO.<sup>3,4</sup> Osteosarcoma, Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, leukemia, Langerhans' cell histiocytosis, osteoid osteoma and osteoblastoma should all be regarded as differential diagnoses. Although most of these diagnoses can usually be ruled out by the histological work-up, osteoid osteoma and osteoblastoma can have significant inflammatory components; therefore, a biopsy that is not representative of the whole lesion might be misleading. Imaging techniques, such as technetium bone scans and total-body MRI, are helpful in selecting a suitable site for biopsy. In choosing the biopsy location, functional and cosmetic aspects must be considered. Biopsies should only be performed for diagnostic purposes and clinicians should not aim to excise the whole lesion; this could lead to unnecessary functional impairment and scarring.<sup>5</sup>

The need for a diagnostic biopsy has repeatedly been questioned in the management of CNO. A diagnosis of CNO seems quite probable if the bone lesions have been present for 6 months or longer and the patient also presents with typical skin lesions. In this case, a biopsy might be omisable; however, a short-term clinical follow-up, including repetition of imaging studies, is mandatory. Unifocal lesions, which have a solely osteolytic appearance and involve the surrounding tissue structures, must be biopsied to exclude malignancy.<sup>5</sup>

The decision to take a biopsy should be carefully considered for every patient. In addition to revealing malignancy, a biopsy can reveal subperiosteal bone formation, which is a sign of chronic inflammation. Granulocytes might be apparent in early lesions, followed predominantly by lymphocytes, plasma cells and monocytes. In later stages, fibrotic changes and hyperostosis are present. A thorough histological work-up of the whole biopsy is recommended to document these features, which might be present in different areas of a single biopsy.

Although early reports considered *Propionibacterium acnes* to be a relevant pathogen in CNO, later studies have not confirmed this. In addition, *Bartonella henselae* rarely causes multifocal osteolytic inflammatory lesions. Treatment strategies involving antibiotics have not proven effective in the long term, and, in several studies, no consistent infectious agent could be detected in lesions in pediatric patients using 'state-of-the-art' microbial techniques.<sup>2,5-8</sup> CNO cannot be distinguished from acute or subacute bacterial osteomyelitis using a histological examination alone.<sup>5</sup> An extensive microbial work-up of the tissue biopsy (long-term cultures), including polymerase chain reaction that targets eubacteria and mycobacteria, is thus essential to establish the diagnosis of sterile inflammation.<sup>5</sup>

Although the CRMO form of CNO has been recognized as a clinical entity for more than 30 years,<sup>9</sup> its origin and pathogenesis are unclear. Autoinflammatory diseases, autoimmunity, errors of metabolism and post-infectious reactive inflammation are all potential areas for the focus of research. CNO might be linked to enthesitis-related arthritis (ERA; also called 'adolescent spondyloarthropathy') and psoriatic arthritis. Several studies have identified arthritis as a concomitant feature in up to 80% of patients.<sup>2</sup> Diagnostic criteria for ERA might not be present at the onset of symptoms; however, ERA and psoriatic arthritis have been reported in the long-term follow-up of several cohorts of children and adolescents, despite anti-inflammatory treatment.<sup>2,7,8,10</sup> The degree of arthritis at the time of diagnosis and during the course of CNO might be underestimated in the literature. Of note, two patients have recently been described to have developed inflammatory bone lesions similar to CRMO while suffering from hypophosphatasia, a genetically inherited metabolic bone disease.<sup>11</sup>

The association of CNO with chronic inflammatory bowel disease has previously been well documented and seems to involve around 10% of CNO patients.<sup>6,12,13</sup> CNO and Crohn's disease are chronic auto-inflammatory syndromes. In patients with familial Crohn's disease, mutations in the caspase activation and recruitment domain 15 gene (*CARD15*), which encodes the nucleotide-binding oligomerization domain 2 (NOD2) protein, have been described. NOD2 is a cytoplasmic protein involved in intracellular pathogen resistance and regulation of inflammation.<sup>14,15</sup> Polymorphisms in the tumor necrosis factor (TNF) promoter have also been associated with a severe form of Crohn's disease.<sup>16</sup> Similar mutations have not yet been described in CNO; however, chronicity, the recurrence of bone and joint inflammation, and the association with psoriasis in patients using TNF antagonists<sup>17</sup> suggest an auto-inflammatory and rheumatologic cause.

A putative mouse model exists for CNO.<sup>18</sup> Genetic analysis of CNO patients initially suggested a chromosomal link to a similar region of the human genome in a limited number of patients,<sup>19</sup> but these findings have not yet been confirmed.

In adulthood, a similar entity to the CRMO form of CNO has been termed 'SAPHO syndrome' (consisting of synovitis, acne, pustulosis, hyperostosis and osteitis).<sup>6</sup> Not all of these characteristic symptoms must be present for the diagnosis, however. The principal management strategy for SAPHO syndrome does not seem to be different to that for CNO. Similar to CNO, SAPHO syndrome can have overlapping symptoms with rheumatologic conditions, including psoriasis arthritis and spondyloarthritis.

### TREATMENT AND MANAGEMENT

There is a consensus that NSAIDs are beneficial for patients with CNO. Since naproxen is widely used,<sup>4</sup> it is important to recognize pseudoporphyria as a typical side effect of this drug.<sup>20</sup> A considerable number of patients receive antibiotics; however, these agents should be discontinued if the biopsy proves to be sterile. DMARDs, particularly sulfasalazine, are usually considered in patients with frequent relapses or if NSAIDs must be discontinued because of ineffectiveness or adverse effects. Oral glucocorticoids can be used as a bridging agent for a limited period of time or low-dose concomitant treatment. In this patient, the combination of

a DMARD and prednisone seemed reasonable because the disease manifestations were severe. If chronic inflammatory bowel disease is present concomitantly with CNO, the treatment strategies must focus on both clinical entities. For CNO, multiple therapies have been used, including immunosuppressants (corticosteroids, methotrexate and TNF blockers<sup>17</sup>), immunomodulators (intravenous immunoglobulins, interferon  $\gamma$ , interferon  $\alpha$ , colchicine and dapsone) and hyperbaric oxygen, in addition to NSAIDs. A combination of azithromycin, calcitonin and bisphosphonates has also been tried.<sup>21</sup> Bisphosphonates or TNF blockers currently seem to be the next choice if the treatment concept mentioned above is unsuccessful. There is an urgent need for controlled and randomized trials that evaluate treatment strategies and compare their short- and long-term effects.

### CONCLUSIONS

CNO includes unifocal and multifocal bone lesions. The latter form is known as CRMO. CRMO and other forms of CNO can evolve into spondyloarthritis and can involve the skin, eyes, lungs and gastrointestinal tract. NSAIDs are recommended as a first-line therapy; DMARDs, steroids, bisphosphonates and TNF blockers have also been used. Multidisciplinary diagnostic and therapeutic approaches are necessary to cover the clinical variability of CRMO and to ensure that this syndrome is managed effectively.

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**Competing interests**

The authors declared no competing interests.

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