A case of adult chronic recurrent multifocal osteomyelitis successfully treated with neridronate

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Summary

Chronic Recurrent Multifocal Osteomyelitis (CRMO) is an inflammatory bone disease characterized by sterile osteomyelitis. CRMO is characterized by the presence of multiple and recurrent foci of sterile osteomyelitis, usually involving the metaphysis of long bones, pelvis, clavicle and jaw. Systemic symptoms may or may not be present (1). CRMO is considered an autoinflammatory bone disorder but the precise pathophysiology remains unknown and the molecular pathogenesis of sporadic CRMO remains undetermined. However, recent findings indicate that an imbalance between pro (Interleukin [IL] 6, Tumor Necrosis Factor α [TNF-α]) and anti-inflammatory (IL-10) cytokines may be involved in the molecular pathology of the disease. This imbalance may be the key feature of the disease since TNF-α and IL-6 contribute to bone resorption and remodelling by inducing the Receptor Activator of NFκB Ligand (RANKL) on stromal cells and favouring osteoclasts differentiation and activation, while IL-10 can suppress RANKL-induced effects on osteoclasts. As a consequence, inflammatory bone lesions may appear (2).

Although CRMO occurs mainly at a young age, studies have shown that the disease remains active in 25% to 59% of cases after a median follow-up of more than 10 years (1). CRMO was long believed to resolve without leaving any consequential residual impairments; recent data suggest, however, that physical impairments may persist in up to 50% of patients (3).

Clinical presentation

A 24-year-old semi-professional male basketball player was admitted to the University of Verona, Rheumatology Division with a history of fever of unknown origin (up to 38°C) lasted 6 months, associated with malaise, fatigue and weight loss. On physical examination, no relevant feature was found, except tenderness elicited by the palpation over lateral side of the knee and distal thigh. At that time, the patient needed to take continuous full-dosage treatment with Cyclooxygenase-2 selective inhibitor (COXIB), specifically etoricoxib 90 mg daily, with only partial benefit. In addition, symptoms invariably quickly flared back after any interruption of COXIB treatment. Laboratory studies showed increased inflammatory markers (Erythrocyte Sedimentation Rate [ESR] 52 mm/h, C-reactive protein [CRP] 59 mg/L). Bone marker serum levels were in range; total alkaline phosphatase was within limits (102 U/L, reference range 50-130 U/L) and serum carboxy-terminal collagen crosslinks moderately elevated (0,693 ng/mL, reference range 0,150-0,450 ng/mL). Immunological tests (including autoantibodies) were completely negative and serial blood cultures and Quantiferon Tb-gold were negative as well.

To exclude a paraneoplastic manifestation of a concurrent malignancy, an 18-Fluorodeoxyglucose (FDG) Positron
emission tomography-computed tomography (PET-CT) was performed, showing only a mild hyper-accumulation on few mediastinal lymph nodes (of note the patient was an active smoker). A bone marrow biopsy was performed afterwards and ruled out any haematological disorder. A bone scintigraphy with 99mTc-methylene diphosphonate was performed and, interestingly, showed hyper-accumulation at the distal right femoral diaphysis and at the right humeral head (Figure 1). X-rays of these skeletal sites did not show any pathological changes. On the contrary, the Magnetic Resonance Imaging (MRI) of the knee and the shoulder reported various areas of altered signal (Figures 2, 3). A hypointense in T1 and hyperintense in STIR sequences area (9x1x1.5 cm) with sclerotic margins located at the distal diaphysis of the right femur was documented. Similar findings were also observed at the right humeral head and smaller areas with the same features were recognized at the ribs and sternum too.

The overall clinical, laboratory and radiological imaging features led to the diagnosis of CRMO. To limit the need for anti-inflammatory treatment and to improve the overall clinical condition of the patient, we then decided to administer intravenous therapy with bisphosphonates, using IV neridronate 100 mg for four consecutive days. This dosage is the one generally used in the treatment of Chronic Regional Pain Syndrome-1 and it is double the dosage used in the treatment of Paget’s disease of bone (4). After few weeks, the patient showed an outstanding improvement of the symptoms and normalization of both CRP and ESR. Clinical remission was stable and, within 12 months, the COXIB treatment was tapered and suspended. CRP and ESR remained within the normal range during the follow-up, and the progressive resolution of the lesions previously documented at MRI was shown after 12 and 24 months from the treatment (Figures 2, 3). Indeed, 24 months after the administration of i.v. neridronate, the patient was still asymptomatic (with also a satisfactory return to sport) with no need for stable treatment with COXIB.

Investigations

CRMO typically presents with non-specific musculoskeletal complaints such as pain, tenderness, swelling, or limited range of motion, while systemic symptoms are not always present. The pain tends to predominate in the metaphysis and epiphyses of long bones, the most common being the distal tibia, proximal tibia, pelvis, proximal femur, clavicle, and calcaneus (5). Conversely, our patient did not complain significant musculoskeletal symptoms, except for mild tenderness of the right knee, almost overlooked at the beginning of our diagnostic workup in consideration of the intense history of sport practice of the subject. Thus, the initial issue of our diagnostic workup was the relative paucity of symptoms except the systemic ones such as fatigue, malaise and fever. The tenderness localized at the knee was even followed by negative X-rays which, in fact, in the early phases of the disease are often normal (5) while in the advanced stage of the disease plain radiographic findings are mixed lytic and sclerotic bone lesions, typically localized at the metaphyses (6). The PET-CT was not helpful too, showing only a slight hypermetabolism of some lymph nodes. Recently, a case of CRMO diagnosed with PET-CT has been described in the literature, reporting a man with a large bulky and destructive lesion with a positive uptake (7). However, in our subject, probably no lesion was severe and extensive enough to emit a sufficiently intense signal. Bone scintigraphy can be useful for identifying asymptomatic lesions and documenting the extension of the disease involving several bones. It can be especially useful in areas that are difficult to evaluate with plain radiography, such as the pelvis and vertebrae (8). The bone scan in this particular case was slightly positive in just two areas but the hint was sufficient to make us perform a more detailed exam such as MRI. On MRI, active disease exhibits edematous marrow changes, including T1 hypointensity and hyperintensity on both T2 and STIR sequences (9). The recently developed whole-body STIR sequences could be very helpful for determining the extent of disease, including clinically occult CRMO sites, with sensitivity comparable to PET-CT and bone scintigraphy. Due to their high accuracy, these sequences may also be used for follow-up and the assessment of the treatment response (10). Even though MRI contrast agent administration is not necessary in CRMO setting, when performed, involved areas manifest early and intense contrast enhancement (9).

To date, there are no validated diagnostic criteria for CRMO, even though they have been proposed in the past (11) and the diagnosis is done on basis of the clinical, laboratory and imaging features.
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Not rarely, biopsy is needed. Jansson et al. recently developed a score to assist in the diagnosis of CRMO while diminishing the number of unnecessary bone biopsies (11). Since our patient presented almost all the typical features of the disease (fulfilling almost completely the score cited above), no bone biopsy of the lesions was performed.

Treatment and discussion

Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered to be the first-line treatment of CRMO, followed by systemic corticosteroids and anti-TNF-α (5, 12, 13). Experience with synthetic immunosuppressive drugs (ie. methotrexate, sulphasalazine, colchicine) is anecdotal (14). Bisphosphonates treatment has already been used with good results and has been proposed to be the treatment of choice in those patients not able to achieve remission with continuous NSAIDs administration (which happens quite frequently) (1, 15). Pastore et al. previously reported the usage of neridronate in CRMO in patients younger than 18 years old, reaching complete remission in 7 out of 11 cases studied and partial remission in other 3 cases (15). To our knowledge, this is the first report of an adult patient with CRMO treated with intravenous neridronate, an amino-bisphosphonate which has already shown to be effective for the treatment of Paget’s disease of the bone, CRPS-1 and osteogenesis imperfecta (4) (in Italy neridronate is not licensed for the treatment of CRMO). The use of amino bisphosphonates is justified from a physiopathological perspective. These drug are able to potently inhibit osteoclast directly and they may also exert anti-inflammatory effects, secondary to their ability to suppress proinflammatory cytokines, such as TNF-α, IL-6 and IL-1 (16, 17), therefore blocking on many different levels the inflammatory mechanism perpetrating bone inflammation in CRMO.

Considered the severity of the symptoms despite continuous etoricoxib treatment, we chose to administer neridronate as per protocol for CRPS-1 achieving, within few months, complete clinical and laboratory remission.

Figure 2 A-F - Right knee MRI acquired before, after 12 and after 24 months from treatment with neridronate. Coronal T1 - W (A) and TIRM (D) images acquired before the treatment demonstrate a wide and multi-focal signal intensity alteration of the bone marrow in the distal femoral diaphysis with low-signal intensity on the T1-weighted images and high intensity on TIRM (arrows). T1-W images performed 12 (B) and 24 months (C) from the first MRI, show a progressive healing with final complete response. Same findings are visible on TIRM images (E, F).
As previously reported (15), the profile of efficacy in pediatric patients was quite good. To our knowledge, this is the first time that neridronate has been used for the treatment of an adult individual affected by CRMO with success, suggesting that it might be considered as an option for the treatment of CMRO in adult patients as well.

Consent
Written informed consent for the case to be published (including images, case history and data) was obtained from the patient for publication of this case report, including accompanying images.

Disclosure statement
Angelo Fassio reports personal fees from: Abiogen Pharma and Novartis.
Maurizio Rossini reports personal fees from: AbbVie, Abiogen, Amgen, Eli-Lilly, Novartis, Pfizer, Sanofi, Sandoz, UCB, BMS. Ombretta Viapiana reports personal fees from: Novartis, Abbvie, Eli-Lilly, Sanofi Genzyme.

Davide Gatti reports personal fees from: Abiogen, Amgen, Janssen-Cilag, Mundipharma, Pfizer.
All the other Authors have no conflict of interest to declare.

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