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CASE REPORT

# Zoledronate-Associated Seizure in Chronic Recurrent Multifocal Osteomyelitis

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**ABSTRACT:** Chronic recurrent multifocal osteomyelitis (CRMO) is an auto-inflammatory disease characterised by sterile bone lesions. We report a case of a seven-year-old female patient who presented at a university hospital in 2010 and 2018 with CRMO. While the most promising results have been observed in patients under treatment with bisphosphonates (BPs), the initial decision to treat the current patient with a dose of zoledronic acid every six months was recalled as the patient developed tonic-clonic seizures immediately following the second dose BP administration. Following recall, the patient maintained a prompt response at follow-up and her disease remained controlled with non-steroidal anti-inflammatory drugs. The current case report speculates a possible relationship between BP use and a possible seizure threshold reduction, thereby emphasising the need for closer monitoring when BPs are used.

***Keywords:*** Chronic Recurrent Multifocal Osteomyelitis; Bisphosphonate; Tonic-clonic seizure; Case Report; Tunisia.

Chronic recurrent multifocal osteomyelitis (CRMO) or chronic non-bacterial osteitis is an auto-inflammatory rather than an autoimmune disease characterised by sterile bone lesions. Described in 1972 by Giedion *et al.*, this disease is characterised by recurrent inflammation of multiple bones reflecting the presence of aseptic osteitis.[1] CRMO is considered by many medical researchers as the paediatric form of synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome.[2] This inflammatory condition results from an activation of the innate immune system leading to the presence of pro-inflammatory cytokines.[3] The diagnosis of CRMO depends on the clinical and radiographic data. Bone biopsy is often required in order to exclude infection, neoplasia or Langerhans' cell histiocytosis.[1] Although, the treatment of CRMO is currently not classified, the most promising results have been observed in patients under treatment with bisphosphonates (BPs).[4] Here we describe the case of a patient with CRMO who developed a seizure post-BP administration.

## Case Report

A seven-year-old female child presented to the Department of Rheumatology at a university hospital in September 2010, with symptoms of insidious pain in the right hip and scapula as well as swelling affecting the left ankle. There were no extra-articular manifestations, cutaneous involvement or inflammatory bowel disease. Subsequently, the patient's physical activity decreased as she developed a limp in her right leg. The erythrocyte sedimentation rate (ESR) was 50 mm/h (reference range: 0–6 mm/h). She had negative antinuclear antibodies, rheumatoid factor and anti-citrullinated protein antibodies. Other laboratory investigations such as human leukocyte antigen B-27, Lyme's disease, anti-streptolysin O serology and tuberculosis were also negative. A radiograph of the hip showed a lytic lesion in the right acetabular roof [Figure 1]. A magnetic resonance imaging (MRI) scan of the whole body showed low signal on T1-weighted images. A high signal was seen on the T2 short-tau inversion recovery (STIR) sequence in the left greater trochanter at the point of insertion in the *gluteus medius and obturator externus* muscles with trochanteric bursitis and edema of the entire right iliac wing [Figure 2]. A scintigraphy was then performed and it illustrated an intense uptake of radioisotopes in the left ilium, femurs and seventh right costo-vertebral junction. At this stage two possible diagnoses were discussed: histiocytosis and CRMO. The bone biopsy of the hip ruled out chronic infection and malignancies and showed bone remodelling and non-specific inflammatory changes, all supporting the diagnosis of CRMO.

The patient was treated with a non-steroidal anti-inflammatory drug (NSAID)—diclofenac— at a dose of 75 mg twice a day, resulting in the control of pain and regression of acute phase reactants (ESR: 7, C-reactive protein: 4). She maintained a prompt response until 2018, when she returned to the current department complaining of a sterno-clavicular joint swelling and right hip pain.

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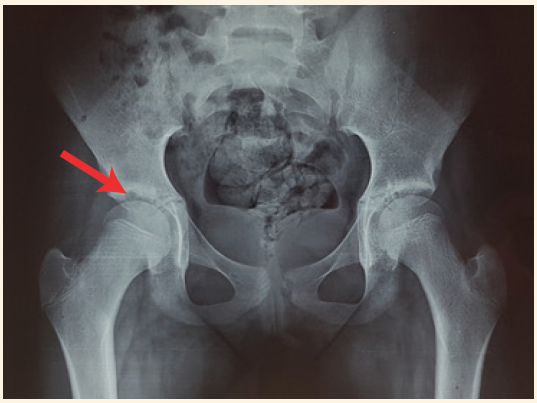

**Figure 1:** X-ray of the hip showing a lytic lesion with surrounding sclerosis in the right acetabular roof (arrow) of a seven-year-old female patient.

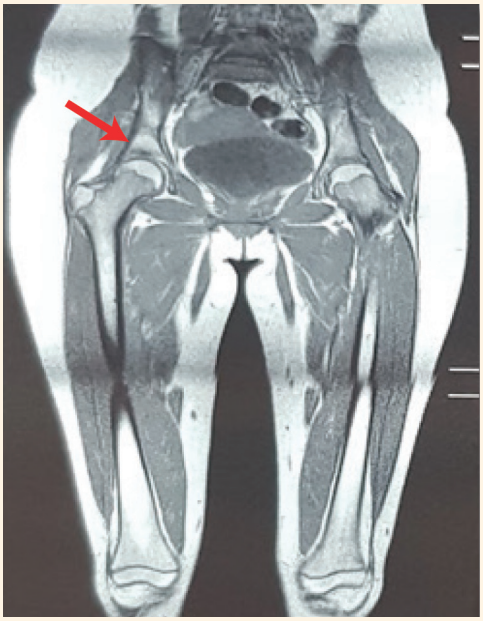

**Figure 2:** A magnetic resonance imaging scan in T2 sequence showing signal abnormalities in the left greater trochanter and right acetabulum (arrow) of a seven-year-old female patient.

A whole-body MRI scan showed sacroiliitis with erosions in the sacral rim and an edema at the left ischium. A trial of two other NSAIDs and prednisolone with a maximum dose of 40 mg/day for 10 days offered the patient limited symptomatic improvement. Following the consensus treatment for CRMO refractory to NSAIDs, a decision was made to switch to administering an intravenous dose of zoledronic acid (ZA) at 0.025 mg/kg every six months.[5] The first dose was given in 2018. A good response was obtained with resumption of mobility of the right hip and reduction of pain from 8 to 6, according to the visual analogue scale.

After six months, the patient relapsed, experiencing pain in the hip and sterno-clavicular joint. As soon as the infusion of the second dose of ZA was initiated, the patient developed generalised tonic-clonic seizures and retrovulsion of the eyeballs that lasted less than one minute. There were no signs of tongue biting, urinary incontinence or a postictal status. The infusion was stopped immediately. The blood pressure reading—initially recorded as 80/60 mmHg—was rechecked and stood at 110/60 mmHg and the blood glucose stood at 5 mmol/L with a heart rate of 60 beats per minute. The electrocardiogram showed no disturbances. Laboratory tests taken before and after the event, such as those taken for blood sugar and serum calcaemia levels were normal. Furthermore, the patient had a brain MRI that ruled out not only the common causes of seizures but also neurological involvement due to CRMO. An electroencephalogram was not performed.

The role of the drug was suspected due to the suggestive delay and spontaneous resolution of symptoms after it was stopped. At follow-up, the patient maintained a prompt response and her disease remained controlled with NSAIDs. Methotrexate would be considered if the patient experiences future flares. More importantly, the patient did not experience any other episodes of seizure and hence did not justify introducing an anticonvulsant medication.

Written consent was obtained from the patient's father for publication of this report.

## Discussion

Chronic non-bacterial osteomyelitis encompasses a wide clinical spectrum of "monofocal bone inflammation to severe chronically active or recurrent multifocal bone inflammation".[4] CRMO represents some of the most severe presentations. Due to the variability of symptoms, epidemiological data is sparse and taken from small case series and cohorts. CRMO mostly affects children and adolescents with the peak age of onset ranging between 7 and 12 years of age.[6] In the absence of diagnostic criteria, experts rely on exclusion of other differential diagnosis including infection, malignancy and Langerhans cell histiocytosis for the diagnosis of CRMO.[4] In the current case, the diagnosis was made based on a clinical assessment in conjunction with acute phase reactants, MRI data and biopsy ruling out differential diagnosis.

Presently, there is no consensus regarding the treatment of patients with CRMO. It usually involves NSAIDs, corticosteroids (CS), disease-modifying anti-rheumatic drugs, anti-tumour necrosis factor agents or bisphosphonates.[4] However, the most efficient treatment and its duration is yet to be determined as large prospective clinical trials are lacking. The

current patient was treated with NSAIDs as a first-line treatment but the condition intensified after eight years. In the literature, a relapse after two years was observed in more than half of the cases.[7] Although CS appeared to decrease pain and control inflammation activity, they were ineffective in maintaining long-term remission as symptoms reoccurred once CS were stopped.[4] Recently, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) developed a consensual treatment plan for patients' refractory to NSAIDs.[5] One of the consensual plans included a monthly dosage of pamidronate at 1 mg/kg/dose or ZA with an initial dose of 0.0125–0.025 mg/kg every 3–6 months. An increase in the per pulse dosage to 0.05 mg/kg/dose (maximum: 4 mg/dose) may be required depending on disease activity.[5] The current patient was treated with ZA (following the above recommendations) and showed marked improvement after the first infusion. However, the beneficial effect could not be fully evaluated as the treatment was stopped when she developed a side-effect at the second infusion.

To the best of the authors' knowledge, this is the first reported case of seizure associated with BP administration in children with CRMO. Indeed, treatment-related cases of seizures occur mainly due to ZA infusion in connection with low level of calcium or glucose in elderly patients.[8–10] Overall, five cases of seizures occurring soon after BP administration have been reported.[11] One case reported a seizure in an 87-year-old man with metastatic prostate cancer receiving ZA, with the patient's symptoms normalising rapidly after correction of serum calcium levels.[9] In another case, an 80-year-old woman suffering from post-menopausal osteoporosis developed a hypoglycaemic seizure 30 minutes after the infusion.[10] The remaining ZA was infused after the glucose level was corrected with good outcomes. In another case, the patient developed a febrile seizure due to a central nervous system infection.[11] Notably, all of the patients had a pre-existing vitamin D deficiency, a well-known risk factor for BP-induced hypocalcaemia. Unlike previously reported cases, Shalit and Tripto-Shkolnik described a seizure after ZA infusion in a 63-year-old woman with a history of well-controlled epileptic disorder.[11] Her creatinine, calcium, parathyroid hormone and vitamin D levels were all normal. Similar to the current case, mineral metabolism abnormality and infection as the precipitating factors for the seizure were unlikely.

The role of the drug was suspected due to the suggestive delay and spontaneous resolution of symptoms after it was stopped. As part of the prevention of side-effects, the CARRA has recommended prescribing a supplement of calcium and vitamin D before initiating ZA, especially in patients at risk of failure of compensatory mechanisms as vitamin D deficiency.[5] The current case report, along with the other scarcely available reports, raises questions about a possible relationship between BP use and a possible seizure threshold reduction. This would impact the clinical management of these children as it stresses on the need for closer monitoring when BPs are used.

## Conclusion

The present case suggests that although BP therapy can be of benefit to patients with CRMO, adverse events may occur. A close surveillance for the occurrence of this phenomenon would be required for adequate clinical management.

### AUTHORS' CONTRIBUTION

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work. All authors approved the final version of the manuscript.

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