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Zoledronate Associated Seizure in Chronic Recurrent Multifocal Osteomyelitis

Saoussen Miladi, *Yasmine Makhlouf, Alia Fazaa, Mariem Sallemi, Selma Chekili, Kawther Ben Abdelghani, Ahmed Laatar

Department of Rheumatology, Mongi Slim Hospital, Tunis, Tunisia; University Tunis El Manar, Tunis, Tunisia.
**Corresponding Author's e-mail: yasmine.mkhlouf@gmail.com*

Abstract

Chronic recurrent multifocal osteomyelitis (CRMO) is an auto-inflammatory disease characterized by sterile bone lesions. We report a case of a patient with CRMO who developed a seizure post bisphosphonate administration. Although, the treatment of CRMO is currently not codified, the most promising results have been observed in patients under treatment with bisphosphonates.

Keywords: CRMO; Bisphosphonate; tonico-clonic seizure.

Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) or chronic non-bacterial osteitis is an auto-inflammatory rather than an autoimmune disease characterized by sterile bone lesions. Described in 1972 by Giedion et al., this disease is characterized by recurrent inflammation of multiple bones reflecting the presence of aseptic osteitis [1]. CRMO is considered by many authors as the pediatric 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 relay 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 (BP) [4]. Here by we describe a case of a patient with CRMO who developed a seizure post BP administration.

Case Report

A 7-year-old girl presented to our department 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 especially no cutaneous involvement or inflammatory bowel disease (IBD). Subsequently, her 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). She had negative antinuclear antibodies (ANA), rheumatoid factor (RF) and anti-citrullinated protein antibodies (anti-CCP). Other laboratory investigations such as human leucocyte antigen B27, Lyme's disease, Anti-streptolysin O serology and tuberculosis were also negative. Radiograph of the hip showed a lytic lesion in the right acetabular roof (Figure 1). An MRI of the whole body showed low signal on T1-weighted images and high signal on T2 short tau inversion recovery (STIR) sequence in the left greater trochanter, at the insertion of gluteus medius and obturator externus muscle with trochanteric bursitis as well as edema of the entire right iliac wing (Figure 2). A scintigraphy was then performed and illustrated an intense uptake of radioisotopes in the left ilium, femurs and in the 7 th right costo-vertebral junction. At this stage two diagnoses were discussed: histiocytosis and CRMO. The bone biopsy of the hip ruled out chronic infection and malignancies, and showed bone remodeling and non-specific inflammatory changes; which supported the diagnosis of CRMO.

The patient was treated with non-steroidal anti-inflammatory drugs (NSAIDs): diclofenac at a dose of 75 mg twice a day, resulting in the control of the pain and the regression of the acute phase reactants: ESR=7, CRP=4. She maintained a prompt response, until 2018, when she complained of a sterno-clavicular joint swelling and a right hip pain.

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

relapsed in the hip and sterno-clavicular joint. Upon initiating the infusion of the second dose of ZA (first drops), the patient developed generalized tonico-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 was 80/60 mmHg rechecked at 110/60 mmHg, the blood glucose was at 5 mmol/L, the heart rate was at 60 bpm. ECG showed no disturbances. Laboratory tests before and after the event such as blood sugar, serum calcemia level were normal. Furthermore, the patient had a brain MRI that ruled out not only common causes of seizures but also neurologic involvement due to CRMO. An electroencephalogram was not performed. The role le 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 will experience future flares. More importantly, she did not experience other episodes of seizure which did not justify introducing an anticonvulsant medication. Written consent was obtained from the patient's father for publication of this report.

Discussion

To our knowledge, this is the first reported case of seizure associated with BP in children with CRMO. 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 the most severe presentations [4]. Because of the variability of the symptoms, epidemiological data is sparse, and taken from small case series and cohorts. CRMO affects mostly children and adolescents with a peak of onset ranging between 7 and 12 years of age [6]. In the absence of diagnostic criteria, the diagnosis of CRMO rely on exclusion of other differential diagnosis including infection, malignancy, and Langerhans cell histiocytosis [4]. In our case, the diagnosis was made according to a beam of arguments: clinical assessment in conjunction with acute phase reactants, MRI data and biopsy ruling out differential diagnosis.

There is no consensus regarding the treatment of patients with CRMO. It usually involves NSAIDs, corticosteroids (CS), disease-modifying anti-rheumatic drugs (csDMARDs), anti-tumor necrosis factor (anti-TNF agents), or bisphosphonates [4]. However, the most efficient treatment and its duration is yet to be determined as large prospective clinical trials are lacking. Our patient was treated with NSAIDs as a first-line treatment but flared after 8 years.

In the literature, a flare after 2 years was observed in more than half of the cases [7]. Moreover, CS appeared to decrease pain and control inflammation activity [4]. However, they are ineffective in maintaining long-term remission as symptoms reoccur once CS are stopped [4]. Recently, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) [5] developed a consensual treatment plan for patients' refractory to NSAIDs. One of the consensual plans included "Pamidronate with a dosage of 1 mg/kg/dose per month or ZA with an initial dose of 0.0125- 0.025 mg/kg every 3-6 months". An increase in the dose to 0.05 mg/kg/dose (maximum 4 mg/dose) per pulse may be required depending on disease activity [5]. Following these recommendation, our patient was treated with ZA with a 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.

In the literature, there are no other reported cases of seizure associated with BP in CRMO children. Indeed, treatment-related cases of seizures are mainly ZA infusion in connection with low level of calcium or glucose in elderly patients [8,9,10]. Overall, 5 cases of seizures occurring soon after BP administration were reported [11]. One case reported a seizure in a 87-year-old man receiving ZA in a metastatic prostate cancer. "The patients' symptoms normalized rapidly after correction of serum calcium levels" [9]. In another case, an 80-year-old woman suffering from a post-menopausal osteoporosis, developed a hypoglycemic seizure 30 minutes after the infusion. The remaining ZA was infused after the glucose level was corrected with good outcome [10]. In another case, the patient developed a febrile seizure due to a central nervous system infection. More importantly, all of them had a pre-existing vitamin D deficiency, which is a well-known risk factor for BP-induced hypocalcaemia [11]. Unlike previously reported cases, Shalit et al, described a seizure after ZA infusion in a 63-year-old woman with a history of well-controlled epileptic disorder. Her creatinine, calcium, parathyroid hormone, and vitamin D were normal. Similar to our case, mineral metabolism abnormality as swell as infection as the precipitating factors for the seizure were unlikely [11].

The role of the drug was suspected due to the suggestive delay and the spontaneous resolution of symptoms after it was stopped. As part of the prevention of side effects, the CARRA 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]. We believe that our case, along with the other scarce reports, raises questions about a possible relationship between BP use and a possible seizure threshold reduction. This impacts the clinical management of these children as it stresses out the need for closer monitoring when BP 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 phenomena should be worthy 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.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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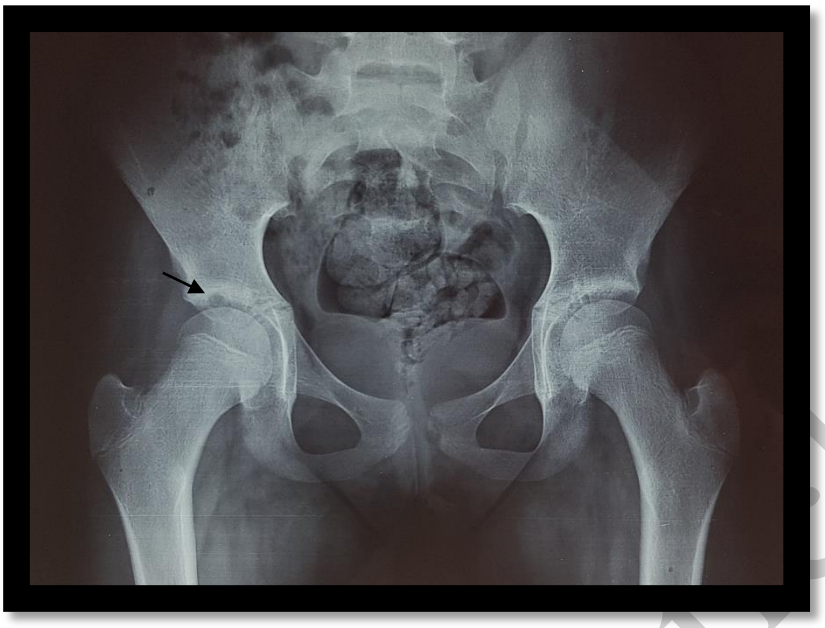

Figure 1: X-ray of the hip showing a lytic lesion with surrounding sclerosis in the right acetabular roof.

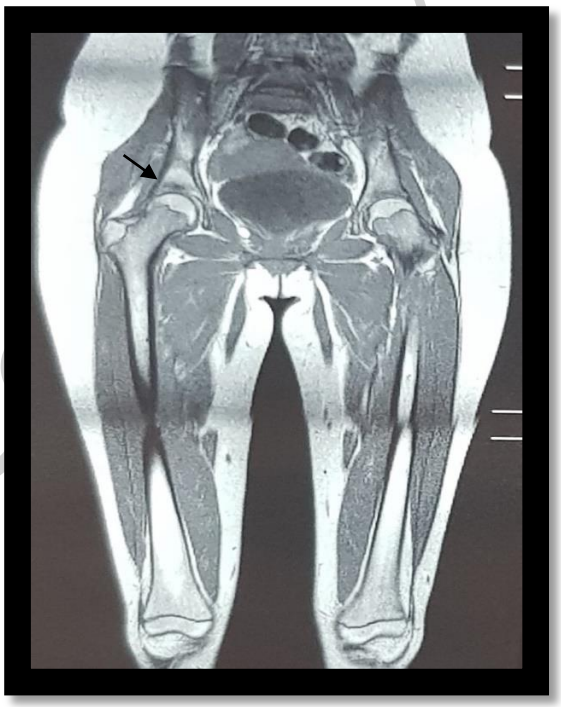

Figure 2: A whole-body MRI in T2 sequence showing signal abnormalities in the left greater trochanter and right acetabulum.