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Case Report

Zoledronic acid is effective in the management of migratory osteoporosis unresponsive to conservative treatment and risedronate: A case report

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Abstract

We describe a case of a 55-year-old woman with migratory osteoporosis (MO) which initially presented as pain with bone marrow edema (BME) evident in magnetic resonance imaging (MRI) of the left ankle and was managed with non-weight-bearing (NWB). The patient was already treated with per os risedronate for postmenopausal osteoporosis. After significant initial improvement, pain and BME relapsed in the left ankle and additionally expanded to insult the foot, while 3 months later the left hip was also affected. Since the combination of NWB, analgesics and risedronate had failed to control the disease, a single infusion of 5mg zoledronic acid (ZA) was administered. One month later the pain in all affected sites was disappeared and BME resolved as shown by MRI performed 3.5 months following ZA infusion. The patient, eventually, returned to her daily routine. This case underlines the effectiveness of ZA in MO and the need for more aggressive treatment in this disease.

Keywords: Bone Marrow Edema, Magnetic Resonance Imaging, Migratory Osteoporosis, Risedronate, Zoledronic Acid

Introduction

Transient osteoporosis (TO), also referred as "primary bone marrow edema syndrome", is a rare metabolic bone disorder with acute or subacute onset, that primarily affects the hip, the knee, the ankle or the foot, causing local bone marrow edema (BME)[1]. Patients are usually middle-aged individuals (preferably males) or pregnant women and the main clinical manifestation is severe lower extremity pain that exacerbates on weight-bearing. The gold standard imaging modality for the diagnosis of TO is magnetic resonance imaging (MRI), in which a homogenous regional signal of increased T2, STIR or decreased T1 intensity is found in the bone marrow. TO is a diagnosis of exclusion, as secondary bone marrow edema can be provoked by many stimuli[1]. Moreover, a TO episode can resemble a flare of an inflammatory arthritis[2]. In about 30% of TO patients a recurrence of the disease in the same area or a migration to another region can occur and this condition is known as migratory osteoporosis (MO)[3-5]. Only scarce data are available about the management of patients with MO. As MO is characterized by locally accelerated bone turnover and subsequent bone loss, bisphosphonates have been used in several MO cases. The severity of the local bone metabolism disturbance in MO indicates that the rationale of using more potent bisphosphonates in these patients might be reasonable. We present here a case of a woman with MO in whom a single zoledronic acid (ZA) infusion alleviated the symptoms and normalized MRI while the combination of weight-bearing avoidance and risedronate had previously failed to prevent two subsequent episodes of the disease. Informed consent was obtained from the patient for publication of her clinical case and accompanying MRI images.

The authors have no conflict of interest.

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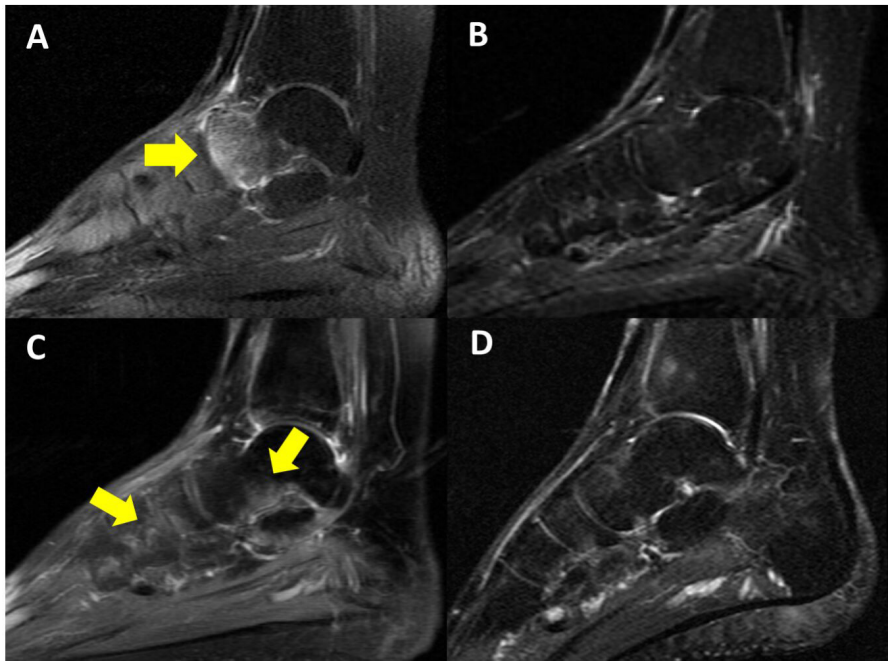

Figure 1. Serial magnetic resonance imaging (MRI) of the left ankle-foot (sagittal T2-weighted) of the patient (A-D). In January 2019, bone marrow edema (BME) was revealed in talus (A, yellow arrow) and conservative treatment with weight-bearing avoidance and analgesics followed. In May 2019, a follow-up MRI showed resolution of the BME (B). After 2 months, the local pain relapsed and a new MRI displayed periarticular (subchondral) BME (yellow arrows) in the bones of the left ankle and the foot (C). Three-and-a-half months after a 5mg zoledronic acid infusion the BME has almost completely resolved (D).

Case Presentation

A 55-year-old postmenopausal woman presented in our clinic in November 2019 complaining for a 2-week, acute-onset, severe pain in her left hip that reflected at the front and the lateral side of the ipsilateral thigh. She was on etoricoxib 90mg daily for the last days, while she was also receiving per os risedronate 75 mg twice monthly for osteoporosis (started on 2015), calcium and vitamin D supplementation (1000 mg/800 IU daily), and a combination of pitavastatin 2 mg/day and ezetimibe 10 mg/day for dyslipidemia. At clinical examination tenderness of the left hip was produced at both active and passive movement of the joint. No other swollen or tender joints or rash was noted. She had no family history of psoriasis, inflammatory bowel disease or inflammatory arthritis. Laboratory testing exhibited normal inflammation markers: ESR 9 mm/h (normal<28 mm/h), CRP 0.37 mg/dL (normal<0.8 mg/dL), and normal bone metabolic profile (serum calcium 9.0 mg/dL; normal range 8.4-10.2 mg/dL; phosphate 3.9 mg/dL; normal range 2.5-4.5 mg/dL; total alkaline phosphatase 101 IU/L; normal range 40-140 IU/L; parathyroid hormone 31.3 pg/mL; normal range 10-55 pg/mL; 25-hydroxyvitamin D3 32.7 ng/mL; normal values>20 ng/mL). Full blood count, liver and renal functional tests were also normal.

In January 2019, three weeks after intense dancing activity, the patient had experienced an episode of acute, severe pain at her left ankle. The pain was produced even by minimum motion and MRI of the left ankle revealed extensive BME of the talus (ankle) (Figure 1A). After evaluation from an orthopedic surgeon, the patient was instructed to use crutches for non-weight-bearing (NWB) and receive paracetamol and/or nonsteroidal anti-inflammatory drugs (NSAIDs) upon pain. The severe pain ameliorated within 1.5 month but did not resolve completely. In May 2019, a follow-up MRI of the left ankle showed resolution of the BME (Figure 1B). As the patient was almost asymptomatic at that time point, she dismissed crutches and returned to her regular daily activities. However, the pain on the left foot relapsed and a third MRI of the left ankle-foot on July 2019 displayed periarticular (subchondral) BME in the bones of the ankle and the foot (Figure 1C). The patient was set again in conservative treatment with NWB and rest for the following two months, till September 2019, with a partial response of pain intensity. One month later, the above reported episode of the left hip insult occurred. To be noted, all these months the patient was taking 500-2000 mg paracetamol daily.

Based on her history and the current clinical condition we considered that MO was the more plausible diagnosis. A MRI of the left hip was performed and revealed typical features of TO (Figure 2A). As the management with crutches, paracetamol/NSAIDs and risedronate had failed to prevent

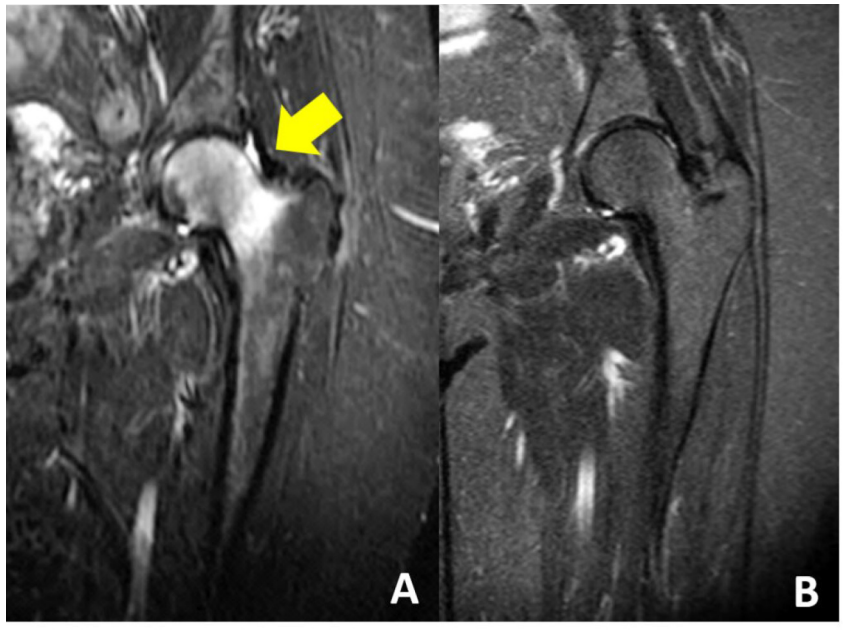

Figure 2. Magnetic resonance imaging (MRI) of the left hip of the patient before (A) and 3.5 months after (B) a zoledronic acid (ZA) infusion (Coronal T2-weighted with fat suppresion). In November 2019, a MRI revealed extensive bone marrow edema (BME) in the left femoral head and neck (A, yellow arrow) and a single 5mg ZA infusion was administered. 3.5 months later, a second MRI of the left hip displayed resolution of BME (B).

the 2nd and the 3rd episode of MO, we discontinued risedronate and administered an intravenous infusion of ZA 5 mg instead, in November 2019. No adverse events were reported by the patient. The patient denied the further use of crutches. Hip pain disappeared within one month and a follow-up MRI of the left hip and the left ankle and foot 3.5 months later showed that BME resolved (Figures 1D, 2B). Five months after the infusion, the patient has returned to her work and her regular physical activities (e.g. dancing), free of analgesics.

Discussion

TO and MO are rare, but possibly underdiagnosed, entities. Sudden limb overuse and low bone mass are known risk factors that are associated with TO development[3,5]. Both were present in our patient, along with compatible age. In such typical cases of TO many authors suggest conservative management for several months[1]: avoidance of weight-bearing, rest and analgesics (paracetamol and NSAIDs). Nevertheless, with this approach symptoms resolve in a mean time of 4-6 months or more[5,6], which is a rather unacceptably long period for a condition that results in prolonged immobilization, reduced self-care and work absenteeism. Moreover, it does not seem to inhibit a future relapse or migration to another joint[4,7]. Although rest can contribute in the recovery from a single episode of TO, this approach might not be suitable for patients with recurrent BME episodes. A next episode of the disease might not present with impressive clinical picture, as indicated by the recurrence of BME in the left foot of our patient.

To date, no drug has been officially approved for MO treatment and due to disease's rarity available data derive from case reports and case series. Among different pharmacological options for MO, bisphosphonates are the most commonly used. Oral bisphosphonates, such as alendronate, have shown moderate efficacy in MO[4]. Data from real-life clinical experience suggest that oral bisphosphonates in the doses used for postmenopausal osteoporosis might be inadequate to control MO[4,7]. In our case, the patient was already receiving risedronate for four years for post-menopausal osteoporosis when MO manifested. However, risedronate did not prevent its development. Intravenous bisphosphonates, such as pamidronate and ZA, have been proven effective in TO[8] and in MO[4,7,9,10] and have led in pain alleviation within 1 month, considerably sooner than with conservative approach and alendronate. ZA is the most potent bisphosphonate and a single 5mg dose exhibits anti-resorptive effect lasting at least 5 years in post-menopausal osteoporosis[11]. In line with this knowledge, ZA seems to have a long-term effect in MO, preventing disease relapses for at least 3 years[7]. Indeed, our patient remained asymptomatic until her last visit 5 months after the ZA infusion. To the best of our knowledge, management of MO with other potent agents used in the treatment of generalized osteoporosis e.g.

denosumab or osteoanabolic treatment has not been tested up to now.

It is true that the high cost of an MRI scan is a deterrent factor in performing such an examination frequently. However, in our patient, repeated MRI scans allowed a more accurate monitoring of disease progression and relapses and facilitated timely and effective management, protecting the patient from prolonged pain and immobilization. Close clinical monitoring of these patients could contribute in early recognition of disease relapse and targeted imaging, as well as in avoidance of unnecessary MRI exams.

In conclusion, this case underlines that conservative approach and risedronate might not be effective in arresting the disease process of MO. NWB and analgesics might not be sufficient for the management of patients that experience multiple episodes of MO and a more aggressive approach should be considered. In such cases, ZA seems to be the most efficacious treatment choice. Close monitoring of TO and MO patients with serial MRI scans could contribute in early intervention and successful management of MO. Finally, as safe conclusion can not be drawn from case reports, prospective single- or multi-center studies are needed to confirm the favorable effect of ZA in MO patients, especially compared to per os bisphosphonates.

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