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Osteoporosis International
https://doi.org/10.1007/s00198-023-07000-5

LETTER TO THE EDITOR

Transient osteoporosis of the hip following discontinuation of denosumab and switch to alendronate treatment

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Received: 29 October 2023 / Accepted: 6 December 2023

To the Editor,

In the recently published systematic review of the efficacy of different therapeutic options for the management of patients with bone marrow edema syndrome (BMES)/transient osteoporosis (TO), the authors reported that bisphosphonates, including oral alendronate (ALN), together with weight bearing restriction, decrease rapidly the pain and are recommended as one of first-line treatments of the condition [1, 2]. Following an appropriate written consent, we report here a patient who developed hip TO during treatment with ALN.

A 60-year-old woman with postmenopausal osteoporosis treated with Dmab 60 mg s.c. once every 6 months, attained osteopenic BMD values at the spine (LS) and the total hip (TH) and stopped this treatment after 7.5 years; she subsequently received ALN 70 mg once weekly, starting 6 months after the last Dmab injection, that she tolerated very well. Seven months later, she presented with acute, severe pain at the right hip with functional disability and an antalgic gait. Bone scintigraphy showed increased uptake in the right hip and MRI was diagnostic of TO (Fig. 1). ALN was stopped and the patient was treated with a single intravenous infusion of zoledronate (ZOL) 5 mg; pain was dramatically reduced within 2 days, the patient was fully mobile and pain-free 15 days later, and decrease of bone marrow edema was documented by MRI 45 days after the ZOL infusion; the following 8 months she remained asymptomatic with no additional treatment. Bone turnover markers increased progressively during ALN therapy to values above the upper limit of normal of postmenopausal women, decreased rapidly following the administration of ZOL and remained low during the rest of the observation period (Fig. 1). BMD values decreased by 3.4% (LS) and 1.4% (TH) during ALN therapy and continued to decrease after the ZOL infusion for a total loss of 7.4% (LS) and 6.9% (TH) compared with the BMD performed 15 months ago at the end of Dmab treatment (6 months after last Dmab injection).

BMES/TO, a self-limiting condition of currently unknown pathogenesis, is not associated with increased bone turnover [3, 4], and different mechanisms have been proposed to explain its development including microtrauma of trabecular bone, microvascular injury, abnormal mechanical stress, or even vasomotor response similar to reflex sympathetic dystrophy [5]. Measurements of markers of bone turnover in bone marrow aspirates and bone biopsy studies, however, have documented local increase in osteoclastic resorption in humans and animals [4, 6, 7], which is associated with pain behavior in the latter and is probably the reason for the favorable clinical response to bisphosphonates.

In this case, patient's adherence and compliance to ALN was checked via the timely executed monthly prescriptions together with her confirmation of medication intake. Given that we cannot exclude a poor medication absorption, in our very compliant patient TO developed during treatment with ALN and was associated with the known overshoot of bone turnover markers that follow the discontinuation of Dmab. Whether this overshoot,

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Published online: 26 December 2023

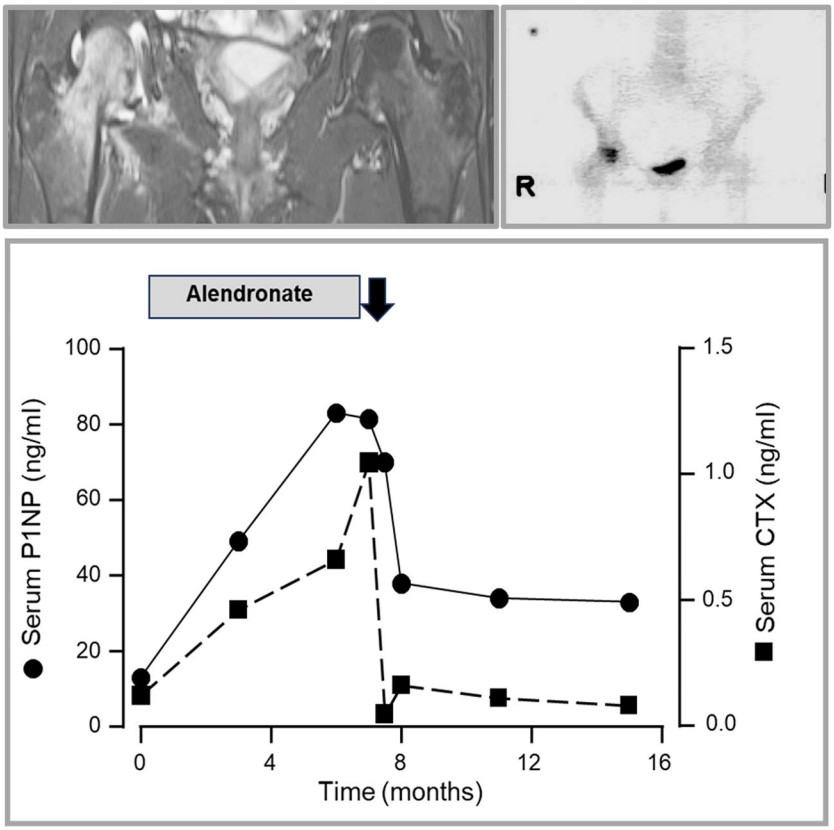

Fig. 1 (Upper panel) Left: Pathologic high-signal intensity on T2-weighted MR image at the time of TO diagnosis, extending to the larger part of right femoral head and neck and to the proximal part of the intertrochanteric zone. The absence of a demarcation line or destruction of the femoral head largely rules out avascular necrosis in the differential diagnosis. Right: Bone scan showing increased uptake of Tc99m in the right hip. (Lower panel) Changes of biochemical markers of bone turnover after discontinuation of denosumab treatment (month 0 corresponds to 6 months after last Dmab injection). Arrow indicates the intravenous administration of zoledronate 5 mg at the end of month 7, and the rectangle corresponds to the duration of alendronate treatment (month 0 through month 7). Upper limit of normal postmenopausal range: CTX 1.0 ng/ml, P1NP 76 ng/ml

which could not be prevented by ALN, triggered the development of TO is not known as this specific skeletal event has not been reported in patients discontinuing Dmab. In contrast, ZOL was highly effective in reducing bone turnover and alleviating the symptoms but did not prevent the significant bone loss previously described in patients treated longer than 3 years with Dmab [8]. Apart from specific questions related to the pathophysiology of TO that need to be addressed, the present case raises concerns about the use of ALN in patients with TO/BMES developed during the year after Dmab discontinuation as well as in patients discontinuing long-term Dmab treatment, while suggesting a more active surveillance to identify a possible unnoticed link of TO with denosumab discontinuation.

Data availability Data will be available upon reasonable request.

Declarations

Ethical approval All procedures performed in this case were in accordance with the ethical standards of the institutional research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient.

Conflict of interest Polyzois Makras reports fees for lectures/advisory boards and research grants from Amgen and Galenica and fees for lectures/advisory boards from UCB, Elpen, Bianex, Eli-Lilly, ITF, Unipharma, and Rapharm; Maria P. Yavropoulou reports fees for lectures/advisory boards and research grants from Galenica; Athanasios D. Anastasilakis reports lecture fees from Amgen, Bianex, Eli-Lilly, Galenica, ITF, Unifarma, and UCB; Athanasios Papatheodorou and Christos Tekedis have nothing to declare; Socrates E. Papapoulos reports consulting/speaking fees from Amgen, Entera Bio, Qualix Dot, Radius Health, and UCB.

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