JCEM Case Reports, 2024, **2**, luae055
https://doi.org/10.1210/jcemcr/luae055
Advance access publication 15 April 2024
Case Report

Attenuation of Bone Mineral Density Decline During Anemia Treatment With Methenolone Acetate in Myelodysplastic Syndrome

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Abstract

In an aging society, addressing the risks and management of osteoporotic fractures is critical to reduce mortality. Similarly, the morbidity of chronic kidney disease and myelodysplastic syndrome increases with aging. The association between chronic kidney disease and fractures is well understood; however, recent reports have indicated an increased risk of incident osteoporosis in patients with prevalent myelodysplastic syndrome. In this case report, we present an older man with stage 4 chronic kidney disease complicated by myelodysplastic syndrome and progressive decline in bone mineral density. He was treated with methenolone acetate and darbepoetin for anemia caused by myelodysplastic syndrome. During anemia treatment, the decline in bone mineral density was attenuated overtime. The case findings suggest the potential association between the use of methenolone acetate as a synthetic anabolic steroid and attenuated decline in bone mineral density.

Key Words: anemia treatment, bone mineral density, bone turnover markers, methenolone acetate, 1,25-dihydroxyvitamin D_3

Introduction

The incidence of osteoporosis continues to increase in aging populations. While primary osteoporosis is mainly associated with aging, secondary osteoporosis is frequently observed owing to various causes. Myelodysplastic syndrome (MDS) represents a group of cancers characterized by immature blood cells in the bone marrow that fail to mature or develop into normal blood cells and are commonly observed in older patients with anemia. A previous study using a longitudinal analysis of routine healthcare data demonstrated a significant increase in the risk of incident osteoporosis in patients with prevalent MDS (1). Another study showed an increased risk of fracture with the prevalence of anemia and decreased levels of hemoglobin (Hb) (2). However, the association between treatment of anemia caused by MDS and bone mineral density (BMD) is poorly understood. Herein, we report a case of an older man with anemia caused by MDS who exhibited an attenuated decline in BMD during treatment for anemia.

Case Presentation

A 73-year-old man was referred to our outpatient clinic owing to stage 4 chronic kidney disease (CKD), with an estimated glomerular filtration rate of 19.0 mL/min/1.73 m^2 (normal range: ≥ 60 mL/min/1.73 m^2) caused by nephrosclerosis. As part of the examination for complications related to CKD, an evaluation of CKD-mineral and bone disorder (MBD) was performed. This married patient had 1 biological child and no history of fractures.

Diagnostic Assessment

During the assessment of CKD-MBD, the levels of plasma intact PTH (normal range: 10-65 pg/mL; 10-65 ng/L), serum calcium ion (Ca^{2+}) (normal range: 4.69-5.21 mg/dL; 1.17-1.30 mmol/L), inorganic phosphorus (iP) (normal range: 2.7-4.6 mg/dL; 0.87-1.48 mmol/L), 25-hydroxyvitamin D (normal range: ≥ 30 ng/mL; ≥ 74.9 nmol/L), 1,25-dihydroxyvitamin D_3 ($1,25[OH]_2D_3$) (normal range: 20-60 pg/mL; 50-150 pmol/L), bone alkaline phosphatase (BAP) (normal range: 3.7-20.9 μg/L), and tartrate-resistant acid phosphatase-5b (TRACP-5b) (normal range: 170-590 mU/dL) were found to be 71 pg/mL (71 ng/L), 1.13 mmol/L (4.53 mg/dL), 2.9 mg/dL (0.94 mmol/L), 13.3 ng/mL (33.2 nmol/L), 21 pg/mL (52 pmol/L), 10.8 μg/L, and 550 mU/dL, respectively (Table 1). The BMD values obtained using dual-energy X-ray absorptiometry (DXA) scanning analysis (Hologic, Inc., Bedford, MA, USA) were as follows: lumbar spine, 1.346 g/cm^2; right femoral neck, 0.819 g/cm^2; and left femoral neck, 0.824 g/cm^2; and the T scores/Z scores were as follows: lumbar spine, +2.8/+2.0

Received: 26 December 2023. **Editorial Decision:** 18 March 2024. **Corrected and Typeset:** 15 April 2024
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Table 1. Laboratory and BMD data of our patient

Parameters	Normal range	1 year and 10 months before treatment ①	1 month before treatment	1 month after treatment ②	Yearly change in BMD (②-①)	2 years after treatment ③	Yearly change in BMD (③-②)
WBC	3600-9300/μL	10 500/μL	6400/μL	4500/μL		5500/μL	
Hb	13.7-16.8 g/dL (8.5-10.4 mmol/L)	7.5 g/dL (4.7 mmol/L)	7.6 g/dL (4.7 mmol/L)	9.1 g/dL (5.7 mmol/L)		12.6 g/dL (7.8 mmol/L)	
Plt	157-382 × 10^3/μL	204 × 10^3/μL	224 × 10^3/μL	216 × 10^3/μL		253 × 10^3/μL	
eGFR	>60 mL/min/1.73 m^2	19 mL/min/ 1.73 m^2	24.2 mL/min/ 1.73 m^2	21.6 mL/min/ 1.73 m^2		23.4 mL/min/ 1.73 m^2	
Serum Ca^{2+}	4.69-5.21 mg/dL (1.17-1.30 mmol/ L)	4.53 mg/dL (1.13 mmol/L)		4.49 mg/dL (1.12 mmol/L)		4.49 mg/dL (1.12 mmol/L)	
iP	2.7-4.6 mg/dL (0.87-1.48 mmol/ L)	2.9 mg/dL (0.94 mmol/L)		3.5 mg/dL (1.13 mmol/L)		3.5 mg/dL (1.13 mmol/L)	
Intact PTH	10-65 pg/mL (10-65 ng/L)	71 pg/mL (71 ng/L)		124 pg/mL (124 ng/L)		70 pg/mL (70 ng/L)	
25(OH)D	>30 ng/mL (>74.9 nmol/L)	13.3 ng/mL (33.2 nmol/L)		11.6 ng/mL (29.0 nmol/L)		11.9 ng/mL (29.7 nmol/L)	
$1,25(OH)_2D_3$	20-60 pg/mL (50-150 pmol/L)	21 pg/mL (52 pmol/L)		14 pg/mL (35 pmol/L)		26 pg/mL (65 pmol/L)	
BAP	3.7-20.9 μg/L	10.8 μg/L		14.9 μg/L		28.4 μg/L	
TRACP-5b	170-590 mU/dL	550 mU/dL		841 mU/dL		1110 mU/dL	
BMD T/Z score lumbar		1.346 g/cm^2+2.8/ +2.0 SD		1.255 g/cm^2+2.0/ +1.5 SD	Δ −4.4%/year	1.184 g/cm^2 + 1.5/ +1.1 SD	Δ −2.9%/ year
right femoral neck		0.819 g/cm^2+0.3/ +1.0 SD		0.714 g/cm^2 −0.8/+0.2 SD	Δ −8.3%/year	0.730 g/cm^2 −0.7/+0.3 SD	Δ + 1.1%/ year
left femoral neck		0.824 g/cm^2+0.4/ +1.1 SD		0.746 g/cm^2 −0.5/+0.4 SD	Δ −8.1%/year	0.744 g/cm^2 −0.5/+0.5 SD	Δ −0.2%/ year

All results and reference ranges, excluding the WBC count, Plt, eGFR, BAP, TRACP-5b, and BMD levels, and the T/Z score, are reported in Système International units (in parentheses). The numbers circled indicate the order in which dual-energy X-ray absorptiometry was performed.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D_3$, 1,25-dihydroxyvitamin D_3; BAP, bone alkaline phosphatase; BMD, bone mineral density; Ca^{2+}, calcium ion; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; iP, inorganic phosphorus; Plt, platelet; TRACP-5b, tartrate-resistant acid phosphatase-5b; WBC, white blood cell.

SD; right femoral neck, +0.3/+1.0 SD; and left femoral neck, +0.4/+1.1 SD, respectively (Table 1). Therefore, medications for CKD-MBD, including active vitamin D, were not administered. Moreover, we were unable to administer native vitamin D for vitamin D deficiency as it is not approved for prescription in Japan. Simultaneously, the patient had refractory anemia with an Hb level of 7.5 g/dL (4.7 mmol/L) (Table 1), despite receiving treatment with an erythropoietin-stimulating agent (epoetin beta pegol, 100 μg/month) for presumed renal anemia. The white blood cell and platelet counts were 10 500/μL (normal range, 3600-9300/μL) and 204 × 10^3/μL (normal range: 157-382 × 10^3/μL), respectively (Table 1).

Treatment

After 1 year and 10 months, a hematologist diagnosed the patient as having MDS (World Health Organization classification: refractory cytopenia with multilineage dysplasia) based on a bone marrow aspiration test result, which can be considered low risk in terms of the International Prognostic Scoring System, and methenolone acetate (20 mg/day, per os), a synthetic anabolic steroid, and darbepoetin (480 μg/month, subcutaneously) were administered to treat the anemia resulting from MDS based on Japanese practice guidelines for hematological malignancies (3). One month before treatment, his Hb level and estimated glomerular filtration rate were 7.6 g/dL (4.7 mmol/L) and 24.2 mL/min/1.73 m^2, respectively (Table 1).

Outcome and Follow-up

After 1 month of treatment, the patient's Hb level increased to 9.1 g/dL (5.7 mmol/L) (Table 1). Serum BAP and TRACP-5b levels increased to 14.9 μg/L and 841 mU/dL, respectively (Table 1). These improvements were at first assumed to be associated with a temporal increase in the plasma intact PTH level to 124 pg/mL (124 ng/L) [serum Ca^{2+}, 1.12 mmol/L (4.49 mg/dL); iP, 3.5 mg/dL (1.13 mmol/L)] (Table 1). BMD values decreased at each site as follows: lumbar spine, 1.255 g/cm^2 (Δ −4.4%/year); right femoral neck, 0.714 g/cm^2 (Δ −8.3%/year); and left femoral neck, 0.746 g/cm^2 (Δ −8.1%/year) (Table 1).

After 2 years of treatment, his Hb level gradually increased to 12.6 g/dL (7.8 mmol/L) (Table 1), despite no observed improvement in MDS when followed up by the hematologist. Notably, serum BAP levels increased to 28.4 μg/L over time, followed by an increase in serum TRACP-5b levels to 1110 mU/dL (Table 1). Despite renal function and serum Ca^{2+} and iP levels [1.12 mmol/L (4.49 mg/dL) and 3.5 mg/dL (1.13 mmol/L), respectively] remaining stable, plasma

intact PTH levels showed a decrease to 70 pg/mL (70 ng/L) (Table 1). The decline in BMD in the lumbar spine slowed (Δ −2.9%/year), while that in the right femoral neck increased (Δ+1.1%/year), and that in the left femoral neck remained almost unchanged (Δ −0.2%/year) (Table 1). No new-onset fractures were detected during the treatment period. No alterations in other medications or the occurrence of side effects, such as elevated prostate-specific antigen levels and liver dysfunction due to methenolone acetate administration, were observed. We used the same DXA scanning device at each of the 3 DXA measurements. The International Osteoporosis Foundation recommends using serum procollagen type I N-propeptide and fasting serum carboxy-terminal telopeptide of type I collagen; however, we used BAP and TRACP-5b to evaluate bone turnover as these bone turnover markers are not affected by renal function and are generally used for patients with advanced renal dysfunction to assess bone turnover in Japan.

Discussion

In the present case of anemia that was primarily caused by MDS, treatment with methenolone acetate and darbepoetin improved Hb levels. This observation could potentially be linked to a mitigated decline in BMD, likely achieved through PTH-independent upregulation of bone turnover.

Methenolone acetate is a synthetic anabolic steroid and hence an agonist of the androgen receptor, which is the biological target of androgens such as testosterone and dihydrotestosterone, that is still used in Japan in the treatment of anemia due to bone marrow failure, unlike in Europe and the United States, where it is no longer used for this purpose. Moreover, this drug has been approved in Japan for more than 50 years for the treatment of osteoporosis. However, basic and clinical data at that time, such as those related to bone turnover markers, were limited and could not support the efficacy of methenolone acetate with respect to bone metabolism, with this drug having been rarely used as a treatment for osteoporosis up until now. Nonetheless, a 1-year randomized controlled study demonstrated that testosterone increased the volumetric BMD of the trabecular bone in the spine site in contrast to a placebo (4). Methenolone acetate can promote bone formation (5), resulting in increased BMD at the radial and lumbar spine sites (6), along with a 3% yearly increase in bone mass in both women and men with osteoporosis (7). These effects of methenolone acetate on bones have been reported to occur via the activation of vitamin D, leading to calcium reabsorption from the small intestine (8). According to animal studies, testosterone can increase the synthesis and decrease the degradation of $1,25(OH)_2D_3$ through the activation of 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) (9) and inactivation of 25-hydroxyvitamin D 24-hydroxylase (CYP24A1) (10), respectively. In this particular case, there was no observed increase in serum Ca^{2+} levels, which remained within the range of 1.12 to 1.13 mmol/L (4.49-4.53 mg/dL). However, the serum $1,25(OH)_2D_3$ level increased from 14 to 26 pg/mL (35-65 pmol/L) over time after treatment. In addition, the androgen receptor is predominantly expressed in osteoblasts and osteocytes but not in osteoclasts (11–13). The androgen receptor in osteoblasts is upregulated by androgen and $1,25(OH)_2D_3$ to promote osteoblast proliferation, differentiation, synthesis of extracellular matrix protein, and mineralization (14, 15). However, the androgen receptor played no role in the direct action on osteoclasts in an animal model study (13). Thus, the effects of methenolone acetate on bone are mediated through its androgenic properties without estrogenic effect. In contrast, it is worth noting that while methenolone acetate has been associated with bone improvements through increased muscle strength and mass in some studies (16), there were no significant changes observed in body weight and nutritional status during the treatment course in the present case. No specific assessment of activities of daily living was performed, but our patient walked to the clinic before treatment and continued to do so after treatment.

MDS is known to affect not only hematopoietic stem cells but also bone marrow mesenchymal stem cells, which are cells involved in bone marrow microcirculation (hematopoietic stem cells niche) and have the ability to differentiate into osteoblasts and other cells, with dysfunctional effects (17, 18). In a study using an MDS mouse model, a marked decrease in bone mass was observed. Measurements of serum bone markers and bone formation data showed a marked suppression of osteogenesis, while osteoclast activity was not increased, suggesting that decreased bone formation was the cause (19). Therefore, bone formation might have been suppressed before the treatment and then recovered after treatment through PTH-independent upregulation of bone turnover by anabolic properties of methenolone acetate in this case. Anemia was improved using methenolone acetate and darbepoetin; however, discontinuation of these medications for anemia owing to MDS was difficult as a progression of anemia and a decline of BMD might have resulted.

To conclude, this case study provides evidence of the attenuation of the BMD decline during the treatment of anemia due to MDS through an osteoanabolic effect of methenolone acetate, including the measurement of bone turnover marker levels. Owing to the retrospective nature of this case report, it is impossible to address the causality between anemia treatment and attenuation of BMD decline. Nevertheless, this observation may provide valuable insights into not only the increased risk of incident osteoporosis and fractures but also their treatment in patients with prevalent MDS in an aging society.

Learning Points

- A previous study demonstrated a significant increase in the risk of incident osteoporosis in patients with prevalent MDS.
- In this case, methenolone acetate was used to treat severe anemia due to MDS, which might have attenuated the decline in BMD as an osteoanabolic agent.
- Based on bone turnover marker levels, the methenolone acetate-induced upregulation of bone turnover might have underlying parathyroid hormone-independent mechanism(s).

Acknowledgments

We would like to thank Editage (www.editage.com) for the English-language editing.

Contributors

All authors made individual contributions to authorship. N.T. was involved in the diagnosis and management of this patient,

manuscript revision, and supervision. S.U. was responsible for writing the first draft of the manuscript. K.S. was involved in manuscript revision and supervision. H.S., M.A., and R.F. were involved in manuscript revision. All authors reviewed and approved the final draft.

Funding

No public or commercial funding.

Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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