Pregnancy and lactation-related osteoporosis associating multiple vertebral fragility fractures treated with romosozumab: a case report

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Contributions: (I) Conception and design: H Nomura; (II) Administrative support: None; (III) Provision of study materials or patients: H Nomura; (IV) Collection and assembly of data: H Nomura; (V) Data analysis and interpretation: H Nomura; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

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Background: Pregnancy- and lactation-related osteoporosis (PLO) is a rare condition of skeletal fragility affecting women during late pregnancy and early lactation. Patients with PLO who experience multiple, rapid-onset vertebral fractures and develop kyphosis face a poorer prognosis when diagnosis and treatment are delayed. Since there is no standard treatment protocol for patients with PLO, treatment should be individually planned. Recently, romosozumab has been recognized as one of the most effective drugs for treating patients with severe osteoporosis. Because it can dramatically increase bone mineral density (BMD) in a short period in postmenopausal women with osteoporosis, it is useful for treating patients with rapidly progressive osteoporosis at a high risk of fracture. Here, we report a case of PLO associated with multiple vertebral fractures treated with romosozumab. To the best of our knowledge, this is the first report on the use of romosozumab alone for PLO.

Case Description: A middle-aged postpartum and lactating woman experienced back pain at 9 months of pregnancy, which worsened after delivery. PLO was diagnosed based on multiple thoracic vertebral and sacral fragility fractures and low BMD. She was treated with romosozumab, and her back pain gradually subsided. After 12 months of romosozumab treatment, her lumbar spine BMD increased by 22.1% from baseline, and no further fractures occurred.

Conclusions: Twelve months of romosozumab treatment successfully improved the clinical condition of the patient with severe PLO, resulting in a remarkable increase in BMD.

Keywords: Pregnancy- and lactation-related osteoporosis (PLO); vertebral fractures; romosozumab; bone mineral density (BMD); case report

Received: 24 July 2024; Accepted: 22 November 2024; Published online: 10 April 2025.

doi: 10.21037/acr-24-163

View this article at: https://dx.doi.org/10.21037/acr-24-163

Introduction

Pregnancy- and lactation-related osteoporosis (PLO) is a rare condition of skeletal fragility that affects women during late pregnancy and early lactation and is associated with multiple vertebral or femoral neck fractures (1-3). The estimated prevalence of PLO is 4–8 per 1,000,000, and its relatively low incidence may result in a delayed diagnosis and treatment (1,4). Patients with PLO who experience multiple, rapid-onset vertebral fractures and develop kyphosis face a poorer prognosis when diagnosis and treatment are delayed (5).

Recently, romosozumab has been recognized as one of the most effective drugs for treating patients with severe osteoporosis (6,7). It binds to and inhibits sclerostin,

with a dual effect of increasing bone formation and decreasing bone resorption (8,9). Because romosozumab can dramatically increase bone mineral density (BMD) in a short period in postmenopausal women with osteoporosis, it is useful for treating patients with rapidly progressive osteoporosis at a high risk of fracture (10).

Here, we present a clinical case of PLO associated with multiple vertebral fragility fractures treated with romosozumab alone. To the best of our knowledge, this is the first report on the use of romosozumab alone for PLO. We present this case in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-24-163/rc).

Case presentation

A middle-aged postpartum and lactating Japanese woman (height, 162.8 cm; weight, 46.5 kg; body mass index, 17.54 kg/m^2) with a 4-month history of progressive middle and low back pain visited our clinic one month after delivering her third child. She had back pain throughout pregnancy (without trauma) that worsened significantly in the first month postpartum. Her back pain, rated 9 on the visual analog scale (VAS, range, 0–10) and causing moderate disability (score of 11 on the Roland-Morris Disability Questionnaire, RDQ, range, 0–24) (11), prompted her to visit the clinic. She had no history of smoking, significant medical conditions, steroid use, alcohol abuse, or crash dieting. Her mother had a femoral neck fracture at 71 years old, treated with osteosynthesis.

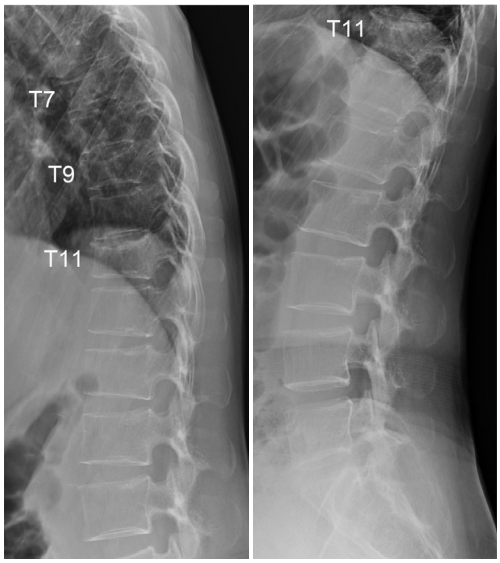

Figure 1 Plain radiographs of the thoracic and lumbar spine on the initial examination showing T7, T9, and T11 vertebral fractures.

Radiological examination of the lateral view of the spine revealed multiple compressions of the anterior components of the vertebrae at T7, T9, and T11 (*Figure 1*). Magnetic resonance imaging (MRI) demonstrated low intensity on T1-weighted imaging and high signal intensity changes on the short tau inversion recovery image at the T9 and T11 vertebrae as well as the sacrum, indicating T9 and T11 recent vertebral fractures, T3 and T7 subacute fractures (*Figure 2* upper panel), and a recent sacral fracture (*Figure 2* lower panel). The laboratory examination results are shown in *Table 1*.

The patient's lumbar spine BMD (L1-4) and left total hip area were evaluated using dual-energy X-ray absorptiometry (DEXA). The BMD, young adult mean (YAM), and T-score of the lumbar spine and total hip at the initial examination are shown in *Table 2*. According to the criteria for primary osteoporosis by the Japan Osteoporosis Society Joint Review Committee, YAM percentage is the mean BMD in healthy young people, at any sites of lumbar spines, femoral neck, or total femoral bones, and osteoporosis or low bone mass status that occurs in older people is defined as <70% or 70–80% of YAM, respectively (12). Laboratory data were negative for secondary osteoporosis, such as Cushing syndrome or hyperthyroidism. Based on these findings,

Highlight box

Key findings

- Pregnancy- and lactation-related osteoporosis (PLO) is a rare condition of skeletal fragility that affects women during late pregnancy and early lactation and is associated with multiple vertebral or femoral neck fractures. We present a clinical case of PLO associated with multiple vertebral fragility fractures treated with romosozumab.

What is known and what is new?

- Since there is no standard treatment protocol or guideline for patients with PLO, treatment should be planned individually. Denosumab and teriparatide were previously utilized effectively; however, there are concerns regarding their several disadvantages.
- There is a limited but growing body of evidence regarding romosozumab administration in patients with PLO. Here, we obtained a significant clinical improvement using romosozumab in a patient with PLO.

What is the implication, and what should change now?

- This report implies the efficiency of romosozumab in the treatment of patients with PLO, which could be recommended as first-line therapy.

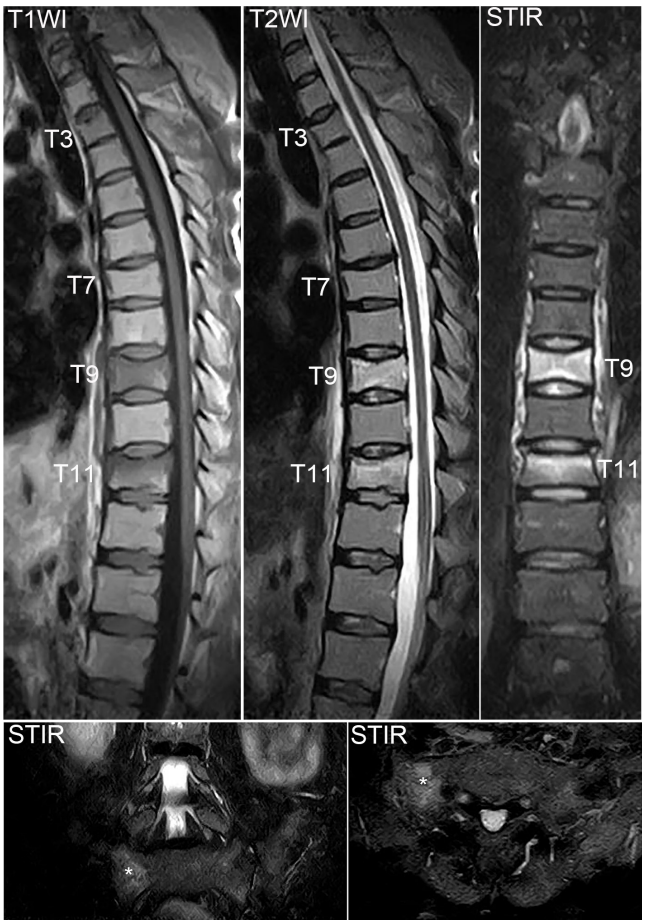

Figure 2 T1- and T2-weighted sagittal MR images and STIR coronal and axial MR of the thoracic spine and sacrum showing T9, T11 and right ala recent (asterisks), and T3 and T7 subacute fractures. MR, magnetic resonance; STIR, short T1 inversion recovery; T1WI, T1 weighted image; T2WI, T2 weighted image.

we diagnosed PLO associated with multiple vertebral fractures, including T9 and T11 acute vertebral and sacral fractures. Her back pain was so severe that she was unable to hold her newborn. To address this debilitating symptom, we implemented a two-pronged approach: administering romosozumab with oral therapy with activated vitamin D3 and fitting her with a Jewett-type spinal orthosis. Within a month, her back pain had decreased sufficiently, and she was able to hold her baby for short periods. At 2 months, osteosclerotic changes in the T9 and T11 vertebrae were observed, and the orthosis was removed. Her back pain was gradually decreased after 6 months. The VAS and RDQ scores were 3 and 3, respectively. The BMD, YAM, and T-score; an increase from baseline in BMD at the lumbar spine and total hip; and laboratory data at 6 months are shown in *Tables 1*,*2*. At 7 months, she was able to perform her daily activities with minimal back pain. BMD, YAM, T-score, increase in BMD, and laboratory data at 12 months are shown in *Tables 1*,*2*. After 12 months of romosozumab treatment, we continuously planned to administer oral therapy with activated vitamin D3; however, she did not visit our clinic the next month and did not reply to our reminder call. Ten months after romosozumab treatment, despite experiencing only slight lower back pain and no difficulties in her daily activities, she returned to our clinic owing to concerns about the state of her osteoporosis without a recent checkup. The VAS and RDQ scores were 2 and 0, respectively. We confirmed that the patient did not receive sequential therapy. The BMD, YAM, T-score, increase in BMD, and laboratory data are shown in *Tables 1*,*2*. Radiological examination revealed no further vertebral fractures (*Figure 3*).

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Regarding the mechanism of PLO, fragility or low-energy fractures in the maternal skeleton during pregnancy and lactation can be related to supplying fetal calcium from the maternal skeleton and promoting high bone turnover due to an extreme drop in estrogen levels after delivery, promoting osteoclast activity without accompanying osteoblast activity, and a loss in bone mass in breastfeeding-only conditions (5,13,14). Risk factors include inadequate calcium intake, low peak bone mass, anorexia nervosa, oligomenorrhea, premature ovarian failure, prolonged bed rest, smoking, hypercalciuria, primipara, genetic anomalies, and pharmacotherapy such as systemic glucocorticoids or anticonvulsants (5,13). In the current case, the patient did not have any obvious risk factors except for a family history of femoral neck fractures. For the diagnosis of PLO, MRI is useful to observe the presence or absence of edema in insufficient vertebral or sacral fractures, as well as to distinguish between acute and/or subacute conditions of the fractures, as in our patient (5). In addition, it is theoretically available to patients during pregnancy because of its lack of

Table 1 Time course of laboratory examination from before treatment to 22 months after treatment

Parameter	Normal range	Before	After 6 months	After 12 months	After 22 months
Corrected calcium, mg/dL	8.8–10.1	8.6	8.4	8.6	8.8
Phosphorus, mg/dL	2.7–4.6	4	2.8	3.7	3.5
Albumin, g/dL	4.1–5.1	4.2	4.9	4.7	4.6
Creatinine, mg/dL	0.46–0.79	0.5	0.58	0.56	0.54
TRACP-5b, mU/dL	120–420	947	182	107	263
P1NP, ng/mL	16.8–70.1	95.8	56	29.6	21
25 hydroxy vitamin D, ng/mL	>30	9.1			
Intact PTH, pg/mL	10–65	94.2			
TSH, mU/L	0.610–4.23	0.283			
Free T3, pg/mL	2.1–4.1	2.5			
Free T4, ng/dL	0.9–1.7	0.9			
ACTH, pg/mL	7.2–63.3	16			
Cortisol, μg/dL	4.5–21.1	6.5			

ACTH, adrenocorticotropic hormone; P1NP, procollagen type 1 N-terminal propeptide; PTH, parathyroid hormone; T3, triiodothyronine; T4, thyroxine; TRACP, tartrate-resistant acid phosphatase; TSH, thyroid-stimulating hormone.

Table 2 Time course of BMD, YAM, and T-score of lumbar and total hip from before treatment to 22 months after treatment

Measurement	Before	After 6 months	After 12 months	After 22 months
Lumbar spine				
BMD (g/cm^2)	0.842	0.995	1.028	1.063
YAM (%)	73	86	89	92
T-score	–2.2	–1.1	–0.9	–0.6
Increase of BMD (%)		13	22.1	26.2
Total hip				
BMD (g/cm^2)	0.721	0.743	0.738	0.747
YAM (%)	75	77	77	78
T-score	–1.8	–1.7	–1.7	–1.6
Increase of BMD (%)		3.1	2.4	3.6

BMD, bone mineral density; YAM, young adult mean.

radiation emissions.

Since there is no standard treatment protocol or guideline for patients with PLO, treatment should be planned individually (15,16). In a non-pharmacological approach, patients with PLO should be advised to discontinue breastfeeding as early as possible. To reduce back pain with vertebral fracture, adequate analgesic drugs as well as the application of spinal orthosis should be considered. When fractures consolidate, reasonable weight-bearing and physical resistance activity should be encouraged (5). A pharmacological approach involves three strategies: supplementations, antiresorptive agents, and bone anabolic agents (*Figure 4*). First, calcium and vitamin D should be improved. Particularly, if a patient with PLO and a recent fracture presents with vitamin D levels below 30 ng/mL, she should be supplemented immediately with at least 1,000

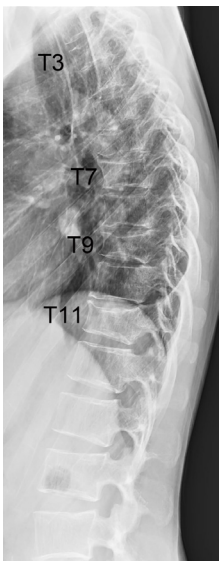

Figure 3 Plain radiographs of thoracic and lumbar spine at 22 months showing T3, T7, T9, and T11 vertebral fractures in no association with further vertebral fractures developed before treatment.

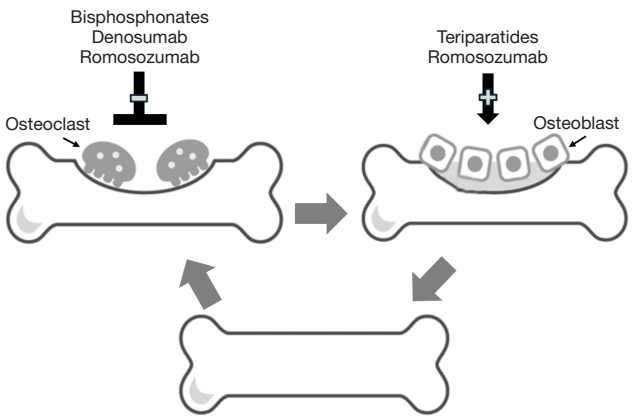

Figure 4 A diagram showing bone remodeling indicating bone resorption by osteoclast cells and followed by bone formation by osteoblast cells, and action sites of the various osteoporosis medications.

to 2,000 IU per day of vitamin D (5). Among antiresorptive agents, the use of bisphosphonates is controversial, because they remain in the bone matrix for years and pass through the placenta (16). One experimental study demonstrated that alendronate given to pregnant rats crossed the placenta and resulted in reduced bone growth and fetal weight (17). Furthermore, a previous literature review paper reported that bisphosphonates including alendronate, etidronate, risedronate, pamidronate, and neridronate possibly cross the placenta, resulting in some adverse infant effects (18). Thus, bisphosphonates may be risky for subsequent pregnancies in patients with PLO who are in their reproductive age (16). Unlike bisphosphonates, denosumab does not accumulate in the bones (19). However, a significant disadvantage for patients in Japan is that healthcare insurance does not cover the cost of subsequent therapy for 6 months after denosumab administration, even if the clinical outcome remains unsatisfactory. This limitation makes using anabolic agents after denosumab impractical owing to financial constraints. In 2022, the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (ESCEO) reviewed the usefulness of anabolic agents as an initial intervention in patients at high risk of fracture, which is called the anabolic-first approach (20). This literature, referencing relevant prescribing guidelines, outlines the ESCEO recommendation for sequential therapy in a patient with severe osteoporosis and high fracture risk: a bone-forming agent for 1–2 years followed by an antiresorptive agent. We also employed an anabolic-first approach. Among anabolic agents, teriparatide was previously introduced as an effective agent for the treatment of PLO (15,16). In the current case, however, considering secondary hyperparathyroidism, we used romosozumab and not teriparatide, because of the contraindication for hyperparathyroidism. We suggest that low vitamin D status in the current case may promote secondary hyperparathyroidism since vitamin D levels are inversely correlated with parathyroid hormone levels (14,21). Indeed, the previous study reported low vitamin D levels in PLO patients with fragility vertebral fractures, similar to the current case (14), which implies that low vitamin D activity after partum might be related to the development of osteomalacia, leading to fragility fractures.

Sclerostin is secreted by osteocytes and negatively regulates osteoblast-mediated bone formation, most likely by binding to low-density lipoprotein receptor proteins 5 and 6 and antagonizing Wnt signaling (9). It also stimulates the production of the receptor activator of nuclear factor-κB ligand (RANKL) and suppresses the production of osteoprotegerin (OPG) in osteoblasts (22,23). Increased RANKL and reduced OPG activates and induces differentiation of osteoclasts. Therefore, blocking sclerostin by romosozumab uniquely results in dual effects by increasing osteoblastic activity and reducing osteoclastic activity; this mechanism of decreasing bone resorption is partly similar to that of the denosumab as a RANKL inhibitor.

Regarding romosozumab administration in patients with PLO, there is a limited but growing body of evidence. Notably, one case report described a 34-year-old primiparous woman who was initially treated with teriparatide for 4 months followed by romosozumab owing to concerns about the long-term effects of bisphosphonates on future pregnancies (24). In this case, teriparatide treatment had to be discontinued because the patient experienced severe nausea after every teriparatide injection and the appearance of new vertebral fractures; consequently, the authors switched to a 12-month romosozumab treatment and achieved excellent clinical outcomes with a great increase in the BMD of the lumbar spine. In the current study, we consequently had an opportunity to observe the natural course of PLO without sequential therapy after 12 months of romosozumab treatment, implying that sequential therapies are unnecessary. It should be noted that patients with PLO are not likely to continue losing bone mass in a time-dependent manner, will spontaneously recover after weaning, and will most likely maintain their skeletal BMD because they have adequate circulating estrogen levels (25). Our patient's BMD in the lumbar spine was increased by 13% at 6 months and 22.1% at 12 months. After 12 months of romosozumab treatment, BMD was increased by 26.2% in the lumbar spine and remained 3.6% higher in the total hip compared to baseline at 22 months. There is a concern about the increased risk of myocardial infarction, stroke, and cardiovascular mortality after romosozumab administration; thus, it should not be introduced in patients who have had cardiovascular events within the past year. Furthermore, because romosozumab is not recommended for women during lactation, it is necessary to discontinue breastfeeding in patients with PLO.

Conclusions

We reported the effect of romosozumab in severe cases of PLO with multiple vertebral and sacral fractures. No further vertebral fractures occurred after romosozumab treatment.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-24-163/rc

Peer Review File: Available at https://acr.amegroups.com/article/view/10.21037/acr-24-163/prf

Funding: None.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-24-163/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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doi: 10.21037/acr-24-163
Cite this article as: Nomura H, Nomura S. Pregnancy and lactation-related osteoporosis associating multiple vertebral fragility fractures treated with romosozumab: a case report. AME Case Rep 2025;9:68.