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Minodronate for severe multiple vertebral fractures due to pregnancy- and lactation-associated osteoporosis: a case report and literature review

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***Abstract*:** Pregnancy- and lactation-associated osteoporosis (PLO) is a rare type of premenopausal osteoporosis, typically occurring during the third trimester of pregnancy and the early postpartum lactation period. This report presents a case involving severe multiple vertebral fractures due to PLO with low bone mineral density (BMD) and heightened bone turnover. A 39-year-old primiparous Japanese woman reported low back pain (LBP) starting at 28 weeks of pregnancy. The pain temporarily improved after delivery, although the LBP recurred and worsened 2 months into breastfeeding. Thereafter, the patient visited the Obstetrics and Orthopedic departments. Plain radiographs of the thoracic and lumbar spine showed loss of vertebral body height at the T4–12 and L1–3,5 vertebrae, leading to a diagnosis of 13 fractured vertebrae. BMD and serum bone turnover markers revealed low bone density and heightened bone turnover. In the absence of any identified alternative cause of secondary osteoporosis, the diagnosis was severe PLO with 13 vertebral fractures related to pregnancy and lactation. After treatment with bisphosphonates and an active vitamin D analog, the patient exhibited an increased BMD and normalization of bone turnover and resumed regular daily activities. Although the optimal PLO treatment strategy remains uncertain, bisphosphonates are an option; however, bisphosphonates can potentially affect the fetus through placental transfer. Therefore, careful consideration is required for patients planning pregnancy. Despite bisphosphonates' widespread use and cost-effectiveness, selecting PLO medications involves multiple factors, necessitating further research.

Keywords: bisphosphonates, bone mineral density, bone turnover, case report, pregnancy- and lactation-associated osteoporosis, vertebral fracture

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Introduction

Pregnancy- and lactation-associated osteoporosis (PLO) is a rare type of premenopausal osteoporosis, typically occurring during the third trimester of pregnancy and the early postpartum lactation period.[1] Despite limited epidemiological data on PLO, its prevalence has been estimated at 4–8 cases per million people.[2] The pathogenesis of PLO remains unclear, and a consensus on its treatment is yet to be established.[3] Given that PLO predominantly affects the vertebral bodies, many patients with vertebral fractures or kyphosis often have bother from back pain as a common clinical manifestation.[4,5] Patients seek endocrinology, orthopedic, or obstetrics and gynecology consultations because there is no specific medical specialty for PLO. Owing to study limitations and a lack of awareness, clinicians frequently encounter challenges in promptly and appropriately diagnosing PLO, potentially resulting in poor prognoses.[5]

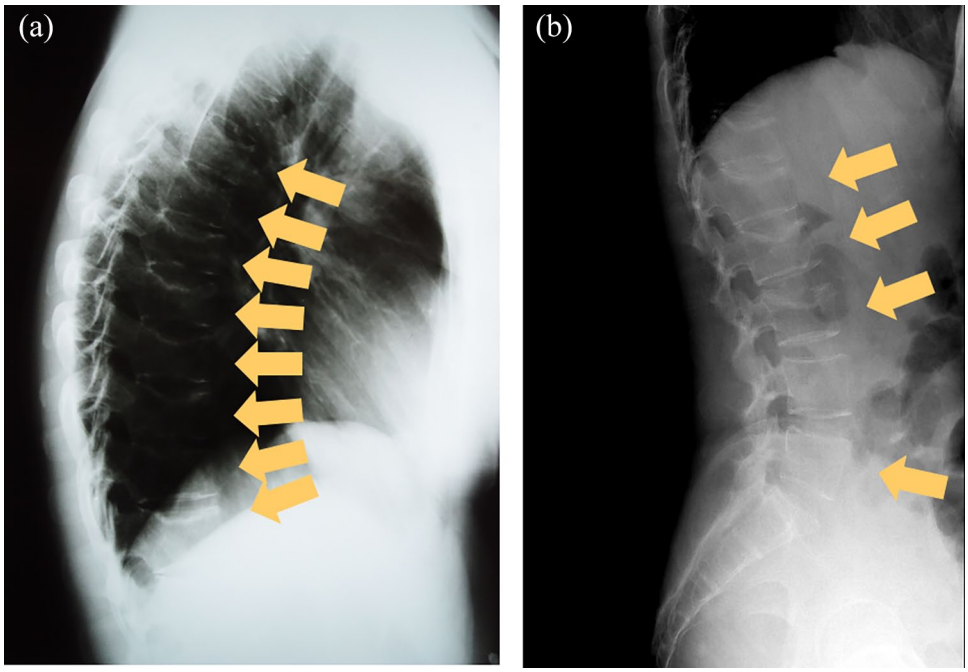

Figure 1. (a, b) Lateral view of the thoracic and lumber spine shows the loss of vertebral height at the T4–12 and L1–3,5 vertebrae (yellow arrows).

Herein, we present a case of PLO characterized by 13 vertebral fractures associated with severe bone mineral density (BMD) loss and subsequently treated with bisphosphonates. Additionally, we reviewed severe cases involving multiple fractures associated with PLO by searching MEDLINE and EMBASE databases and analyzed the clinical features, treatment, and prognoses of these cases.

Case presentation

A late 30s primiparous Japanese woman reported low back pain (LBP) starting at 28 weeks of pregnancy. The pain temporarily improved with the administration of acetaminophen (Calonal® Tablets; Showa Yakuhin Kako Co., Ltd, Japan) at 1200 mg/day after delivery, and she was no longer visiting the hospital due to not subjective LBP. However, 2 months into breastfeeding, the LBP recurred and worsened compared with the pain experienced during the perinatal period. Consequently, the patient visited the Obstetrics and Orthopedic departments.

The patient had a height of 163 cm and weighed 49 kg, with a body mass index (BMI) of 18.4 kg/m^2. She consumed alcohol occasionally and had a history of smoking 15 cigarettes per day from the age of 18 until she learned she was pregnant. The patient's thyroid function, assessed using blood tests, was within normal limits. No signs of pallor, icterus, or edema of the feet were observed during physical examination, which revealed kyphosis with tenderness over the lumbar region. The patient had (i) no history of sensory impairment, (ii) no history of falls or trauma to the spine, (iii) no history of bone fracture, endocrine disease, or connective tissue disease, and (iv) no evidence of malabsorption. Plain radiographs of the thoracic and lumbar spine showed loss of vertebral body height at the T4–12 and L1–3,5 vertebrae [Figure 1(a) and (b)], leading to a diagnosis of 13 fractured vertebrae.

Laboratory results indicated normal levels of serum calcium (9.2 mg/dL, normal range: 8.1–10.4 mg/dL), serum phosphorus (4.6 mg/dL, normal range: 2.7–4.6 mg/dL), albumin (4.4 g/dL, normal range: 3.5–5.5 g/dL), intact parathyroid hormone (PTH; 40.1 pg/mL, normal range: 14.0–72.0 pg/mL), PTH-related peptide (1.1 pmol/L, normal range: 0–1.1 pmol/L), cortisol (12.1 μg/dL, normal range: 3.09–16.66 μg/dL), thyroid-stimulating hormone (0.88 μIU/mL, normal range: 0.35–5.50 μIU/mL), free T3 (125 ng/dL, normal range: 65–150 ng/dL), free thyroxine (2.94 ng/dL, normal range: 0.78–1.54 ng/dL), and undercarboxylated osteocalcin (7.9 ng/mL,

normal range: 2.5–13 ng/mL). However, the alkaline phosphatase level was elevated (491 U/L, normal range: <240 U/L). Elevated bone turnover markers were also observed, including urine crosslinked N-telopeptide of type 1 collagen (NTX; 176.1 nmolBCE/mmol·Cr, normal range: 9.3–54.3 nmolBCE/mmol·Cr) and bone alkaline phosphatase (BAP; 40.7 μg/L, normal range: 3.8–22.6 μg/L). Other serum biochemistry tests, including kidney and liver function tests, yielded results within normal ranges.

The patient's BMD was measured using dual-energy X-ray absorptiometry. The BMD values were 0.643 g/cm^2 [*T*-score: −3.1, *Z*-score: −3.0, young adult mean (YAM): 64%] at the lumbar spine (L2–L4) and 0.460 g/m^2 (*T*-score: −3.0, *Z*-score: −2.6, YAM: 61%] and 0.426 g/m^2 (*T*-score: −3.3, *Z*-score: −3.0, YAM: 57%) at the right and left sides of the femoral neck, respectively. In the absence of secondary osteoporosis, the diagnosis was established as extremely severe multiple vertebral compression fractures related to PLO.

After thorough explanation and counseling, the patient, who did not desire to have another baby, preferred an oral bisphosphonate-like drug over more expensive subcutaneous injections like romosozumab or teriparatide. She was administered a single monthly dose (50 mg) of oral minodronate (Recalbon®; Ono Pharma Pharmaceutical Co. Ltd, Osaka, Japan), along with oral supplementation of eldecalcitol, an active vitamin D analog, at 0.75 μg/day (Edirol; Chugai Pharmaceutical Co., Tokyo, Japan), following the cessation of breastfeeding. Four months later, the patient reported significant LBP improvement. The BMD values had increased to 0.078 g/cm^2 (+7.0% in YAM from baseline) at the lumbar spine, 0.022 g/cm^2 (+3.0% in YAM from baseline) at the right femoral neck, and 0.051 g/cm^2 (+7.0% in YAM from baseline) at the left femoral neck. In addition, other BMD values were improved from *T*-score: −3.1 and *Z*-score: −3.0 at baseline to *T*-score: −2.4 and *Z*-score: −2.4 in the lumber spine, and from *T*-score: −3.0 and *Z*-score: −2.6 at baseline to *T*-score: −2.8 and *Z*-score: −2.4 in the right side of the femoral neck, and from *T*-score: −3.3 and *Z*-score: −3.0 at baseline to *T*-score: −2.8 and *Z*-score: −2.5 in the left side of the femoral neck (Table 1). Additionally, plain radiographs of the lumbar spine showed obsolete compression fractures and no new fractures [Figure 2(a)]. And magnetic resonance imaging findings for the thoracic and lumbar spine showed osteoporotic changes and compression fractures [Figure 2(b) and (c)]. Comprehensively, no further progression of the patient's vertebral deformities/reduction in vertebral height was observed.

Table 1. The alteration of bone mineral density following treatments.

	Baseline	4 months after treatment
Lumber spine		
T-score	−3.1	−2.4
Z-score	−3.0	−2.4
Right femoral neck		
T-score	−3.0	−2.8
Z-score	−2.6	−2.4
Left femoral neck		
T-score	−3.3	−2.8
Z-score	−3.0	−2.5

Furthermore, the treatment significantly decreased urinary NTX levels by 15.4% to 27.2 nmol BCE/mmol·Cr (equivalent to an 84.6% reduction from baseline). Similarly, BAP levels were significantly reduced by 19.4% to 7.9 μg/L (equivalent to an 80.6% reduction from baseline), indicating a state of quiescent bone turnover. No new vertebral fractures have occurred during the follow-up for 6 months, and the patient has chosen to continue minodronate and eldecalcitol therapy because of her decision to not have another child. The reporting of this study conforms to the CARE guidelines.[6]

Discussion

We present a challenging case involving extensive vertebral fractures resulting from osteoporosis during pregnancy and lactation, characterized by low bone density and heightened bone turnover after childbirth. However, following the administration of minodronate, the patient experienced a significant increase in bone density and normalization of bone turnover, leading to the resumption of regular daily activities.

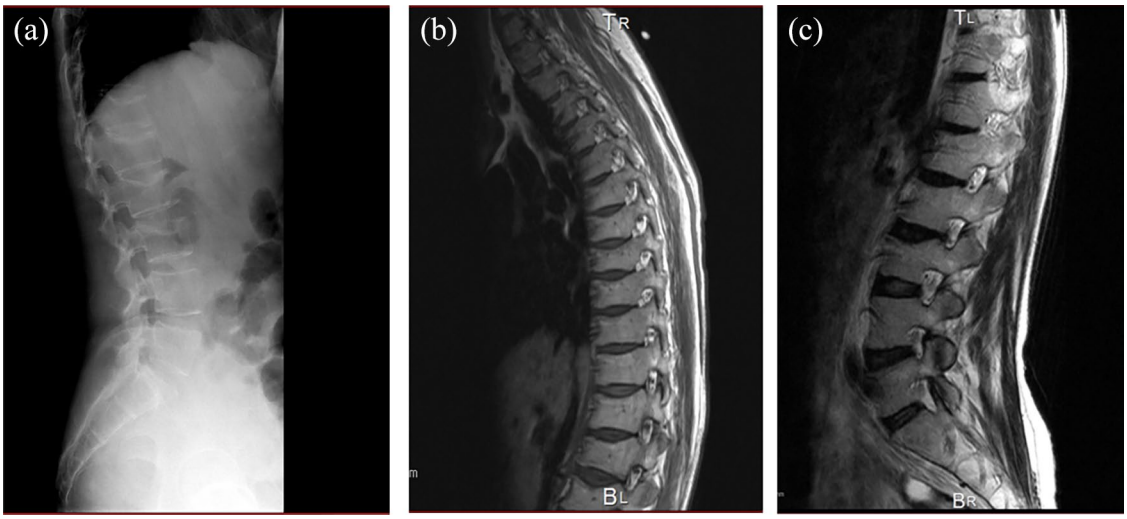

Figure 2. (a) Lateral view of the lumber spine shows no new fractures. Magnetic resonance imaging findings for the thoracic and lumbar spine. (b) Thoracic spine T1-weighted image. (c) Lumbar spine T2-weighted image shows osteoporotic changes and compression fractures.

PLO is a rare clinical condition that is prevalent worldwide. Despite an increasing number of reported cases, the documentation of PLO remains limited, and its underlying mechanism remains unclear. However, based on current knowledge, PLO is likely to be a multifactorial disease. The disease onset is difficult to predict in many cases because the fractures occur suddenly in healthy women during late pregnancy and postpartum lactation.

Risk factors for PLO include breastfeeding, low bone density, poor nutritional intake, and low body weight before pregnancy, smoking, and use of medications, such as steroids, heparin, anticonvulsants, and gonadotropin releasing hormone analogs, which are risk factors for secondary osteoporosis.[7] In the present case, breastfeeding, low body weight, and smoking were identified as risk factors for the development of PLO. Although breastfeeding was likely a strong contributor, the interactive effects of the other factors were unknown. Furthermore, some gene mutations have been identified as predisposing factors for PLO,[8] and specific genetic factors such as LRP5, COL1A1, and COL1A2 may be involved.[9] In the present case, genetic factors might have contributed to PLO because the patient's mother was diagnosed with postmenopausal osteoporosis. Although family history could be linked to premenopausal osteoporosis in this patient, the etiology remains unclear because of the absence of genetic screening.

The main symptoms of PLO include severe back pain and functional limitations. Loss of height in the vertebral bodies is also observed. The thoracolumbar transition region is most commonly affected, specifically T12, L1, and L2. The onset of symptoms occurs in more than two-thirds of cases during the first pregnancy, primarily in the third trimester or the first few weeks postpartum.[7] Despite the well-known clinical manifestations of PLO, little is known about its pathogenesis, natural history, and risk factors. Additionally, the optimal management and pharmacologic treatment of PLO have not been established owing to a lack of randomized controlled trials.

The treatment goals for PLO are to prevent subsequent vertebral and new nonvertebral fractures, relieve pain, and enhance BMD. A fundamental approach to PLO treatment involves discontinuing breastfeeding and commencing calcium supplementation with or without vitamin D. In severe or complicated cases with multiple fractures, several osteoporosis medications, including bisphosphonates, denosumab, teriparatide, strontium ranelate, and romosozumab, have been administered for PLO treatment.[10,11]

Bisphosphonates increase BMD by inhibiting bone resorption. Several studies have demonstrated that patients with PLO who received bisphosphonates, along with calcium and vitamin D supplementation, exhibited an average annual increase in lumbar spine and femoral neck BMD

of 10.2–17.0% and 2.6–6.5%, respectively.[12,13] Notably, bisphosphonates have a long half-life of up to 10 years, and they can cross the placenta, potentially posing teratogenic effects on a fetus.[14,15] Hence, bisphosphonate administration should be carefully considered if the patient intends to have subsequent pregnancies.

Minodronate is categorized as a third-generation bisphosphonate, and inhibit farnesyl pyrophosphate synthase in the mevalonic acid metabolic pathway in osteoclasts so that osteoclasts can be inactive and induce osteoclast apoptosis, although first-generation bisphosphonates, such as etidronate and clodronate, convert themselves into ATP analogs after being metabolized in the osteoclasts and induce osteoclast apoptosis.[16] Minodronate is 10,000 times more active for the inhibition of bone resorption than first-generation bisphosphonates such as etidronate and 10–100 times more active than second-generation bisphosphonates such as alendronate and risedronate.[17] Moreover, minodronate which the anti-resorption effect of is achieved by its inhibitory effect on osteoclasts significantly decreased the value of NTX and BAP compared with other bisphosphonates such as alendronate or risedronate.[18] In this case, we thought that minodronate was best available since BAP and NTX of the bone turnover marker were increased.

Bisphosphonates are significantly less expensive than other drug classes and are the most cost-effective initial therapy for osteoporosis.[19] Considering cost and effectiveness, a systematic review concluded that bisphosphonates are presently the most widely administered treatment for PLO.[7] Recently, there have been reports of treatment using human monoclonal antibodies such as denosumab and romosozumab.[10,11] The patient in our study chose not to take these drugs because they are expensive, and she did not wish to have a second child; therefore, bisphosphonates were used on the condition of no breastfeeding. Given that PLO is a form of juvenile-onset osteoporosis, economic considerations should also be considered, as long treatment periods and expensive drugs can increase the financial burden on patients. The cost comparison of the drugs shows that denosumab is priced at $270 per month, romosozumab at $2318 per month, teriparatide at $4039 per month, and bisphosphonates at $12 per month, with bisphosphonates being the most economical and cost-effective option. In addition, both denosumab and romosozumab improve bone density and reduce the risk of clinical fractures compared to bisphosphonates; however, a rebound activation of bone turnover and subsequent bone loss is likely to occur; if those treatment needs to be terminated for one reason or another.[20] Therefore, bisphosphonates taking easily and cheaply may be adequate for the treatment and long-term management of osteoporosis.

Calcium from the mother is transferred to the fetus for skeletal development, resulting in reduced calcium levels in pregnant women during the perinatal period. Hence, dietary intake and calcium and vitamin D supplements are important for modifying adequate bone density and preventing fractures in suspected PLO cases. Hassen-Zrour *et al.*[14] reported that BMD increased by 5–15% after administering vitamin D combined with bisphosphonates. In the present case, the patient received eldecalcitol with bisphosphonates, resulting in a 3–7% improvement in BMD.

On the other hand, it is important to remember that these young women's skeletons are capable of experiencing spontaneous recovery of BMD and strength through the following years because of young-aged patients although pharmacological treatment should be considered due to symptoms.[12] After discontinuing lactation, female skeleton experiences an important increase of BMD. Actually, although BMD of most postpartum women is a decrease of 3–10% during the first 2–6 months of lactation,[21] this loss is completely reversed between 6 and 12 months after weaning.[22] Postpartum women complicated with PLO should therefore be advised to quit breastfeeding as early as possible, as in this case, to reduce the high rate of bone resorption during lactation. This patient is being followed up with bisphosphonates, but 3–6 months after the fracture has set, patients with PLO may be advised to perform moderate, weight-bearing, and resistance activities to maintain bone mass, muscle mass, and mobility not to depend on pharmacological treatments. Furthermore, in this patient, she was seriously pathogenesis with 13 vertebral fractures. If the subjective pain had been taken into account, it is possible that the patient could have been treated before this status worsened. Recently, the Leeds Assessment of Neuropathic Symptoms and Signs pain scale and the pain DETECT questionnaire have been developed to assess the early onset of LBP associated with osteoporotic

vertebral fractures,[23] and these pain scales should be used for early detection of PLO.

Our literature review identified four previously reported cases and the present case involving >10 vertebral fractures due to PLO that required treatment (Table 2).[24–27]

Approximately 70 case reports or case series on PLO were found, but only 5 severe cases involving >10 vertebral fractures have been reported. To the best of our knowledge, this patient is identified as the most severe case of PLO, complicated with the greatest number of vertebral fractures. All cases were observed in Asian populations, suggesting the possibility of racial differences in the complications of severe multiple vertebral fractures associated with PLO. The patient in the present study was the oldest, and the ages of patients in other reported cases varied. BMI was identified as a risk factor for PLO, with a noticeable trend toward low BMI. Bone turnover markers were measured in two cases, including the present one, and BMD deterioration was observed in both cases, showing the pathophysiology of high-turnover osteoporosis. In three cases, treatment consisted mainly of vitamin D, calcium, and vitamin K supplementation; however, it took >6 months for the patients to experience pain improvement. In one case, teriparatide was also administered and is likely to have been expensive. Considering these factors and the rapid symptom improvement using bisphosphonates, we believe the present case conveys a compelling message for the future treatment of PLO. On the other hand, there are currently no randomized controlled trials of drug treatments in women with PLO; therefore, the benefit of medications in treating this condition remains uncertain because it has raised the possibility that PLO may improve over a natural course of time.

Conclusion

Severe PLO with severe multiple vertebral fractures significantly impacts the well-being of women, reducing their quality of life. Hence, early diagnosis and treatment are vital for pregnant women to manage osteoporosis severity, with the aid of radiography and densitometry for diagnostic purposes. In the current study, following treatment of severe PLO with 13 vertebral fractures with minodronate and vitamin D, notable improvements in both pain and BMD were observed. However, bisphosphonates can

Table 2. Severe cases involving >10 vertebral fractures due to pregnancy- and lactation-associated osteoporosis.

No.	Race	Age (years)	BMI (kg/m²)	Onset of LBP	BMD-LS (g/cm² or Z-score)	BMD-FN (g/cm² or Z-score)	Bone turnover	No. of fractures	Treatment	Clinical outcome	Authors/year of publication
1	Turkish	22	NA	Third trimester of pregnancy	−3.6	−1.5	NA	10	Calcitonin (200–400 IU daily), calcium (1000 mg daily), and vitamin D (880 IU daily)	Pain improvement within 6 months	Ozturk *et al.*, 2014
2	Japanese	30	22.2	Second month of lactation	0.662	0.768	High	12	Alfacalcidol (0.5 µg daily) and vitamin K (30 mg daily)	Pain improvement within 8 months	Nakamura *et al.*, 2015
3	Turkish	36	22.4	First month of lactation	0.593	NA	NA	10	Calcitonin (200 IU daily), calcium (1000 mg daily), and vitamin D (880 IU daily for 18 months)	Pain improvement within 12 months	Ozdemir *et al.*, 2015
4	Korean	36	17.6	Immediately after delivery	−2.7	−1.6	NA	10	Teriparatide	NA	Yun *et al.*, 2017
Current	Japanese	39	18.4	Second month of lactation	0.643, −3.0	R: 0.460, −2.6 L: 0.462, −3.0	High	13	Minodronate (50 mg monthly) and eldecalcitol (0.75 µg daily)	Pain improvement within 4 months	Ota *et al.*, 2023

BMI, body mass index; BMD-FN, bone mineral density-femoral neck; BMD-LS, bone mineral density-lumber spine; LBP, low back pain, NA, not available.

potentially affect the fetus through placental transfer; hence, careful consideration is required for patients planning pregnancy. Despite the widespread use and cost-effectiveness of bisphosphonates, the selection of PLO medications involves multiple factors, necessitating research for future recommendations.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki. Ethical review and approval for this study was waived due to a case report by the Institutional Review Board of Tokyo Rosai Hospital.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and all accompanying images. We are prepared to provide a copy of the consent form upon request.

Author contributions

Kuniaki Ota: Conceptualization; Investigation; Methodology; Writing – original draft.

Yuta Asanuma: Formal analysis; Investigation; Methodology.

Hideyuki Hirasawa: Data curation; Formal analysis; Methodology.

Hiroaki Ohta: Conceptualization; Writing – review & editing.

Toshifumi Takahashi: Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supplemental material

Supplemental material for this article is available online.

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