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| Author(s) | Takahashi, Naoto; Arai, Itaru; Kayama, Satoru; Ichiji, Kenji; Fukuda, Hironari; Handa, Jun-Ichi; Konno, Shin-Ichi |
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[Case Report]

FOUR-YEAR FOLLOW-UP OF PREGNANCY-ASSOCIATED OSTEOPOROSIS : A CASE REPORT

NAOTO TAKAHASHI^{1,2)}, ITARU ARAI¹⁾, SATORU KAYAMA¹⁾, KENJI ICHIJI¹⁾,
HIRONARI FUKUDA^{1,2)}, JUN-ICHI HANDA^{1,2)} and SHIN-ICHI KONNO²⁾

¹⁾Department of Orthopaedic Surgery, Southern Tohoku General Hospital, Fukushima Japan, ²⁾Department of Orthopaedic Surgery, Fukushima Medical University School of Medicine, Fukushima, Japan

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Abstract : A 22-year-old woman presented with complaints of severe pain in a wide region of the thoracolumbar spine. She developed severe pain in the thoracolumbar spine region 2 months after her first delivery and was referred 1 month later. A lateral thoracic X-ray showed depressed degenerative vertebrae (T7, T9). One month after the initial examination, thoracic sagittal magnetic resonance imaging showed low intensity areas on T1-weighted imaging and iso-high intensity areas on T2-weighted imaging at T5, 7, 8, 9 and 11. Bone mineral density measured by ultrasound was low (%YAM 76%). The bone metabolic markers were high, suggesting accelerated osteoclast activity. These findings prompted a diagnosis of pregnancy-associated osteoporosis. She was asked to stop breastfeeding and to wear a lumbar brace, and treatment with nutritional calcium, activated vitamin D3, and risedronate sodium was started. Her low back pain almost disappeared after treatment. Bone metabolic markers showed normalization 8 months after the initial examination. Risedronate sodium was stopped 2 years and 2 months after the initial examination. Teriparatide treatment was started because her bone mineral density remained low ; however, the osteoblast marker P1NP was not increased 5 months after the start of teriparatide treatment.

Key words : Pregnancy-associated osteoporosis, long-term follow-up, conservative treatment, bisphosphonate, teriparatide

INTRODUCTION

Osteoporosis is a disease of aging that is usually seen in patients after 50 years of age, most commonly postmenopausal women. However, osteoporosis associated with pregnancy and lactation is rare. The prevalence, etiology, and pathogenesis of pregnancy-associated osteoporosis remain unclear. Moreover, there have been few reports dealing with the long-term follow-up of patients with pregnancy-associated osteoporosis. The case of a young woman who was treated for pregnancy-associated osteoporosis for more than 4 years is reported. The patient and/or family was informed that data from the case would be submitted for publication and gave consent.

REPORT OF THE CASE

A 22-year-old woman (height 163 cm, weight 60 kg at the initial examination, gravida 1, para 1) presented with complaints of severe pain in a wide region of the thoracolumbar spine. There was no history of trauma, menstrual irregularity, or underlying diseases such as diabetes mellitus, renal failure, hypertension or thyroid disease. She had never taken drugs such as steroids or antiepileptics that could adversely affect bone. She was an irregular, mild smoker for 3 years and had no other risk factors or positive family history for osteoporosis. Her menarche occurred at 13 years of age, and her menses had been regular. She developed severe pain in the thoracolumbar spine region about 2 months after her first delivery, which caused difficulties in her

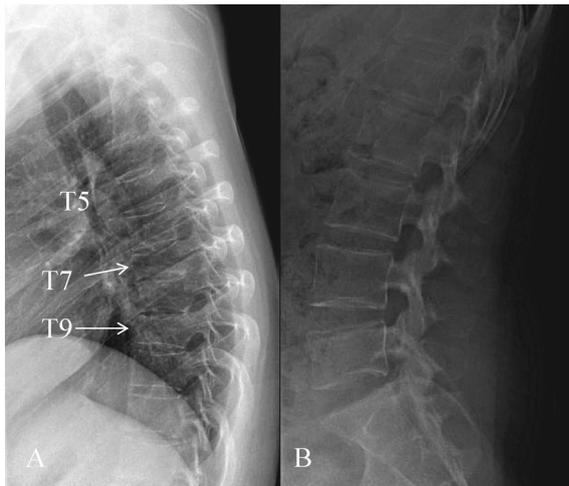


Fig. 1. X-ray findings at the initial examination
 A : Lateral thoracic X-ray view shows decompressed degenerative vertebrae at T7 and T9.
 B : Lateral lumbar X-ray shows no obvious bone injury.

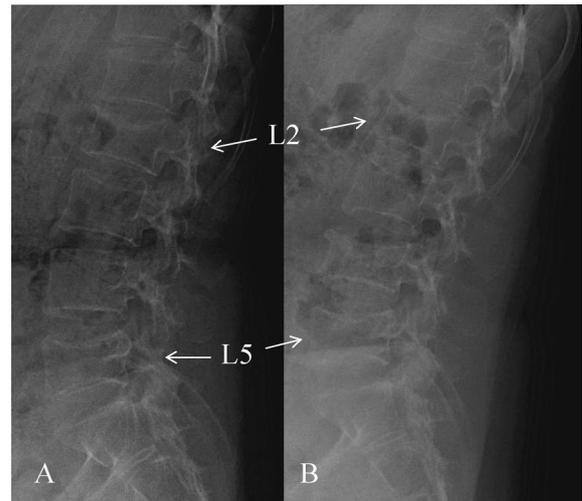


Fig. 2. Lumbar X-ray findings at 1 month (A) and 2 months (B) after the initial examination
 A : Lateral lumbar X-ray shows depressed, degenerative vertebrae at L2 and L5.
 B : Lateral lumbar X-ray shows a fresh depressed, degenerative vertebra at L4.

daily activities, and she was initially referred to our outpatient clinic 3 months after her first delivery, after which time she had started breastfeeding her infant. She had no pain at rest or nocturnal pain, and no signs of metabolic, infectious, or malignant bone diseases as “red flags.”

She had pain on percussion over a wide region of the thoracic spine and severe low back pain on flexion and extension at the initial examination. There was no evidence of a neurological deficit.

A lateral thoracic X-ray showed depressed degenerative vertebrae at T7 and T9 (Fig. 1A), and a lateral lumbar X-ray showed no obvious bone injury (Fig. 1B) at the initial examination. Because she was breastfeeding, she was started on conservative therapy with a poultice alone. Lateral lumbar X-rays 1 and 2 months after the initial examination showed depressed, degenerative vertebrae at L2 and L5, respectively (Fig. 2A, B). Thoracic sagittal magnetic resonance imaging (MRI) showed low intensity areas on T1-weighted imaging and iso-high intensity areas on T2-weighted imaging at T5, 7, 8, 9 and 11 (Fig. 3A, B). The bone mineral density (BMD) by speed of sound (SOS) was low (1,492 m/s, %YAM 76%) (Fig. 4). Blood test results showed serum parathyroid hormone-c terminus (PTH-C) 0.1 ng/mL, thyroid stimulating hormone (TSH) 3.04 μ U/mL, calcium (Ca) 9.2 mg/dL (measured value), phosphorus (P) 4.3 mg/dL, and alkaline phosphatase (ALP) 339 IU/L; all were normal. There were no signs of thyroid or parathyroid dysfunction or malignant disease on blood testing. The bone metabolic



Fig. 3. Magnetic resonance imaging (MRI) findings at the initial examination
 A : Thoracic MRI, sagittal view, T1-weighted image, shows low intensity areas at T5, 7, 8, 9 and 11.
 B : Thoracic MRI, sagittal view, T2-weighted image, shows iso-high intensity areas at T5, 7, 8, 9, and 11.

markers, DPD-U/Cre conversion (14.8 nmol/mc), and NTx-U/Cre conversion (152.2 nmol/BCE) were high, suggesting accelerated osteoclast activity (Fig. 4). Serum PTH-C, Ca, and P levels remained within

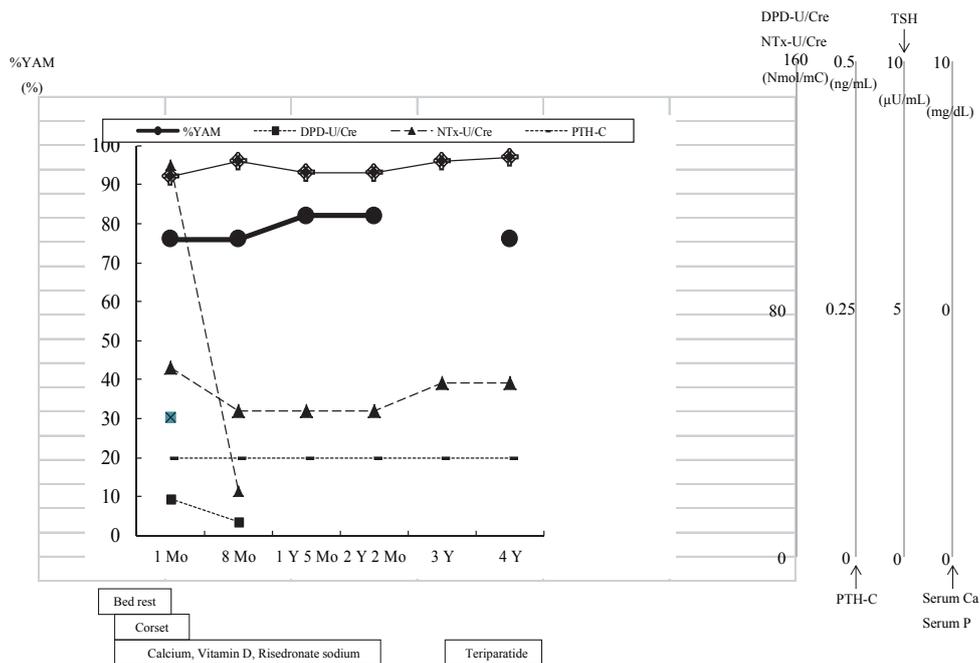


Fig. 4. Clinical course and bone mineral density changes
 The bone mineral density shows initial loss and then maintains the same level for more than 4 years.
 The bone metabolic marker levels are high at the initial examination, but they normalize 8 months after the initial examination.

the normal ranges for 4 years (Fig. 4).

The diagnosis was pregnancy-associated osteoporosis based on the above physical findings. She was asked to stop breastfeeding and to wear a lumbar brace, and treatment with nutritional calcium, activated vitamin D3, and risedronate sodium was started. She never restarted breastfeeding, and she developed menstrual irregularity after the start of treatment. A lateral lumbar X-ray 2 months after the initial examination showed a fresh depressed, degenerative vertebra at L4 (Fig. 2B), but her low back pain almost disappeared. The bone metabolic markers, DPD-U/Cre conversion (5.5 nmol/mc), and NTx-U/Cre conversion (17.9 nmol/mc), showed normalization at 8 months after the initial examination (Fig. 4). Risedronate sodium was stopped 2 years and 2 months after the initial examination (Fig. 4). There was no recurrence of her subjective symptoms from 8 months after the initial examination. However, teriparatide treatment (Forteo, Eli Lilly Japan K.K, Kobe, Japan) was started from 3 years after the initial examination because her BMD did not recover (Fig. 4).

There were no fresh vertebral fractures, collapse, or deformity at 4 years and 2 months after the initial examination on lateral thoracolumbar X-ray examination (Fig. 5A, B). However, the osteoblast marker P1NP, which was 63.5 µg/L, was not in-

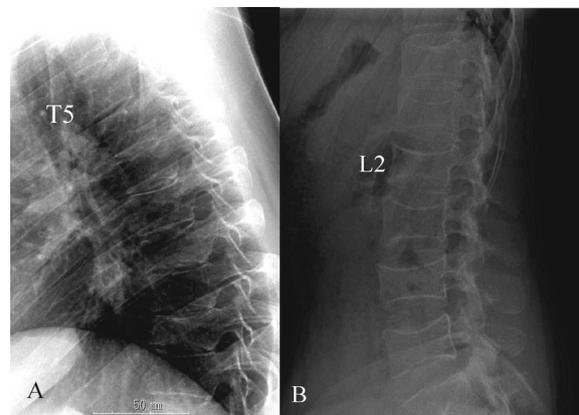


Fig. 5. X-ray findings at 4 years and 2 months after the initial examination

- A : There are no fresh vertebral fractures, collapse, or deformity on the lateral thoracic X-ray.
- B : There are no fresh vertebral fractures, collapse, or deformity on the lateral lumbar X-ray.

creased 5 months after the start of teriparatide treatment.

DISCUSSION

There is no clear definition of pregnancy-associated osteoporosis, but it is generally characterized by the presence of back pain, and in some cases, vertebral fractures and height loss could occur from

immediately before delivery to 6 months after childbirth. Women pregnant or nursing for the first time or several times are known to have more osteoporosis. In 1955, Nordin reported the first four cases of osteoporosis in pregnant or nursing women¹⁾. Pregnancy-associated osteoporosis is classified as a primary osteoporosis in the Japanese Osteoporosis Society Guideline 2011. Primary osteoporosis is classified as regressive osteoporosis, which includes postmenopausal osteoporosis or elderly osteoporosis, and as idiopathic osteoporosis, which includes juvenile osteoporosis and pregnancy-associated osteoporosis. Pregnancy-associated osteoporosis and juvenile osteoporosis are rare, and their timing differs. Juvenile osteoporosis occurs from adolescence to youth, while pregnancy-associated osteoporosis occurs from immediately before delivery to 6 months after childbirth.

There are some etiologies of pregnancy-associated osteoporosis, but its cause and pathophysiology remain unknown. One hypothesis for the pathology of pregnancy-associated osteoporosis is that a woman with a normal BMD level before pregnancy may develop severe BMD loss, because some factors related to pregnancy, delivery, and nursing are associated with a nutritional lack of calcium, phosphorus, proteins, etc.^{2,3)}. Another hypothesis is that a woman with a naturally low BMD level before pregnancy may develop the pathology of osteoporosis after pregnancy, delivery, and nursing, because it is difficult to imagine that the development of obvious X-ray findings of osteoporosis could occur during the short term of pregnancy^{4,5)}. Yet another hypothesis is that inherited factors are associated with pregnancy-associated osteoporosis⁶⁾. Although pregnancy-associated osteoporosis is classified as a primary osteoporosis in the Japanese Osteoporosis Society Guideline 2011, it may be the result of an independent disease, i.e., a secondary osteoporosis.

The frequency of back and low back pain appears to be higher for women after childbirth due to an increase in weight or the act of holding a baby in their arms. It is necessary to evaluate the condition of vertebral bone and BMD in patients with postural changes, loss of height, and severe low back pain. Patients who are found to lose BMD should be examined for underlying disease that triggers secondary osteoporosis, such as endocrine diseases (hyperthyroidism, hyperparathyroidism, Cushing disease, and diabetes mellitus, etc.), metabolic diseases (amyloidosis), inflammatory diseases (rheumatoid arthritis or sarcoidosis), and hematological diseases (multiple myeloma, lymphoma, leukemia,

etc.). Pregnancy-associated osteoporosis may be diagnosed if such diseases are excluded⁷⁾.

In this case, although her symptoms were very severe, her BMD was %YAM 76%, which was comparatively not very low. This fact demonstrated that a low BMD was not responsible for her symptoms, including severe back pain. Her symptoms may have been associated with brittle bone, but not with a lower BMD.

The therapeutic management of pregnancy-associated osteoporosis has not yet been established. The therapeutic guide for secondary osteoporosis in the Japanese Osteoporosis Society Guideline 2011 recommends therapy appropriate for pregnancy-associated osteoporosis⁷⁻¹¹⁾. Specifically, the priorities of therapy are treatment for the underlying disease, replenishment of calcium, and treatment for osteoporosis with accelerated bone resorption. If the underlying disease appears to be pregnancy or nursing, it would be necessary to control bone resorption and to stop breastfeeding in order to control the excretion of calcium as part of the therapy. Osteoblastic or osteoclastic markers are accelerated in the second half of pregnancy and after childbirth. Because nursing women's osteoblastic or osteoclastic markers are higher than those of non-nursing women, nursing appears to accelerate metabolism^{12,13)}. Therefore, if breastfeeding is stopped, the acceleration of bone metabolism may end. Nutritional calcium and activated vitamin D₃¹⁴⁾ are given to replenish calcium. If accelerated bone resorption continues, bisphosphonate treatment is needed¹⁵⁾. However, it has been reported that bisphosphonate could be teratogenic for the embryo. Therefore, informed consent with respect to this issue would be needed. There have been some reports of the therapeutic effect of teriparatide for patients with pregabalin-associated osteoporosis with severe BMD loss¹⁶⁻¹⁸⁾. Teriparatide treatment is associated with a lower risk of its accumulation; therefore, the next pregnancy would be safer after teriparatide treatment is stopped, unlike with bisphosphonate therapy. Consequently, it may be necessary to consider teriparatide treatment if the patient has multiple vertebral fractures, for which osteoblasts are required as early as possible. Teriparatide treatment has some merits, including osteogenesis and prevention of vertebral fractures. It also has some disadvantages, including the need to avoid pregnancy and the burden of self-administration. Therefore, one must be cautious about the use of teriparatide in young women.

Because it took about a month for the diagnosis

of pregnancy-associated osteoporosis to be made in the present case, multiple vertebral fractures occurred, and bone resorption was accelerated, which indicated the need to stop breastfeeding and start bisphosphonate treatment at once. This treatment improved her pain immediately. Thus, multiple vertebral fractures occurred during breastfeeding, and the patient's back pain decreased immediately after stopping breastfeeding. It may be important to stop breastfeeding as soon as possible when pregnancy-associated osteoporosis is diagnosed. However, the patient's BMD did not recover even though she was treated for more than 4 years, suggesting that this patient might have a hidden pathology that caused BMD loss.

The present case report has some limitations. The patient's BMD was not evaluated exactly in this study because it was measured only by the speed of sound. It may be difficult to evaluate the recovery of the patient's BMD in this study. In the future, patients' BMD should be evaluated by dual-energy X-ray absorptiometry.

There have been few reports of the long-term follow-up of patients with pregnancy-associated osteoporosis^{14,19}. In the present case, teriparatide was used for the treatment of pregnancy-associated osteoporosis, but long-term follow-up of the patient's BMD level has yet to occur. The treatment for pregnancy-associated osteoporosis is mostly completed when the patient's symptoms have recovered. However, some patients have a persistently low BMD even after their subjective symptoms have improved. It can be expected that such patients will develop severe osteoporosis at menopause. Although more than 60 years have passed since the first report of pregnancy-associated osteoporosis in the 1950s¹, the prognosis of pregnancy-associated osteoporosis remains unclear. However, patients who develop osteoporosis in pregnancy and lactation would have a greater risk of fracture if they did not receive sufficient treatment to improve their BMD. Therefore, it is very important to treat osteoporosis in pregnancy and lactation as much as possible.

In conclusion, a case of pregnancy-associated osteoporosis that was followed-up for more than 4 years was presented. The patient's severe pain was relieved 2 months after the start of conservative therapy. However, recovery of the patient's BMD was not evident despite long-term treatment. These findings suggest that the patient may have a hidden pathology that caused BMD loss. This patient appears to require long-term treatment and follow-up for the osteoporosis.

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