

Challenges in the Management of Pregnancy and Lactation-Associated Osteoporosis (PLO) in Women of Childbearing age With Multiple Vertebral Fractures

Yang Liu¹, Genlong Jiao¹, Zhizhong Li¹ 

¹Department of Spinal Surgery, The First Affiliated Hospital of Jinan University, Guangzhou City, Guangdong Province, China

Abstract: Pregnancy and lactation-associated osteoporosis (PLO) is a rare but serious and difficult to be diagnosed disease, which occurs in the late gestation and early lactation, mainly manifested by low back pain, vertebral fracture and reduction of hip bone density. It is difficult to diagnose and has a high rate of misdiagnosis and mistreatment. We present the case of a 39-year-old woman who suffered from acute low back pain and walking difficulty after a sudden stoop in 2 months postnatal. The X-ray and MRI examination showed that fractures occurred in the first, second and fifth lumbar vertebrae. Bone mineral density (BMD) examination confirmed osteoporosis. After stopping lactation, calcium and vitamin K2 supplemented, compared with zoledronic acid injection, the low back pain was relieved and the BMD increased gradually. The incidence of PLO is seriously underestimated in clinical practice. Women in pregnancy and lactation with acute low back pain should be highly alert to the occurrence of PLO, and early treatment need to be taken in case of further serious consequences such as vertebral compression fracture or hip fracture.

Keywords: Pregnancy and Lactation-Associated Osteoporosis (PLO), Osteoporosis, Vertebral Fracture, Bone Mineral Density

Introduction

PLO is a rare disease that causes back pain and multiple vertebral compression fractures in women of childbearing age, with which the pathogenesis is not clear and no standard diagnosis or treatment were carried out at present. Patients with PLO were generally in good health before pregnancy, and were admitted to the hospital with acute back pain or hip malaise as the chief complaint three months after pregnancy or two months before lactation. The routine laboratory biochemical examination was mostly normal, spine X-ray and MRI could show the vertebral fracture, and bone density examination could find decrease in BMD. The primary and secondary osteoporosis should be excluded first before the diagnosis of PLO, therefore the clinical diagnosis is often delayed for several months and may be misdiagnosed and mistreated. To our knowledge, only about 100 cases of PLO altogether have been reported in the current literature since the first case been reported by Nordin B E. et al in 1955 [1], and all of which are exclusionary diagnosis. To date, diphosphate combined with calcium, vitamin C and vitamin D is considered as the main treatment for osteoporosis. Here we present a case of 39-year-old woman suffering from PLO with multiple lumbar compression fractures (L1, L2, L5), who obtained a visibly relieve by the combined treatment of calcium, vitamin D, vitamin K2 and zoledronic acid. About a

quarter of patients with PLO will have secondary fractures, therefore, for women of childbearing age suffering from back or hip pain, clinicians should be alert to the occurrence of this disease.

Case Presentation

A 39-year-old primipara had a severe back pain accompanied by walking difficulties after a sudden stooping at 2 months postnatal, without lower limb weakness or numbness, and the Lasegue sign was negative. The X-ray suggested multiple compression fractures of the lumbar spine. T2 fat suppression sequence of lumbar MRI showed that the L1, L2 and L5 vertebrae got high signal and decreased in height, indicating the fresh compression fracture with myelodema (Figure 1). She was healthy and menstruating regularly before becoming pregnant, and had been breast-feeding for six months before menstruating again, with no history of blue sclera, dental dysplasia or long-term use of corticosteroids.

The serum alkaline phosphatase (ALP), parathyroid hormone (PTH) and 25-hydroxytotal vitamin D was 135 U/L, 6.96 pg/mL and 29.0 ng/mL respectively. The levels of adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), sex hormone, 24h urine free cortisol, plasma cortisol, serum calcium and phosphorus were normal. Bence Jones protein was

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Zhizhong Li (Correspondence)

+0086-20-38688619; Fax:0086-20-38688619

negative, and serum protein electrophoresis had no abnormality. Single photon emission computed tomography (SPECT) indicated no obvious radioactive concentration or lesion except the lumbar fractures. The bone density examination indicated that the Z score of one to four lumbar spine was -3.1.

Stop breastfeeding, then Calcium, vitamin D and vitamin K2 were supplemented orally, with salmon calcitonin injection given intramuscularly and bisphosphonates such as zoledronic acid injection given intravenously. The followed-up Z scores of bone mineral density of lumbar vertebrae in second, seventh and eighteenth month were -2.8, - 2.2, - 2.0, respectively (Table 1). The followed up lumbar MRI in second and seventh month showed that edema of vertebral fracture decreased significantly and no new fracture was found (Figure 2, 3).

Discussion

PLO is a rare but serious disease, which occurs in the late pregnancy and early lactation with the main manifestations are back pain, reduction of bone density, vertebral compressed fracture and hip fracture. During the occurrence of PLO, osteoblasts decrease and bone conversion increase, resulting in decreased bone formation and increased bone resorption, leading to osteoporosis. However, the exact pathogenesis has not been revealed, which is generally considered to be related to multiple factors such as genetic, weight, inadequate calcium and vitamin D intake, together with hormone level changes during pregnancy and lactation. Most of the patients with PLO were healthy before pregnancy, and multiple fractures mainly occurred in the thoracic and lumbar vertebrae. According to Smith and O'Sullivan's report [2,3], in about 70% of cases, PLO was diagnosed during the first pregnancy. Some researches [4,5] have shown that mothers of PLO patients have a higher incidence of fractures and the children of PLO patients have a lower bone mass than the general population, suggesting that PLO is genetically related. Butscheidt, S et al [6] detected some new mutations in LRP5, COL1A1 and COL1A2 genes in 7 patients with PLO, which played an important role in the occurrence and development of Pregnancy and lactation-associated osteoporosis.

Cohen, A et al [7] found that PLO patients may have potential osteoblastic dysfunction, which affects their response to osteogenic anabolic drugs. In late pregnancy, parathyroid hormone-related peptide (PTHrp) secreted by placenta and mammary gland reached its peak, which can produce biological effect similar to PTH, enhanced osteoclast activity and increased bone absorption. Cooke-hubley, S et al [8] conducted a prospective, multicenter, randomized cohort study founding that parity and lactation had no adverse relationship with clinical vertebral fracture, or the rate of BMD decline over 10 years. It is not clear whether PLO accelerates bone resorption or begins to

cause significant bone loss during pregnancy.

The X-ray examination can find vertebral and hip fracture, but further CT examination is needed for patients with burst fracture, which can clearly show whether the fragment enters the spinal canal. Fresh fractures show fat suppression high signal in T2 W of MRI, so patients with suspected fractures can be well identified. In addition, MRI can also observe the intervertebral disc herniation and Spinal tumors. Emission computed tomography (ECT), such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), can identify tumors based on differences in the concentration of radionuclides in different tissues [9]. Since the patient was a 39-year-old primipara, we performed a SPECT examination to rule out potential malignancies. The dual-energy X-ray bone densitometer uses two different types of X-ray energy attenuation to measure the BMD of vertebrae and hip. It is considered to be the current gold standard for osteoporosis diagnosis. The results of BMD mainly show the t-score and Z-score. The t-score is used for the diagnosis of osteoporosis while Z-score reflects whether the BMD measured is lower than the average level of the same age group.

The clinical diagnosis of PLA is challenging. It mainly depends on the exclusion of currently known diseases that cause osteoporosis, so the diagnosis period is long and it is easy to be misdiagnosed and mistreated. This patient is a woman of childbearing age, with regular menstruation before pregnancy and no blue sclera and abnormal tooth development, so the primary osteoporosis and osteogenesis imperfecta were excluded. The levels of ACTH, sex hormone, serum calcium and phosphorus were normal. Bence Jones protein was negative, and no history of long-term use of corticosteroids, Combined with lactation, the patient was finally diagnosed with PLA. The most important and challenging differential diagnosis of PLA is secondary osteoporosis, such as genetic diseases, autoimmune diseases, endocrine diseases and malignant tumors [10].

There are currently no guidelines for the diagnosis and treatment of PLO. After stopping lactation, supplementing calcium and vitamin D, adding parathyroid hormone derivatives and bisphosphonates, most patients may achieve a favorable prognosis [11]. In addition, the administration of denosumab can significantly improve patients' symptoms and bone density [12]. Stopping breastfeeding could reduce the loss of calcium, and the longer of the lactation lasting, the more fractures occur on average[13]. Bisphosphonates have a relatively short bone retention time and are highly effective and well tolerated in the treatment of PLO, but they need to be cautious or stop breastfeeding because of their potential harm to the fetus [14,15]. Most of the patients could not return to the normal level of BMD after treatment, and the BMD

does not decrease again during the second pregnancy, but the safety of re-pregnancy needs more prospective clinical study.

Conclusion

Pregnancy and lactation-associated osteoporosis is a rare cause of back and hip pain in women of

childbearing age, and its incidence is seriously underestimated. Women suffering from acute back pain during pregnancy and lactation should be highly alert to the occurrence of PLO, and early treatment need to be taken to avoid further serious consequences such as vertebral compression fracture or hip fracture.

Table 1 Statistical table of mean bone mineral density (BMD) and Z-score of the lumbar vertebrae

item	1st examination	2nd month	7 th month	18 th month
BMD (g/cm ²)	0.706	0.687	0.780	0.734
Z-score	-3.4	-2.8	-2.1	-2.0

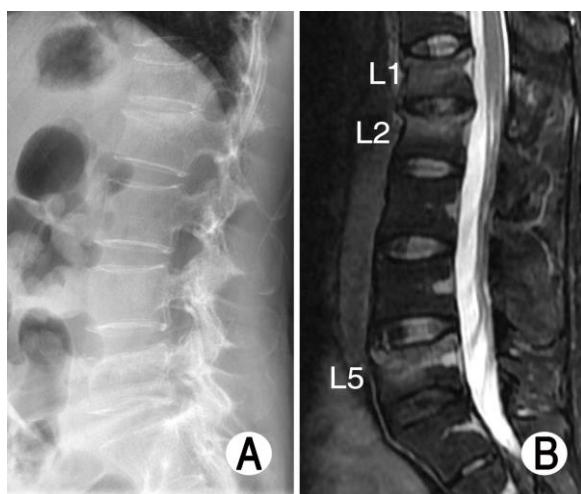


Figure 1

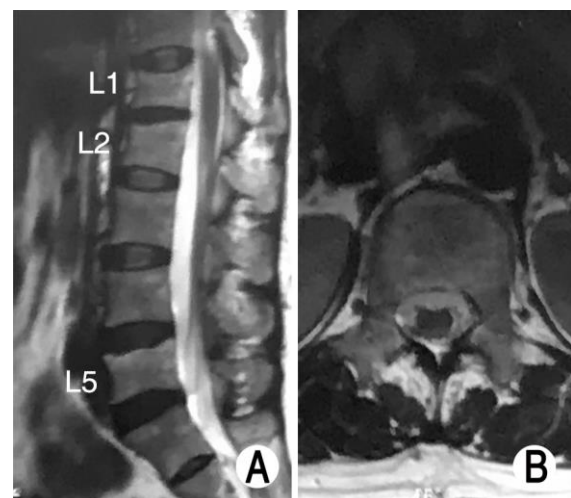


Figure 3

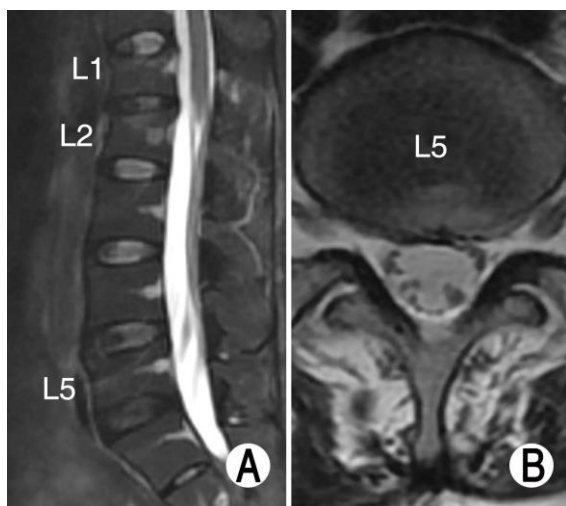


Figure 2

Figure 1 X-ray films and MRI shows the multiple lumbar compression fractures. **A** Lateral view, multiple lumbar compression fractures at L1, L2, L5; **B** Mid-sagittal view, L1, L2 and L5 vertebrae got high signal in T2 fat suppression sequence and decreased in height

Figure 2 The followed up lumbar MRI in second month showed that edema of vertebral fracture decreased significantly. **A** Mid-sagittal view; **B** Axial view

Figure 2 The followed up lumbar MRI in seventh month showed no new fracture. **A** Mid-sagittal view; **B** Axial view

Conflict of Interest:

The authors declare that there is no conflict of interest regarding the publication of this paper.

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