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Case Report

Teriparatide and denosumab treatment for pregnancy and lactation-associated osteoporosis with multiple vertebral fractures: A case study

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ABSTRACT

Objective: Pregnancy and lactation-associated osteoporosis (PLO) is a rare disease, which can lead to vertebral fractures in women of reproductive age. No treatment strategy for PLO has been established. Here we report a case of PLO treated with teriparatide followed by denosumab, in which remarkable improvement in bone mineral density (BMD) was achieved.

Case report: A 27-year-old woman experienced severe back pain two weeks after her first delivery. PLO was diagnosed from her low BMD and multiple vertebral compression fractures. She was treated with teriparatide for 6 months, followed by denosumab. After 1 year, her BMD increase from baseline was 16.5% in L2~4 and her pain had been relieved.

Conclusion: In addition to weaning, administration of teriparatide followed by denosumab led to remarkable improvement in the patient's symptoms and BMD. Therefore, we regard this method as a promising choice for the treatment of PLO.

Introduction

Pregnancy and lactation-associated osteoporosis (PLO) is a rare condition typically presenting with vertebral fractures and back pain during pregnancy, the early post-partum period and/or lactation [1]. The mechanism of PLO is unclear, and no treatment strategy has yet been established. Bisphosphonates (BPs) have been used, but these are known to have a strong binding affinity to bone, and the accumulated BPs are released after treatment [2]. The fetus of a subsequent pregnancy may be exposed to BPs even long after the discontinuation of therapy, and the potential risk is unclear [3,4]. There have been some reports of PLO treated with teriparatide [5]. It has also been reported that switching from teriparatide to denosumab leads to better therapeutic effects in postmenopausal patients [6,7]. Here we describe a case of PLO with multiple vertebral fractures, treated with teriparatide followed by denosumab, in which improvement in physical activity and a remarkable increase in bone mineral density (BMD) were achieved.

Case presentation

A 27-year-old woman suddenly experienced severe back pain when she bent forwards two weeks after delivery of her first baby in the 39th week. She visited an emergency room, and vertebral fractures in L1, L2, and L3 were revealed by magnetic resonance imaging (MRI) (Fig. 1). Her pain worsened despite treatment with a lumbar corset. One month after delivery, PLO was suspected, and she was referred to our department.

At the first visit, she could not move without assistance. She had taken no bone-affecting medication, and there was no family history of fractures. She neither smoked nor consumed alcohol. Her menstrual cycle was approximately 35 days. Her body mass index (BMI) was 17.1 kg/m^2 (height: 163 cm; body weight: 45.5 kg). Her BMD had not previously been measured.

BMD measured by dual-energy X-ray absorptiometry (DXA) was 0.711 g/cm^2 in L2~4 (T-score: −2.6, L2: 0.729, L3: 0.752 g/cm^2, L4: 0.659 g/cm^2), and 0.589 g/cm^2 in the left femoral neck (T-score: −1.8, left total hip: 0.650 g/cm^2). Alkaline phosphatase, serum calcium, urine calcium, serum phosphorus, urine phosphorus, parathyroid hormone (PTH), and undercarboxylated osteocalcin were 375 U/l (112–334 U/l),

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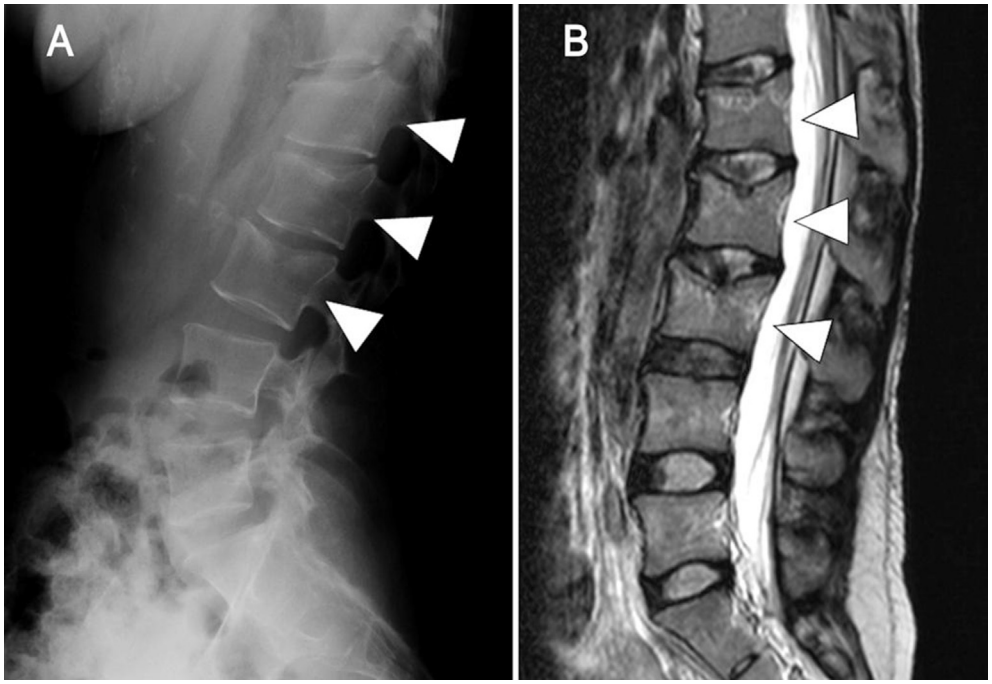

Fig. 1. A: X-ray image of the spine; B: T2-weighted magnetic resonance image. Multiple vertebral fractures were detected at L1, L2, and L3.

9.7 mg/dl (8.8–10.1 mg/dl), 4.6 mg/dl (2.6–4.4 mg/dl), 4.8 mg/dl, 49.3 mg/dl, 17 pg/ml (15–65 pg/ml), and 22.2 ng/ml (<4.50 ng/ml), respectively. As far as bone turnover markers (BTM) are concerned, urine crosslinked N-telopeptide of type 1 collagen (NTX) was 154 nmol BCE/mmol· Cr, and procollagen 1 N-terminal propeptide (P1NP) was 132 μg/l. Taking these findings together, she was diagnosed as having multiple PLO-related vertebral compression fractures. Breast-feeding was terminated, and to ameliorate her serious condition teriparatide therapy was initiated by subcutaneous injection of Teribone® 56.5 μg weekly (Asahi Kasei; Tokyo, Japan).

The treatment course is shown in Fig. 2. After six months, BMD had increased to 0.755 g/cm^2 (+6.2% from baseline) in L2~4 but was unchanged in the left femoral neck. Urine NTX and P1NP were 79.1 nmol BCE/mmol· Cr (−62% from baseline), and 72.8 μg/l (−45% from baseline). At this point, she could walk without a walker. However, she requested alternative treatment to avoid frequent injections, so teriparatide was discontinued, and subcutaneous injection of denosumab (Pralia Subcutaneous Injection Syringe, Daiichi Sankyo Ltd.; Osaka Japan) 60 mg/6 months was initiated. At six months after the first denosumab injection, her BMD had increased significantly to 0.828 g/cm^2 in L2~4 (+16.5% from baseline) and to 0.613 g/cm^2 in the left femoral neck (+3.9% from baseline). Urine NTX and P1NP had decreased to 17 nmol BCE/mmol· Cr (−89% from baseline) and 13.8 μg/l (−90% from baseline), respectively. Her pain had been relieved, and she could walk slowly without wearing a corset.

Discussion

During the final six weeks of pregnancy, 300–500 mg of calcium per day is lost to fetal osteogenesis, and approximately 200 mg of calcium is lost daily in the breast milk during lactation [4], which significantly affects the calcium metabolism of the mother. During pregnancy, intestinal calcium absorption is increased [4]. After delivery, to satisfy the required calcium levels in the milk, resorption of maternal bone may increase [4].

Although many prospective studies have reported BMD loss in pregnancy, the degree of BMD change has varied. It has also been reported that a 5–10% trabecular BMD loss occurs during lactation; however, this is restored within 6–12 months after weaning [4]. It is conceivable that only women with severe BMD loss develop symptoms of PLO.

The risk of fragile bone fracture during pregnancy or lactation rises in women who have low BMD before pregnancy for reasons such as anorexia nervosa, ovarian dysfunction, or the use of medications associated with bone mass decrease, including heparin, warfarin, and corticosteroids. The present subject did not suffer from anorexia nervosa but had low body weight.

Treatment for PLO is controversial. Although weaning increases BMD, clinicians aim to increase BMD effectively and safely using medications. BPs increase BMD by inhibiting osteoclast activity. O'Sullivan et al. reported BPs to be more effective in treating PLO than weaning and supplementation with vitamin D and/or calcium [9].

The half-life of BPs in the bone is estimated to exceed ten years [10]. Papapoulos et al. reported that pamidronate was detectable in the urine for up to eight years after discontinuation of long-term oral treatment during childhood [2]. Because BPs easily cross the placenta, pregnant women treated with BPs before pregnancy might expose their fetus to these drugs. Administration of high doses of BPs to pregnant rats resulted in fetal skeleton abnormalities [10]. Losada et al. reported in a review that with therapeutic doses of BPs, malformation was found in 2.94% of newborns, a rate not significantly different from that in the general population [3]. They also investigated a series of ten patients who took BPs before and during pregnancy, and congenital malformation was reported in two cases (20%); one case had a ventricular septal defect and the other had renal and cardiac malformations. However, the subjects in this report were taking azathioprine, sulfasalazine, or cyclosporine too [3]. Although their teratogenicity is inconclusive, BPs need to be used with caution.

Teriparatides are human PTH formulations, which stimulates bone formation. There have been six cases in the literature in which

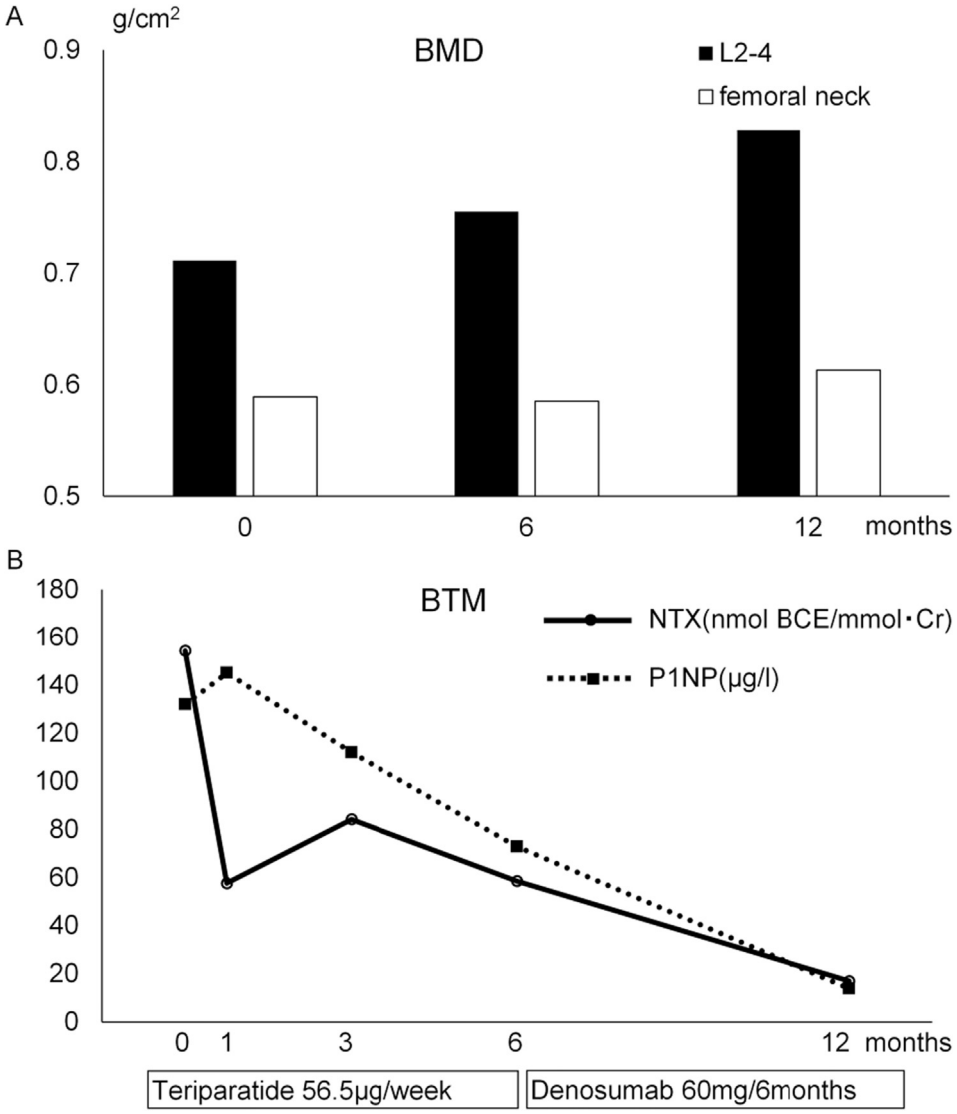

Fig. 2. A: Bone mineral density (BMD). BMD in L2–4 increased by 6.2% after six months of treatment with teriparatide and further increased to 16.5% with denosumab. BMD in the femoral neck was unchanged after teriparatide therapy but increased by 3.9% after denosumab therapy. B: Bone turnover marker (BTM). Procollagen 1 N-terminal propeptide (P1NP) was elevated at one month with teriparatide but subsequently declined. Urine crosslinked N-telopeptide of type 1 collagen (NTX) decreased with both teriparatide and denosumab treatment.

PLO was treated with teriparatides, and remarkable increase in BMD was observed in all cases [5]. An important side effect of teriparatide is the risk of bone tumors, depending on the dosage and duration of treatment. In animal studies, teriparatide exposure during organogenesis at levels over 60 times the human dosage caused increased fetal incidence of skeletal deviations or variations such as interrupted ribs and extra vertebrae or ribs [11]. Teriparatides have not been studied in human fetal development, and no clinical data are available to determine whether teriparatides are secreted into the breast milk; however, teriparatides have a half-life of one hour and do not accumulate in the skeletal bones [11], suggesting that the fetus will not be affected if administration is discontinued before pregnancy.

Denosumab is a human monoclonal antibody that binds to the receptor activator of nuclear factor κB-ligand (RANKL) and inhibits the activation of osteoclasts and osteoclast precursors. This leads to the suppression of bone turnover in osteolytic bone disease, and a curative effect of has been reported in postmenopausal women [12]. Cynomolgus monkeys receiving subcutaneous denosumab during organogenesis at a higher dose than recommended human dosages showed no evidence of either maternal toxicity or fetal harm [13]. However, in RANKL knockout mice, fetal lymph node agenesis, and postnatal impairment of dentition and bone growth was observed [14]. The mean half-life of denosumab is 25.4 days, and denosumab concentrations decline over a period of 4–5 months. No accumulation of denosumab has been observed [15]. Therefore, we suggest establishing a contraception period of approximately six months after the last injection of denosumab.

The present subject was switched from teriparatide to denosumab in the belief that this sequential therapy may have benefits because antiresorptive medication after teriparatide therapy is known to prevent subsequent decline in BMD [6]. Ebina et al. reported the increase in BMD due to sequential therapy with teriparatide followed by denosumab to be greater than followed by bisphosphonates in postmenopausal osteoporosis [7]. Furthermore, sequential therapy with denosumab followed by teriparatide has been observed to lead to progressive or transient bone loss, indicating that in sequential therapy the order of medications is important [8].

It should be noted that the BTM change caused by PTH in this case did not follow a typical course, which should increase both P1NP and NTX. P1NP decreased gradually for three months and NTX decreased rapidly for one month. These decreases in BTM may be due to recovery from extremely increased bone turnover caused by lactation and multiple fractures.

In the present case, severe PLO with multiple vertebral fractures was treated by teriparatide and denosumab, in addition to weaning. Remarkable improvement in BMD was achieved, especially with denosumab treatment. PLO may involve successive bone fractures and greatly affect the quality of life of young women. Immediate treatment is necessary to improve the patients' symptoms, and denosumab or sequential teriparatide-denosumab therapy is a promising candidate.

Conflicts of interest

The authors declare that they have no conflict of interest.

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