Two cases of pregnancy- and lactation- associated osteoporosis successfully treated with denosumab

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Summary

Case 1. A 35-year-old woman in the 8th month of her first pregnancy suffered acute lumbar pain that persisted for 4 months. In the 5th month postpartum an acute increase in the low back pain led to a MRI which showed recent deformity in L1 and deformities of undetermined time of evolution in L2, L4, and L5. Laboratory evaluation did not reveal metabolic derangements. She had low bone mineral density (BMD, DXA) and severe deterioration of the microarchitecture of distal appendicular bone (HR-pQCT). Kyphoplasty of all 4 vertebrae was performed in 2 stages, and treatment with subcutaneous denosumab, 60 mg every 6 months, was begun. There was rapid and almost complete improvement in pain. An increase in trabecular bone was documented with HR-pQCT.
Case 2. A 33-year-old mother who was breastfeeding her first-born child experimented acute dorsal pain. RMI revealed partial compression fractures in vertebrae D5-7. Her axial BMD was low. There was no family history of osteoporosis, and causes of secondary osteoporosis were ruled out. Her pain slowly subsided with conservative measures, oral analgesics, and nasal calcitonin. Then, treatment with oral strontium ranelate was prescribed; after 3 months serum alkaline phosphatase and osteocalcin had not increased, and after one year lumbar bone mineral density (BMD) was unchanged. Treatment was switched to subcutaneous denosumab. After one year, lumbar BMD had increased 14%, and the pain had almost completely subsided.

KEY WORDS: osteoporosis; pregnancy; lactation; HR-pQCT; treatment; strontium ranelate; denosumab.

Introduction

Osteoporosis presenting during pregnancy or lactation (OPL) is very rare. It was first described in 1955 (1).

Clinical cases

Case 1

A 35-year-old woman in the 8th month of her first pregnancy suffered acute lumbar pain that persisted for 4 months. In the 5th month postpartum an acute increase in the low back pain led to a MRI study which showed recent deformity in L1 and deformities of undetermined time of evolution in L2, L4, and L5. Her height was 1.62 m (historical height 1.67 m). Kyphoplasty of all 4 vertebrae was performed in 2 stages, and treatment with subcutaneous denosumab, 60 mg every 6 months, was begun. There was rapid and almost complete improvement.
Bone mineral density (BMD) of the lumbar spine could not be carried out because of the vertebral fractures, BMD of the femoral neck by DXA (Lunar) was 0.669 g/cm^2 with a Z-*score* of -1.5. Further evaluation was performed using high-resolution peripheral quantitative computed tomography (HR-pQCT; XtremeCT, Scanco Medical AG, Bassersdorf, Switzerland) of the distal radius and tibia (2). At baseline, bone microarchitecture parameters were significantly lower compared to a control group of healthy women. Cortical thickness and density, and trabecular density, number and thickness were clearly deteriorated (Figure 1) (Table 1).
After one year of treatment with Dmab, BMD of the femoral neck did not change, but there was marked improvement in bone microarchitecture measured by HR-pQCT: trabecular volume had increased by 17% at the radius and 7% at the tibia; trabecular thickness had increased by 21% and 13%, respectively. There was no increase in the cortical compartment. After an additional year of treatment, these changes remained stable.

Case 2

ND, kinesiologist, age 33, consulted in 2014, three months after giving birth to a healthy male weighing 3.21 kg, whom she was breast-feeding; labor lasted 12 hours (a Caesarean section had to be performed). This was her first pregnancy. She reported an acute back pain in the 3rd week postpartum. An X-ray film of the spine was of poor quality, so an MRI was done, which showed deformity of the upper plates of D5, D6, and D7 (Figure 2). Height was 1.47 m (historical height: 1.57); she weighed 61 kg. Her diet was rich in dairy products, and she had no personal or family history of relevance. She had a normal CBC and blood chemistries. Further laboratory studies were performed: serum calcium, phosphate, magnesium, cortisol, CTX, TSH and PTH were normal, 25OHD was 23 ng/ml, and serology to rule out celiac disease was negative; urine calcium also was normal. Bone densitometry showed Z-*scores* of -4.6 at the lumbar spine and -2.5 at the right femoral neck. In addition to oral ibuprofen and paracetamol – which were being used used as analgesics –, nasal calcitonin, 2 daily applications of 100 MRC units were prescribed. Treatment was initiated with strontium ranelate (SrR) 2 g/day, and 100,000 IU of vitamin D_3 per month. The pain subsided gradually, calcitonin was discontinued, and the patient could initiate a plan of low-impact physical exercise (walking and swimming). Three months later serum calcium and phosphate were normal; the 25OHD level was 31 ng/ml, and no change in serum alkaline phosphatase or osteocalcin was ob-

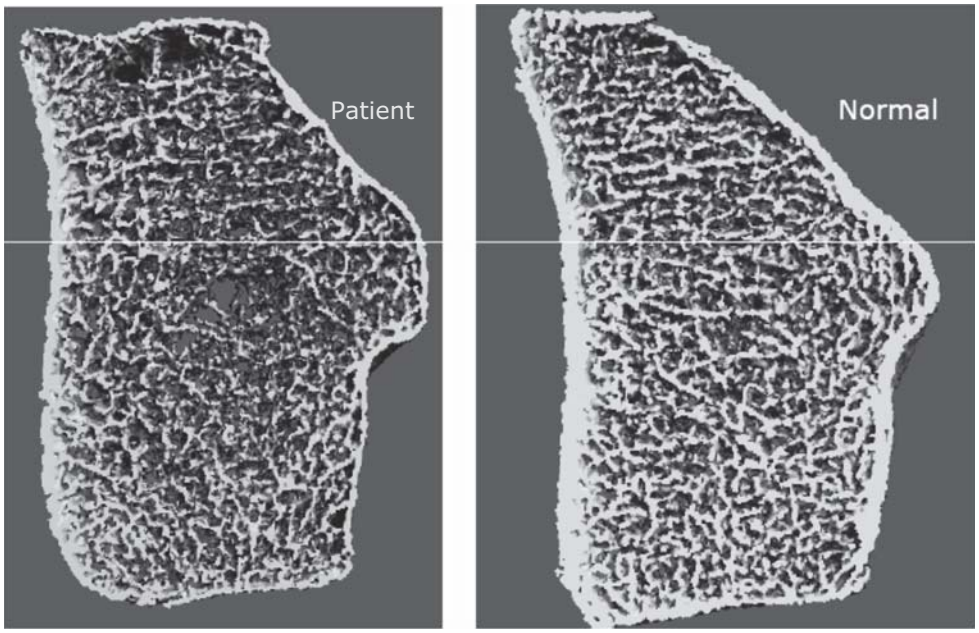

Figure 1 - HRp-QCT three-dimensional images of the radius of Case 1 at the time of diagnosis (left) and a control subject (right). Note the clear differences in the trabecular network.

Table 1 - Case 1: deficits in the trabecular and cortical compartments of distal radius by HR-pQCT, in comparison with a control group of young healthy women.

	Healthy controls (n=22)	**Patient Baseline** (% difference compared to controls)
Cortical density (mg HA/cm^3)	894 ± 43	745 (-16.6%)
Cortical thickness (mm)	0.75 ± 0.132	0.39 (-48%)
Trabecular density (mg HA/cm^3)	162 ± 33.6	80 (-50.6%)
BV/TV (%)	13.5 ± 2.8	6.60 (-51%)
Trabecular number (1/mm)	1.89 ± 0.26	1.64 (-13.2%)
Trabecular.thickness (mm)	0.071 ± 0.008	0.04 (-43.6%)

served. An MRI control study showed no change in vertebral morphology, but edema had disappeared. After one year of treatment with SrR lumbar bone mineral density (BMD) was unchanged, so the treatment was switched to subcutaneous denosumab, 60 mg every six months. After 2 applications, lumbar spine BMD had increased 14% (Table 2). The pain had decreased significantly, although there was some discomfort during certain movements.

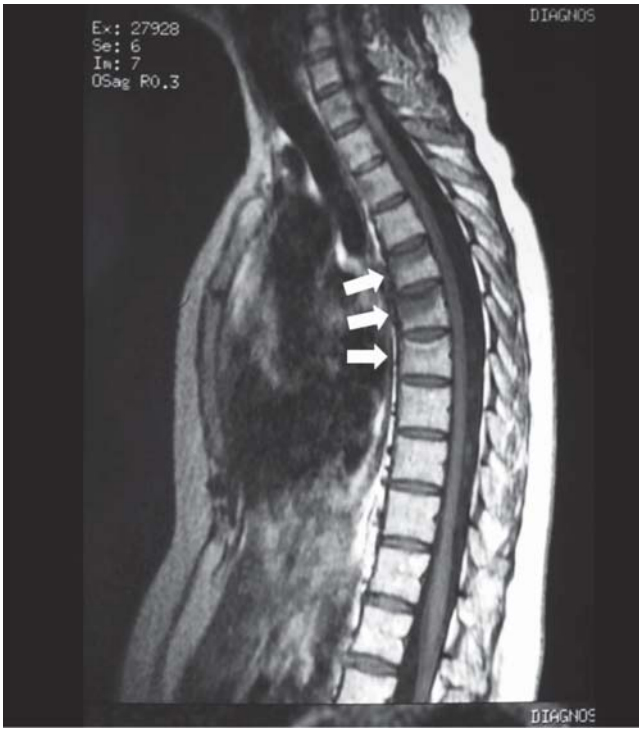

Figure 2 - Case 2: RMI of the spine, lateral view, showing partial deformities of D5-7 (arrows). Note edema of the vertebral bodies.

Discussion

Osteoporotic fractures during pregnancy or lactation are infrequent: around 120 cases have been reported in the medical literature (3). The largest series was published by Dunne et al., reporting 35 cases collected with the help of the National Osteoporosis Society in the UK (4).

There are important changes in the metabolism of calcium and phosphorus in women during this physiologic period. Calcitropic hormones, and vitamin D and its metabolites, show several variations that have been previously reviewed (5, 6).

Four different types of clinical presentation can be recognized: an idiopathic form, generally in the third trimester of pregnancy; a transient local osteoporosis or edema of the hips; a predominantly vertebral form during the first trimester of lactation; and drug-induced (usually associated with prolonged use of heparin) (7). Another type should be added: secondary osteoporosis aggravating a previous disease; regional osteoporosis of both hips has been reported in a young pregnant woman known to have osteogenesis imperfecta (8). In Dunne et al.'s series, 29 of the 35 women were found to have idiopathic osteoporosis (4).

Presumably, women suffering from this condition have started their pregnancy with a low bone mass, and the obligatory transfer of mineral through the placenta or the breast to the fetus or the baby causes an increased bone turnover and a critical aggravation of the initial osteopenia, so that fractures occur. Several risk factors

Table 2 - Case 2: lumbar densitometric values (DXA) before and after one year of treatment with denosumab.

	DMO (g/cm^2)	Change
Initial *(Lunar, L2-4)*	0,633	
Control after 1 year	0,717	+14%

have been identified: low body weight, poor intake of calcium in the diet, alcohol or tobacco abuse, past history of eating disorders or menstrual irregularities, and family history of osteoporosis. In normal women there is little change in BMD following pregnancy and breastfeeding (7, 9, 10).

In Argentina there are only two reported series of patients with OPL: the first showed 3 cases (11), and the second one reviewed 8 cases (two with regional osteoporosis of the hip) (12).

Reported treatment of this form of osteoporosis includes oral supplements of calcium and vitamin D, polar metabolites of this vitamin (calcitriol or alphacalcidol), calcitonin, bisphosphonates, teriparatide, and strontium ranelate (3, 13-15). In more severe cases, surgical intervention may be necessary (vertebroplasty, kyphoplasty, vertebral fusion) (16, 17). There is no previous report on denosumab use in this situation in the literature.

The use of bisphosphonates in an attempt to reduce bone turnover is reasonable. However, there is concern about the fact that these drugs cross the placenta and may be deposited in the child's skeleton. Also, their persistence in the mother's bones might be detrimental in future pregnancies (18).

In our case 2, SrR was used initially, but there was no biochemical or densitometric response. Tanriover et al. (15) reported one patient who received SrR after a short course of oral alendronate. In the case of Zarattini et al. (19), SrR was the drug of first choice. In both cases the clinical and densitometric response was excellent. Probably due to allelic variations in the calcium sensing receptor, not all patients respond to strontium. In our experience, the rate of responders with significant increments in BMD at the spine or hip is 60% (20, 21).

When our case 2 was switched from SrR to denosumab, an important increase in lumbar BMD was obtained. Since in both cases BMD is still low two years post-partum, treatment with denosumab has continued.

Conclusion

Two cases of OPL, a very rare entity, are presented. Both patients responded well to denosumab. Denosumab can be considered another option in the therapeutic approach to this rare disease.

Conflicts of interest

None.

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