

Uncommon Transient Osteoporosis of Pregnancy at Multiple Sites Associated with Cytomegalovirus Infection: Is There a Link?

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Transient osteoporosis is an idiopathic condition characterized by attacks of periarticular pain and swelling in the lower limbs and the development of localized osteoporosis in the subjacent periarticular bone. It was first reported 50 years ago in the hip in the last trimester of pregnancy [1], but it may affect middle-aged men and non-pregnant women as well [1]. Transient osteoporosis has rarely been reported to affect the knees or talus. Complete recovery is the rule but the clinical manifestations, which may last up to one year, adversely affect the quality of life and may be complicated by insufficiency fractures. We report an exceptional case of transient osteoporosis at multiple sites occurring unusually in the second trimester of pregnancy, after cytomegalovirus infection, successfully treated with an intravenous bisphosphonate.

PATIENT DESCRIPTION

A 26 year old previously healthy woman presented to her family physician in the 18th week of her first pregnancy with a severely swollen and painful right ankle. She refused treatment. At week 30 of the pregnancy she complained of bilateral knee pain. She was referred by her obstetrician for rheumatologic consultation at week 36 when she also began to experience severe pain in her right hip. She was unable to walk, requiring crutches for ambulation. She refused any form of imaging during her pregnancy.

There was no history of trauma, fever or other systemic complaints. At the beginning of the pregnancy, her husband sustained a CMV infection presenting initially as fever of unknown origin lasting 3 weeks. When her husband was diagnosed, she was tested and found to have serologic evidence of a recent asymptomatic CMV infection with positive anti-CMV immunoglobulin M antibodies detected at 6 weeks of pregnancy, borderline at 9 weeks, and negative with positive IgG 45% avidity at delivery. At 22 weeks she underwent amniocentesis which was entirely normal. Her pregnancy was otherwise uneventful. An elective cesarean section was performed at 41 weeks because of suspected excessive fetal growth and she gave birth to a normal child weighing 4.150 kg.

At clinical examination 2 days after delivery she could not walk. There was painful restriction of abduction and internal and external rotation of the right hip; bilateral knee tenderness was present without effusion, and a painful right ankle was diffusely swollen. The general physical examination was not contributory.

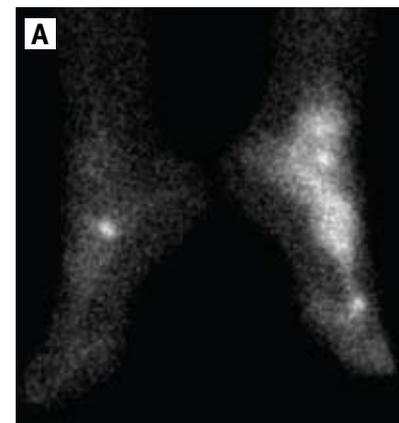
On laboratory evaluation the complete blood count was normal, erythrocyte sedimentation rate was 40 mm/hour and C-reactive protein 0.9 mg/dl (normal < 0.5). Electrolytes, liver enzymes, renal

function tests, calcium, phosphorus, parathyroid hormone, vitamin D, and thyroid function studies were within normal limits. Antinuclear antibody, rheumatoid factor, as well as other autoantibodies (anti-dsDNA, anti-CCP, anticardiolipin) were negative, as were serologies for hepatitis B and C.

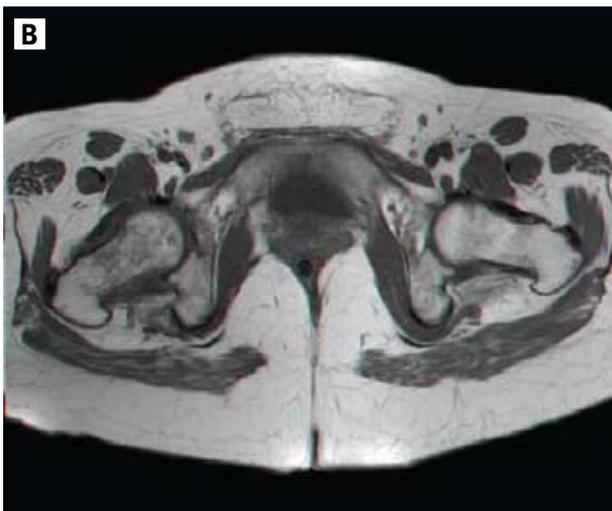
X-rays of the pelvis, knees and ankles showed severe osteopenia of the right hip, right knee and right ankle. A technetium bone scan revealed intense increased uptake in the right hip, right ankle and both knees [Figure A]. On magnetic resonance imaging of the right hip [Figure B] there was evidence of bone marrow edema with low signal intensity on T1-weighted images and high signal intensity on T2-W and short T1 inversion-recovery (STIR) MR images, without fracture lines or imaging of osteonecrosis.

A diagnosis of transient osteoporosis

[A] Tc-99m-MDP bone scintigraphy showing an uptake in the left ankle due to transient osteoporosis



CMV = cytomegalovirus
Ig = immunoglobulin



[B] T1 MRI scan. Note the low signal in the right femur neck

of multiple sites during pregnancy was proposed and treatment with intravenous pamidronate 60 mg was initiated. An impressive rapid recovery was observed. Within 2 weeks, the pain and edema had decreased considerably and she could walk without canes. She received pamidronate IV weekly, then every 2 weeks – four infusions in all. Six weeks after starting pamidronate, the patient reported 85% amelioration of joint pain and only mild osteopenia could be seen on the right hip X-ray, without radiological change in the right ankle and knee. The results of dual-energy X-ray absorptiometry revealed a T score of -1.5 at the right hip versus -0.7 at the left unaffected hip, with normal bone density at the lumbar spine. Three months after treatment onset she was asymptomatic. In order to reduce fracture risk in this young active individual with radiologic osteopenia at the right knee and ankle, oral alendronate sodium 70 mg/week and 1000 mg calcium with 800 IU vitamin D 3 times a day was prescribed for a short period of 6 months. The long-term use of an oral bisphosphonate in such cases is controversial and warrants well-controlled studies regarding the actual risk of fracture as well as the use of alendronate in premenopausal women.

COMMENT

Pregnancy-induced osteoporosis is an uncommon problem with unclear origins, which may relate to increased number of pregnancies, long duration of lactation, and vitamin D deficiency. An atypical case of transient osteoporosis in pregnancy at multiple sites is presented. This case is unusual in various aspects: onset early in the second trimester of pregnancy, severity of the clinical picture, and multiple sites of transient osteoporosis involving four joints in the lower limbs. Finally, concomitant CMV infection was detected during the first trimester of pregnancy.

Transient osteoporosis has a predilection for the last trimester of pregnancy or the immediate postpartum period, and for unilateral hip involvement most commonly, although it has been described bilaterally in 25% of patients. Knee and ankle involvement are rare and were reported only in isolated cases.

The differential diagnosis includes infection, primary or metastatic malignancy, joint inflammation, synovial chondromatosis, fractures, osteonecrosis and regional migratory osteoporosis. Regional migratory osteoporosis predominantly affects middle-aged men, with the ankle,

foot and knee most commonly affected and with the same picture of bone marrow edema on MRI. The differentiation between transient osteoporosis and avascular necrosis is essential for prognosis and avoidance of unnecessary therapies, such as surgical decompression or arthroplasty for putative avascular necrosis.

The pathogenesis of transient osteoporosis in pregnancy remains obscure. Compression of the obturator nerve by the fetus's head, compression of the pelvic nerves by the enlarged uterus, or hemodynamic changes such as reduced systemic vascular resistance and impaired venous return are suggested etiologic factors. A possible link between the CMV infection and multiple-site transient osteoporosis may be suggested since the bone marrow has been reported to be a reservoir of human herpes virus infection. Experimentally, there is an accumulation of monocytes/macrophages in the bone marrow of CMV-infected CCR2-deficient mice; these cells play a critical role, producing inflammatory cytokines and promoting chemokine production in the bone marrow [2]. CMV infection of plasmacytoid dendritic cells induces elevated production of both tumor necrosis factor- α and interferon- γ by natural killer cells [3]. IFN γ has both direct anti-osteoclastogenic and indirect pro-osteogenic properties *in vivo*. Under conditions of infection the net balance of these opposing actions is biased toward bone resorption by stimulated antigen-dependent T cell activation [4].

The treatment proposed for transient osteoporosis includes bed rest followed by assisted weight bearing, physiotherapy, rehabilitation therapy, analgesics and non-steroidal anti-inflammatory drugs. Calcitonin was reported to alleviate the pain but failed to prevent new attacks. Successful treatment of severe transient osteoporosis with intravenous pamidronate has been reported during the last decade. The results are generally rapid and safe, with complete and long-lasting

IFN γ = interferon- γ

remission of the symptoms and renewal of the patients' previous activities, thus adding to the list of rheumatic disorders successfully treated by this modality, as recently reviewed by us [5].

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