Severe transient osteoporosis of the hip during pregnancy. Successful treatment with intravenous biphosphonates

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ABSTRACT

A young woman with transient osteoporosis of the hip (TOH) during pregnancy, severe pain, physical disability and marked generalized osteoporosis was treated with intravenous biphosphonates with prompt beneficial effects on both clinical symptoms and bone density. The features of this rare and sometimes underdiagnosed condition are reviewed. Intravenous biphosphonates seem to be an effective therapy for TOH.

Introduction

TOH is an uncommon condition characterized by transitory pain and disability and radiological osteopenia in the hip area. Middle-aged men and females during the last trimester of pregnancy or the immediate post-partum period are the main populations at risk. Complete recovery is the rule but the clinical features, which may last up to one year, have a deleterious influence on the quality of life and may be complicated by insufficiency fractures (1-6). Therefore there is the need for specific treatments with rapid action and prolonged activity. Intravenous biphosphonates are effective therapeutic agents for metabolic bone diseases (7). We report the beneficial effect of intravenous biphosphonate therapy in a case of severe TOH.

Case report

A 30-year-old, previously healthy female was admitted for severe pain in the left hip area and inability to walk. The symptoms (left inguinal pain with irradiation to the upper thigh and knee, progressive limitation of motion and sensation of locking of the hip joint) appeared three and a half months earlier, at the end of the sixth month of her first pregnancy and had aggravated continuously since. During the last two months she could not walk and was confined to a wheelchair. There was no history of trauma and there were no systemic complaints. The pregnancy was not affected and two weeks before hospitalization she gave birth to a normal child. Previous treatment with NSAIDs and traction of the left lower limb for presumed synovitis of the hip (synovial fluid in the hip joint was detected by ultrasonography) was ineffective.

At admission she was suffering from unbearable pains in the left hip area and could not walk. There was marked sensitivity and muscle spasm in the hip area and joint movements were limited. The general examination was not contributory. ESR was 22 mm/hour, and a complete blood count, routine serum biochemistry and urine analysis were normal. X-rays of the pelvis and knees (Fig. 1 a-b) showed severe osteopenia in the left hip and left knee areas. Osteopenia could also be seen in radiographs of the lumbar spine. X-ray absorptiometry (Lunar DEXA, model 1997) of the lumbar spine and proximal femurs (femoral necks, trochanteric areas and Ward's triangles) revealed advanced osteoporosis. Thyroid function tests, serum PTH, serum levels of vitamin D metabolites [1,25 $(OH)_2$ D3 and 24,25$[OH]_2$ D3] and the results of a 24-hour urine collection for calcium and phosphorus were normal. Serum osteocalcin and urinary deoxypyridinnoline were elevated. The results of bone densitometry at the lumbar spine and femoral neck, those of the laboratory markers of bone metabolism, and the changes in these parameters are summarized in Table I.

A diagnosis of TOH during pregnancy was proposed and treatment with intravenous biphosphonates (Bonefos = clodronate = dichlorometylene biphosphonate, 300 mg a day for 10 days) was initiated together with calcium and vitamin D supplements. An impressive recovery was quickly witnessed. Within 2 weeks the pain had considerably decreased and the patient could walk with just a slight limp. Two months after beginning of the treatment she was asymptomatic and resumed all previous activities. At that time the bone mineral density (BMD) at the left hip had considerably increased (+16%). After another two months no further increase in the BMD at this site was found. In order to reduce the fracture risk in a young and active individual with a very low bone mass, a second course of intravenous clodronate for 5 days was administered. Two months later an additional augmen-

tation (+19.5%) in the bone mineral density at the left hip was observed, resulting in a total gain of 32.5% during the last six months. At the end of the same period the BMD was unchanged at the right hip and slightly diminished (-1.8%) at the lumbar spine, as compared with the initial values.

Discussion

TOH is a rare disorder characterized by disabling pain in the hip area and marked radiological osteopenia. The usual clinical evolvement includes three distinctive phases: (1) rapid aggravation of pain and functional disability; (2) peak intensity of the symptoms and appearance of osteopenia; and (3) gradual resolution of the clinical signs and restitution of bone mineralization. Roentgenograms, which show various degrees of osteopenia and an invariably preserved joint space, are suggestive, although complementary diagnostic techniques such as radionuclide bone scan, computed tomography and magnetic resonance imaging are often needed. Invasive local investigations are rarely necessary (8-11).

The differential diagnoses include infection, primary or metastatic malignancy, synovial chondromatosis, joint inflammation, fractures and avascular necrosis of bone (AVN). The differentiation between TOH and AVN is critical in order to predict the prognosis and to prevent unnecessary therapies such as decompression or arthroplasty in cases of TOH. Some authors have suggested that TOH may be the initial phase of avascular necrosis of bone. However, an accurate medical history which often reveals the presence of risk factors for AVN; the insidious onset and the relentless progression of untreated AVN as compared with the acute onset and spontaneous recovery in TOH; suggestive features in late-stage standard radiographs and computed tomography, and especially scintigraphy and magnetic resonance are invaluable diagnostic indications (12, 13).

The pathogenesis of TOH remains obscure. Familial presentation has been rarely reported. In some cases type IV hyperlipidemia seems to play a part. Neural mechanisms such as inflammation of the nerve ends and ischemia of vasa nervorum have been suggested to be involved (14). About one-third of cases occur during the last trimester of pregnancy or the immediate post-partum period. In this population, compression of the obturator nerve by the child's head, compression of the pelvic nerves by the enlarged uterus or haemodynamic changes such as reduced systemic vascular resistance and impaired venous return are possible etiologic factors (1, 15).

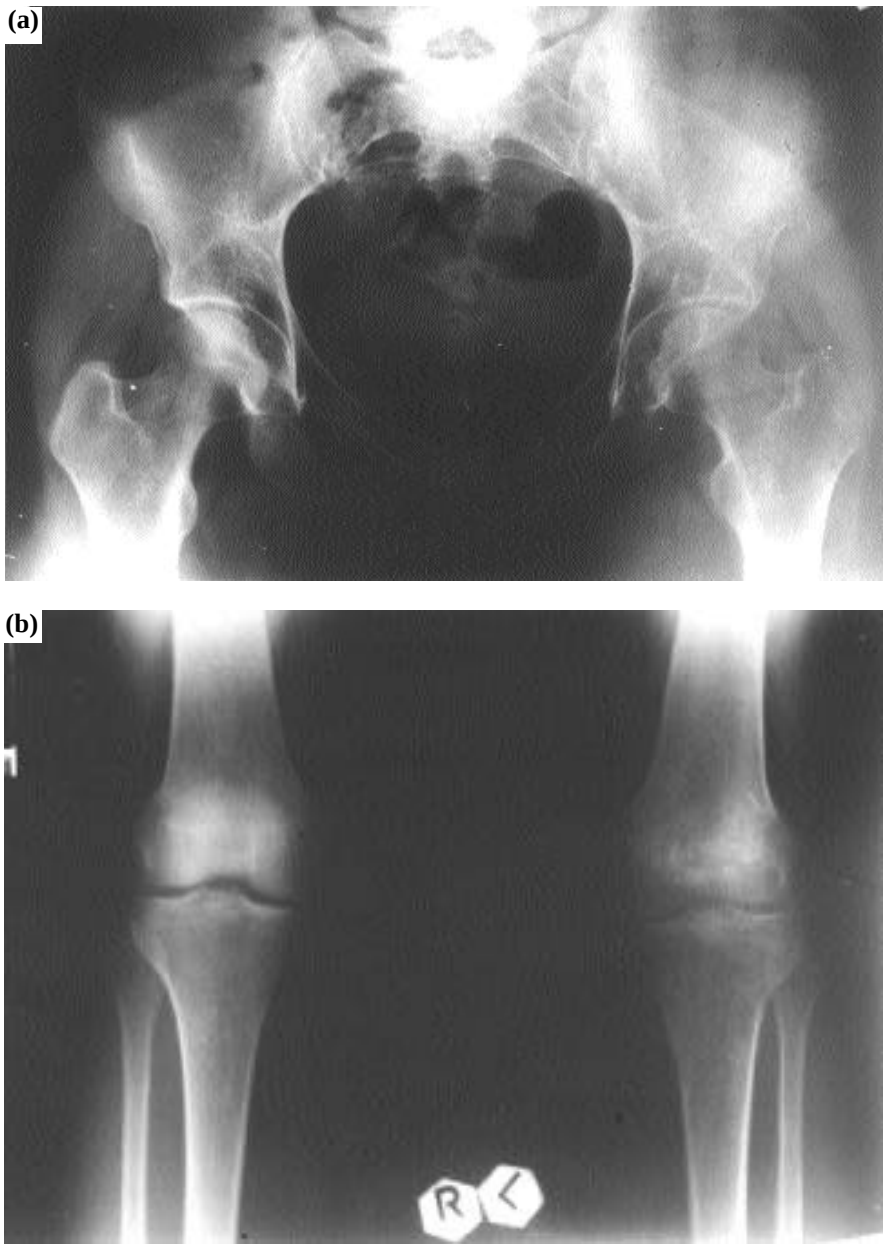

Fig. 1. (a) Pelvic X-ray showing marked osteopenia of the left hip area. **(b)** Radiograph of the knees showing advanced osteopenia in the left knee area.

Joint protection, analgesics, NSAID and sometimes calcitonin are the main treatments for TOH. Biphosphonates are efficient therapeutic agents for osteoporosis, Paget's disease of bone and other metabolic bone diseases. They bind to the hydroxyapatite crystals in the bone tissue, prevent the attachment of osteoclasts precursors, induce a direct cytotoxic effect and inhibit the function of osteoclasts. The intravenous products in this group are characterized by potent anti-resorptive

Table I. Changes in bone densitometry and parameters of bone metabolism due to intravenous clodronate treatment.

Period of treatment (mos.)	Baseline	+2	+4	+6
BMD (g/cm^2)				
L1 - L4	0.938	0.968	0.946	0.921
T score	-2.04	-2.00	-2.00	-2.06
Right hip	0.763	0.745	0.752	0.763
T score	-1.81	-1.96	-1.90	-1.81
Left hip	0.390	0.453	0.465	0.578
T score	-4.92	-4.39	-4.29	-3.35
Deoxy-pyridinoline crosslinks				
NM/mM creatine (3 – 7.4)	20.3	17.4	14.7	9.8
Osteocalcin G/L (2.7 – 6.9)	9.3	8.1	12.5	10.3

properties, rapid-onset action, and sustained effects without impairing mineralization and they seem to be particularly effective in diseases characterized by high bone turnover (16,17). Due to these qualities their use has been recently extended to conditions such as reflex sympathetic dystrophy and regional migratory osteoporosis (RMO) (18, 19).

Our case is unusual for a variety of reasons, beginning with the coexisting generalized osteoporosis (as evidenced by the low BMD in the spine and right hip areas). A familial history of osteoporosis (T score - 4.5 in an asymptomatic 55-year-old mother), a relatively low intake of lactate products and prenancy itself were the presumed risk factors. Secondly, the severity of the clinical and densitometric findings in the left hip area was striking; equally impressive was the increase in BMD in this area as compared to the similar or slightly diminished values at the right hip and lumbar region, respectively, at the end of the treatment period. We have no definite explanation for these findings, although it may be assumed that TOH, when superimposed on osteoporosis of pregnancy, has a higher bone turnover and reacts faster and better to treatment then the underlying condition (20). Finally, concomitant bone tissue rarefaction was seen in the left knee region. The association of TOH with osteoporosis of the knee has been rarely reported (21). The simultaneous involvement of these areas in our patient is not compatible with RMO, a condition which affects mainly middle-aged males, is characterized by migratory attacks of para-articular inflammation and by severe periarticular osteoporosis in the lower extremities, and in which the hip area is rarely affected (22).

The histological features of TOH have not yet been fully elucidated. Some studies present it as a special reversible form of femoral head necrosis in which increased bone formation exceeds the rare foci of active osteoclastosis (23, 24). However, the results of other investigations which show active osteoclastic bone resorption in most patients and scintigraphic evidence which suggests a regional increase bone turnover in TOH (25, 26) support the use of anti-resorptive agents in this condition. Sporadic reports have shown favorable results of oral biphosphonate therapy for TOH (21). To our knowledge only 3 patients with TOH have been previously treated with intravenous biphosphonates (27). Based on this report we preferred to use clodronate, a product which even in high doses has been shown not to impair bone mineralization (16), following the same therapeutic protocol as Varenna *et al.*. In our case it seems that despite a possible contribution of childbirth to the increase in BMD at the left hip, most of the recovery should be attributed to the treatment.

Intravenous biphosphonate therapy should be considered in patients with TOH, severe pain and physical disability. The use of these agents may substantially contribute to the regional increase in bone mass, hasten clinical recovery and reduce the risk of insufficiency fractures.

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