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Axial osteomalacia with sacroiliitis and moderate phosphate diabetes: Report of a case

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ABSTRACT

We report a new case of axial osteomalacia diagnosed in a 51-year-old white Caucasian male, made particular by its association with sacroiliitis, positive HLA-B27 antigen, and also moderate phosphate diabetes responsible for a decreased appendicular bone mass. The diagnosis was suspected when X-ray evaluation showed increased density and coarse trabeculation mainly involving the pelvis and spine. Dual energy X-ray absorptiometry confirmed the elevated bone density at the lumbar spine (T score: +1.92) contrasting with a decreased bone mass at the femoral neck (T score: -2.33). The diagnosis was confirmed by histomorphometry of the iliac crest showing marked thickening of the cortices (2190 μm ± 0.574, N = 780 ± 40) and an increased trabecular bone volume (33.24%, N = 14 ± 3). Osteoid parameters were also markedly increased with an osteoid volume of 2.1% (N = 1.2 ± 0.5) and a mean osteoid thickness of 28.7 μm (N = 13 ± 2.5), with a normal bone fluoride content (0.082%, N < 0.10). Bone resorption as assessed on bone biopsy and by the measurement of markers of bone remodeling (serum procollagen type I C-terminal telopeptide and 24 hr urinary cross-laps to creatinine ratio) was increased. This latter finding was not necessarily due to axial osteomalacia and could be the consequence of moderate phosphate diabetes.
The patient was treated with calcitriol which was promptly discontinued due to gastrointestinal symptoms and replaced by calcidiol without any significant effect on the low back pain.

Introduction

Axial osteomalacia is a rare bone disease characterized by a dense, coarsened and sponge-like appearence of the axial skeleton on X-ray examination. Since the first case reported by Frame in 1961 (1) several other cases have been published (2-6). The cause of axial osteomalacia is unknown and some authors suggest that the disease could be due to a genetic abnormality. Indeed, Whyte *et al.* reported 2 cases affecting a mother and son (2). Furthermore, other authors suggest the existence of a genetic link between axial osteomalacia and ankylosing spondylitis. In fact Nelson *et al.* reported in 1978 four cases, 2 of whom had both diseases (3). Usually patients with axial osteomalacia suffer from moderate back pain without significant biological abnormalities. A moderate increase in total alkaline phosphatase has been reported in 3 patients, however (1,3) (it is important to note that 1 of these had a concomitant liver disease). In contrast, an osteoblast defect has also been suggested (2). One patient with low phosphate levels has been also reported (3). In the absence of clinical, biological and X-ray features the diagnosis is made based on iliac crest bone biopsy showing regions of true histological osteomalacia.
We report a new case of axial osteomalacia that was fully investigated by means of bone densitometry using dual energy X-ray absorptiometry (DXA), and markers of bone remodeling. This case is unusual because of its association with sacroiliitis, and also the presence of decreased femoral neck bone mineral density (BMD) possibly due to a moderate phosphate diabetes.

Case report

The patient is a 51-year-old white male (height: 166 cm, weight: 73 kg) who has suffered from continuous back pain for 1 year associated with left buttock pain and morning stiffness lasting 10 minutes. The pain did not respond to analgesic or nonsteroid anti-inflammatory agents.
No relevant past history (medical or surgical) was noted and the patient was in good general health. The patient did not smoke or drink alcohol. The physical examination showed minimal limitation of motion of the lumbar spine and chest expansion measured 7 cm. The remainder of the clinical examination was considered normal and, in particular, no synovitis was noted.
Laboratory studies showed a hemoglobin of 14.6 g/dL, erythrocyte sedimentation rate (ESR) 14 mm/1 hr, C-reactive protein 8.4 mg/L (N < 10) and positive HLA-B27 antigen. The other laboratory tests showed protein-adjusted plasma calcium 2.4 mmol/L (N = 2.15-2.55), inorganic phosphate 0.7 mmol/L (N = 0.74-1.25), total alkaline phosphatase

204 U/L (N = 80-220), bone alkaline phosphatase (Hybritech, Inc®, San Diego, USA) 15.4 ng/mL (N < 20.4), osteocalcin (Cis-Bio International, Gifs/Yvette, France) 5.4 ng/mL (N = 2-8), 25-hydroxyvitamin D 35 nmol/L (N = 25-150), 1,25-dihydroxyvitamin D 47 pmol/L (N = 50-150), intact PTH (ELSA-PTH, Cis-Bio International, Gifs/Yvette, France) 25 pg/mL (N = 10-55), rate of tubular reabsorption of phosphate 0.70 (N = 0.85-0.92), phosphate clearance 34 mL/mn (N <15), and maximal renal tubular phosphate transport 0.7 (N = 0.8-1.3). Bone resorption was increased as evaluated by urinary hydroxyproline 30.24 mg/24 h/m^2 (N = 6-22), serum procollagen type I C-terminal telopeptide (ICTP, Orion Diagnostica, Espoo, Finland) 5.8 ng/mL (N = 1.8-5) and the 24 hr urinary cross-laps (CTX) to creatinine ratio (Osteometer, A/S®, Rodovre, Denmark) 543 mg/mmol (N = 50-270).

X-rays of the pelvis and spine (both cervical thoracic and lumbar) showed increased density and coarse trabeculation mainly in the pelvis (Figs. 1, 2). They also showed narrowing and irregularity of the sacroiliac joints with a coarse, bony trabeculation which was confirmed on computerized tomographic examination (Figs. 1, 3). Some degenerative changes were also noted on the lower lumbar spine (L3-L4 level), whereas an early syndesmophyte was seen at the T12-L1 level (Fig. 1).

BMD was measured using a Hologic QDR-2000W instrument (Hologic Inc., Waltham, MA, USA). Lumbar spine BMD (L2-L4) in antero-posterior view was increased: 1.30 g/cm^2 (T score: +1.92, Z score: +2.34). In contrast both the femoral neck and Ward's triangle BMD were decreased: 0.72 g/cm^2 (T score: -2.33, Z score: -1.11) and 0.53 g/cm^2 (T score: - 2.52, Z score: - 0.86). Finally BMD was in the normal range at the greater trochanter (0.76 g/cm^2, T score: - 0.33, Z-score: + 0.18) and at the hip (0.94 g/cm^2, T score: - 1.05, Z score: - 0.36).

A transiliac crest bone biopsy was performed without tetracyclin double labeling. Histomorphometric examination showed increased thickening of the iliac cortices 2190 mm ± 0.574 (mean ± standard deviation for 24 measurements, N = 780 ± 40). Trabecular bone volume was markedly increased 33.24 % (N = 14 ± 3). Parfitt's parameters (7) showed slightly increased trabecular thickness 188.78 µm (N = 140 ± 40), increased trabecular number 1.76/mm (N = 1.4 ± 0.3) and decreased trabecular spacing 379.11 µm (N = 600 ± 160). Bone turnover as assessed by measurement of both osteoblast and osteoclast surfaces was increased: 15.82% (N = 9 ± 3) and 6.28% (N = 3 ± 1) respectively. Osteoid parameters were markedly increased with the osteoid volume at 2.1% (N = 1.2 ± 0.5) and mean osteoid thickness at 28.7 µm (N = 13 ± 2.5). Microradiographic examination showed a mineralization defect. Finally, the bone fluoride content was 0.082% (N < 0.10).

In the presence of a moderate phosphate diabetes which could partly explain the low BMD measured at the femoral neck treatment associating oral phosphate (1.5 g/day) and calcitriol (0.25 µg/day) was recommended (8). This treatment was quickly discontinued due to gastrointestinal symptoms and was replaced by calcidiol (2000 U/day) with satisfactory clinical and biological tolerances (absence of hypercalcemia and hypercalciuria). However, after 15 months of follow-up the pain did not change. Analogously X-rays of the lumbar spine were unchanged. Finally DXA showed a slight decrease of the BMD at the lumbar spine (-5.6%) and slight increases at the femoral neck (+4.3%), the greater trochanter (+1.6%), the Ward's triangle (+ 13.9%) and the hip (+ 3.0%).

Conclusions

The association between axial osteomalacia with ankylosing spondylitis has been previously reported by Nelson *et al.* (3). Indeed among the 4 patients with axial osteomalacia that they reported, 2 of them had a positive HLA-B27 antigen associated with sacroiliitis. Our patient had also a positive HLA-B27 antigen but inflammatory parameters were in the normal range and nonsteroid anti-inflammatory agents were not effective. Therefore these findings argue against the diagnosis of ankylosing spondylitis. Abnormalities characterizing axial osteomalacia are located in the axial skeleton in contrast with the apparently normal appearance of the appendicular skeleton. We demonstrated that lumbar spine BMD, as expressed by both the T- and Z-scores was increased, as did Demiaux-Domenech *et al.* (6). Conversely they showed that hip BMD was in the normal range (T score: +0.6). The contrast between the axial and peripheral skeletal sites was dramatic in our case since the femoral neck BMD was decreased (T score: -2.33). Low BMD at the femoral neck was probably due to moderate phosphate diabetes in the current case. We recently demonstrated in a large cohort that moderate phosphate diabetes is one of the main causes of male osteoporosis (9). Whereas urinary metabolism is normal in axial osteomalacia, some authors have reported slight abnormalities in phosphate metabolism, as we did. In fact one patient of Nelson *et al.* (3) had a trend to decreased plasma phosphate and Demiaux-Domenech *et al.* (6) stated that the maximal renal tubular phosphate was 0.8 mmol/L (N = 0.8-1.3). The presence of phosphate metabolism abnormalities must be clarified in further case descriptions of axial osteomalacia.

Biochemical findings were quite normal in our case, as in previous cases, particularly for 25-hydroxyvitamin D and PTH. 1,25-dihydroxyvitamine D was slightly decreased and this finding might have been due to the patient's moderate phosphate diabetes.

Bone remodeling was increased in the present case particularly for bone resorption, as assessed on bone biopsy and by the measurement of bone resorption markers. Total alkaline phosphatase was shown to be elevated in 3 previous cases (1, 3), but for one of them a concomitant liver disease was also noted. The osteocalcin level was found to be normal in the present case, in agreement with the report of Demiaux-Domenech *et al.* (6). In contrast it is well-known that osteocalcin levels are increased in diffuse osteomalacia (10). Finally, the bone alkaline phosphatase level was also in the normal range in our case. To our knowledge this marker has not been assessed in the previous reported cases. The new markers of bone resorption such as CTX and ICTP and which were found to be increased in the present case, were not

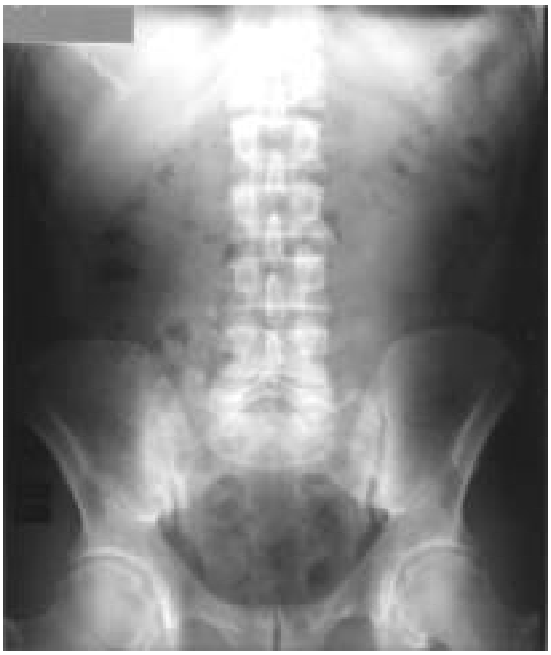

Fig. 1. Frontal lumbar spine and pelvis X-rays showing increased density with a coarsened and sponge-like appearance (particularly at the pelvis), but also narrowing and irregularity of the sacro-iliac joints.

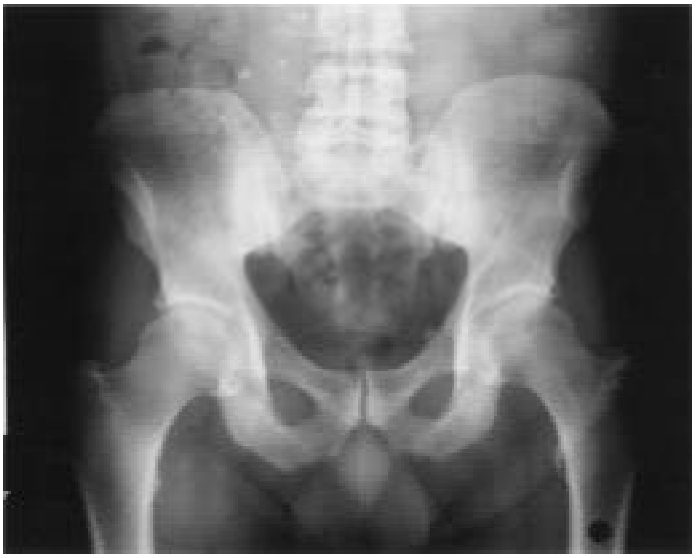

Fig. 2. Pelvis X-ray showing increased density with coarsened and sponge-like appearance.

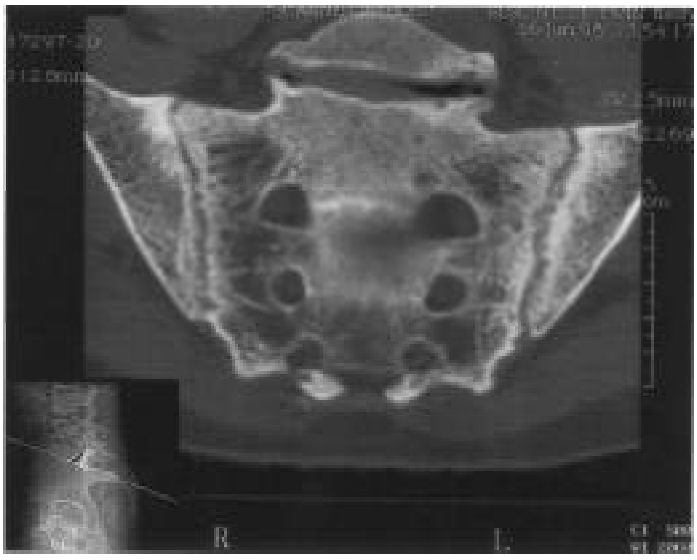

Fig. 3. Computed tomography of the sacroiliac joints showing narrowing and irregularity but also a coarsened and sponge-like appearance.

assessed in the previous cases. The increase of bone resorption showed in the present case is not necessarily the consequence of osteomalacia and could be due to moderate phosphate diabetes. In fact, Laroche *et al.* (11) demonstrated that moderate phosphate diabetes causes osteoporosis with increased bone resorption but not osteomalacia.

The histomorphometric data in the present case are in agreement with those previously published, indicating increased thickening of the cortices, increased trabecular bone volume associated with increased osteoid features and, particularly, osteoid thickness (1, 4, 5).

Despite the absence of vitamin D deficiency, some patients are treated with vitamin D (perhaps due to the existence of osteomalacia), but without significant improvement (3, 4). Our patient was treated initially with oral phosphate associated with calcitriol as recommended for moderate phosphate diabetes (8). However the treatment was not well tolerated and then was replaced by calcidiol which was well tolerated and led to a slight increase of BMD at the hip.

In conclusion, this new case of axial osteomalacia is particular for several reasons. On one hand the increased density of the axial skeleton has been proven by DXA. On the other hand increased BMD at the spine was associated with decreased BMD at the femoral neck possibly due to moderate phosphate diabetes. Moreover this case is also particular due to its association with sacroiliitis and the presence of HLA-B27 antigen.

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