Osteomalacia and Insufficiency Fracture in a Hemodialysis Patient with Autosomal Dominant Polycystic Kidney Disease

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Abstract

A 61-year-old Japanese woman on hemodialysis with autosomal dominant polycystic kidney disease (ADPKD) was admitted to the hospital with gluteal pain. Radiographs demonstrated a fracture of the left pubis. The serum 1,25(OH)2-vitamin D and 25(OH)-vitamin D levels were low. A biopsy of the right iliac crest disclosed osteomalacia. Active vitamin D sterol was administered in conjunction with dietary modification. Her gluteal pain was resolved three years later, and healing of the fracture was confirmed by radiology. This case emphasizes that vitamin D deficiency and malnutrition can cause osteomalacia in dialysis patients, even if calcium (Ca) and phosphate (P) levels are controlled by calcium carbonate.

Key words: osteomalacia, vitamin D deficiency, autosomal dominant polycystic kidney disease, insufficiency fracture, chronic kidney disease-mineral and bone disorder

Introduction

Bone changes that occur in patients with chronic renal failure are known by the general term of renal osteodystrophy (ROD). Osteomalacia, one type of ROD, can lead to major clinical problems including fractures (1, 2). Osteomalacia has not been a very important clinically condition, since aluminum-related osteomalacia was overcome by the use of reverse osmosis equipment and the avoidance of medications containing aluminum derivatives (3). Although active vitamin D analogues are used for treating secondary hyperparathyroidism (HPT), their use for treating osteomalacia due to 1,25(OH) vitamin D3 deficiency has not been described. Recently, the term chronic kidney disease-mineral and bone disorder (CKD-MBD) has been proposed, because of the increased morbidity and mortality observed in patients with ROD is considered to be secondary to cardiovascular calcification (4). ROD is a term used to express bone histological change in CKD-MBD. CKD-MBD is a broader term, which includes of abnormal laboratory tests, bone metabolism and soft tissue calcification. The K/DOQI guidelines recommended lowering the dose of vitamin D, if Ca and P levels are controlled within the specified range, since treatment with calcitriol can increase calcium and phosphate levels and promote vascular calcification.

A patient with autosomal dominant polycystic kidney disease (ADPKD) presented with absolute vitamin D deficiency and malnutrition that were thought to have contributed to osteomalacia with an insufficiency fracture of the pelvis. Patients with ADPKD have been reported to develop malnutrition due to an increase of intra-abdominal pressure due to enlarged kidneys and liver (5, 6). Osteomalacia is discussed with respect to the importance of calcitriol and the nutritional status of an ADPKD patient.

Case Report

A 61-year-old Japanese woman on hemodialysis for chronic renal failure secondary to ADPKD was admitted to the hospital in January 2005, for the evaluation of severe pain in the gluteal region. The pain had occurred suddenly
Nicols Institute Diagnostics, San Clemente, CA, USA) was diagnosed in 1967. She subsequently developed progressive abdominal distension as a result of renal and hepatic enlargement. Hemodialysis was started in 2000, for chronic renal failure and her right kidney was resected. However, a sensation of abdominal fullness gradually progressed along with loss of appetite. Transcatheter artery embolization (TAE) was performed to reduce the size of her liver (calculated as 7,620 cm$^3$ by morphometric analysis based on computed tomography scans) in October 2002, and further TAE was done for the left kidney (volume calculated as 2,700 cm$^3$) in November 2003 (Fig. 1).

She was 160 cm tall and weighed 60 kg at the time of admission. Her blood pressure was 106/77 mmHg. The abdomen was markedly distended with a maximum circumference of 105 cm. Emaciation was severe in the thoracic region and the upper and lower extremities. Activities of daily living were decreased. Radiographs demonstrated a fracture of the left pubis (Fig. 2a). Bone scintigraphy with $^{99m}$Tc-labeled methylene diphosphonate (MDP) demonstrated strong uptake in the left pubis and bilateral ribs (Fig. 3).

Computed tomography showed marked enlargement of her liver and kidney along with ascites. Her bone mineral density (BMD) was measured by dual energy X-ray absorptiometry, revealing a T-score of -3.75 SD for the lumbar spine (L2-L4 in the lateral view), which was consistent with osteoporosis (less than -2.5 SD) according to the WHO classification. A complete blood count revealed a white blood cell count (WBC) of 3,100/μL, hemoglobin of 9.4 g/dL, and platelet count of 136×10$^3$/μL. Biochemistry tests showed a total protein of 7.9 g/dL, albumin of 2.7 g/dL, alkaline phosphatase (ALP) was elevated to 670 IU/L (predominantly the bone-type isoenzyme). Urea nitrogen (UN) was 52 mg/dL, creatinine (Cr) was 6.6 mg/dL, total cholesterol was 89 mg/dL, glucose was 107 mg/dL, calcium (Ca) was 7.9 mg/dL, albumin-adjusted Ca [= serum-Ca (mg/dL)-albumin (g/dL)+4.0] (7) was calculated to be 9.2 mg/dL, and phosphorus (P) was 4.0 mg/dL. Intact parathyroid hormone (iPTH, Nichols Institute Diagnostics, San Clemente, CA, USA) was increased to 450 pg/mL and osteocalcin was increased to 63 ng/mL (normal: 2.5 to 13). The serum 1,25(OH)$_2$-vitamin D level was reduced to 6.0 pg/mL (normal: 20 to 60) and 25 (OH)-vitamin D was reduced to 6.7 ng/mL (normal: 10 to 33). The serum aluminum level was less than 10 μg/L. She was being treated with 6 g calcium carbonate (CaCO$_3$) daily for hypocalcemia and hyperphosphatemia, but active vitamin D had not been administered.

**Bone histomorphometry**

Biopsy of the right iliac crest was performed after double tetracycline labeling with a schedule of 3 days on-7 days off-3 days on-11 days off (using doxycycline at 200 mg daily) in March 2005. Histomorphometric analysis was performed by Mrs. Akemi Ito from the Ito Bone Histomorphometry Institute (Niigata, Japan) and the histomorphometric parameters (8) were calculated using the ASBMR Histomorphometry Nomenclature (9). Unsealed thin sections (5 μm thick) were prepared from the bone biopsy specimen and were stained by the Villanueva method. Sections were observed under an epifluorescence microscope with ultraviolet light. There was a reduction of cortical bone due to increased cortical porosity, and cancellous bone connectivity was disturbed (Fig. 4a). A histomorphometric analysis of the cancellous bone adjacent to the thin cortex indicated a diagnosis of osteomalacia according to the Sherrard classification (1) (Fig. 4b, c), since tetracycline labeling was not seen along most of the trabecular surfaces and the osteoid volume greatly increased (osteoid volume/bone volume ratio =43.1%; normal: 2.17±1.14%), as was the osteoid surface (osteoid surface/bone surface ratio =89.6%; normal: 16.7±7.0%) and the osteoid thickness (29.3 μm; normal: 9.16±2.0). The total bone volume to total tissue volume ratio also increased (24.3%; normal: 20.8±1.5%). However, the ratio of fibrous tissue volume to total volume was calculated as 0.0% (normal <0.5%), while the ratio of eroded surface to bone surface increased (8.44%; normal: 5.6±1.9%). Both osteoblasts and osteoclasts were sparsely distributed near the inside of the resorption cavities. New bone formation was not detected (bone formation rate/bone surface =0.0 mm$^2$/mm$^2$/y).

**Clinical course**

Oral active vitamin D sterol (alfacalcidol) was started at 1.0 μg daily, and a more nutritious diet was recommended. Her appetite improved along with gradual reduction of the liver and kidney volumes after TAE. The fracture healed gradually, and the patient regained the ability to walk in January 2006. Re-evaluation was performed in May 2008, when her gluteal pain had resolved completely. The maximum circumference of the abdomen had decreased to 95 cm, along with reduction of both liver volume (5,411 cm$^3$) and left kidney volume (680 cm$^3$) as well as the disappearance of ascites. The serum albumin level increased to 3.3 g/dL, total cholesterol was 185 mg/dL, 25(OH)-vitamin D was 36.7 ng/mL, and ALP was 360 IU/L. The intact PTH level...
Figure 2. a: Radiograph displays fracture of the left pubis (arrow). b: There is healing of the fracture with new ossification (arrow).

Figure 3. a: Bone scintigraphy with 99mTc-labeled methylene diphosphonate (MDP) demonstrates strong uptake in the left pubis (arrow) and bilateral ribs (arrow). b: Bone scintigraphy demonstrated a markedly improvement of the left pubis and bilateral ribs.

decreased to 153 pg/mL. Her BMD (T-score) at L2-L4 had increased to -1.4 SD. Serum calcium and phosphorus levels were 8.5 mg/dL (adjusted Ca: 9.2) and 5.8 mg/dL, respectively, with phosphate binder therapy such as sevelamer. Radiographs demonstrated healing of the fracture and new ossification (Fig. 2b). Bone scintigraphy demonstrated a marked improvement of the left pubis and bilateral ribs (Fig. 3b).

Discussion

Osteomalacia is a low turnover bone disease and features defective mineralization of the newly formed bone matrix. ROD-related osteomalacia was classically due to aluminum (Al) toxicity, because aluminum inhibits bone mineralization (1). Osteomalacia due to Al or Fe deposition was frequently found in the late 1970s and 1980s. Vitamin D deficiency is common in patients with end-stage renal failure.

Osteomalacia was a severe problem before active vitamin D agents became widely available in clinical practice. However, osteomalacia has become uncommon with the adoption of reverse-osmosis equipment and avoidance of medications containing aluminum derivatives as well as administration of active vitamin D analogues. Osteomalacia has not been described as a subset of ROD that causes clinical problems including fracture, since 2000 (3).

The specific radiographic hallmark of osteomalacia is known as Looser zones, which are pseudofractures that manifest as radiolucent bands 2 to 5 mm wide with sclerotic borders, usually oriented perpendicular to the bone surface (10). Osteopenia and osteoporosis, manifesting as reduced bone density with thinning of the cortex, are the most common findings in patients with osteomalacia.

Sherrard’s classification states that a diagnosis of osteomalacia can be confirmed by bone histomorphometric analysis when the zone of double tetracycline labeling along most
Figure 4. a: Most of the cancellous bone has disappeared and has been replaced by adipose tissue. A decrease of cortical bone (arrow) is also apparent. Original magnification; 50×. b: natural light, c polarized light, d fluorescent light. There is no tetracycline labeling along most of the trabecular surfaces and the osteoid volume is greatly increased (arrow). Original magnification; 200×.

trabecular surfaces is narrow or absent, and the ratio of total osteoid volume to bone volume is more than 15% (1). Active osteoblasts along the trabecular bone surfaces are usually small when adult osteomalacia is caused by hypophosphatemia, malnutrition, or renal osteodystrophy.

In conclusion, an insufficiency fracture of the pelvis occurred in an ADPKD patient on hemodialysis with severe hepatomegaly and nephromegaly. An iliac crest biopsy revealed osteomalacia with osteoporotic changes, and the BMD was consistent with severe osteoporosis. The serum 1,25(OH)2-vitamin D and 25(OH)-vitamin D levels were very low, thus active vitamin D was administered and a highly nutritious diet was recommended. In addition, TAE was performed to reduce the volume of the enlarged kidney and liver. Thereafter, her fracture healed gradually and her malnutrition slowly improved. This case indicates that TAE was effective for treating osteomalacia in ADPKD patients with hepatomegaly and nephromegaly via an improvement of her malnutrition.

The authors state that they have no Conflict of Interest (COI).

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References