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Adult Acquired Hypophosphatemic Osteomalacia: Bone Biopsy and Skeletal Features in Two Patients

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Abstract

Objective: Little information is available in the literature regarding bone histologic features in patients with the interesting but rare condition of acquired hypophosphatemic osteomalacia. Our objectives here were to document bone features and provide bone histomorphometric and clinical and serum biochemistry findings on two patients with this disorder.

Subjects: A 36-year-old female and a 53-year-old male.

Methods: Studies were performed following institutional review board review. Histories and radiologic examinations showed multiple fractures. Biochemical evaluation showed serum phosphorus values of 2.0 mg/dl and serum alkaline phosphatase values of 263 and 313 IU/l. Iliac crest bone biopsies following tetracycline labeling were performed; quantitative histomorphometry showed elevated osteoid thickness (114 and 91 μm) and % osteoid volumes (41% and 54%). Indices of bone resorption were normal.

Conclusions: Here we present quantitative bone histomorphometric data and other skeletal and biochemical features, from two adults with acquired hypophosphatemic osteomalacia which expand the information available on patients with this rare and challenging condition of hypophosphatemic osteomalacia. The first patient reported here expired due to a tumor which was diagnosed late in the patient's course, but no tumor was identified in the second patient after 7.6 years of follow-up.

Keywords: Hypophosphatemic osteomalacia; Bone histomorphometry; Tumor-induced osteomalacia

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Introduction

Biochemical abnormalities are commonly noted in adult acquired hypophosphatemic osteomalacia [1-3], but there are few reports in the literature which characterize bone features with quantitative bone histomorphometric analysis [3-6]. Patients with tumor-induced osteomalacia experience bone pain, fractures and muscle weakness which is now known to be due to fibroblast growth factor 23 (FGF23) secreted by endocrine tumors [2]. Tumor-induced osteomalacia can be present in patients with prostate cancer, oat cell cancer, hematologic malignancies, neurofibromatosis and other conditions. In the series reported by Chong et al. [2] tumors were identified in 61% of the patients. Tumors in tumor-induced osteomalacia may often be small, and located in obscure areas [1]. Even with current diagnostic techniques, these tumors may remain difficult to locate in some patients [7]. In their review of tumor-induced osteomalacia summarize the characteristics of hypophosphatemic (from renal phosphate wasting) and inappropriately normal or low 1,25-dihydroxyvitamin D levels seen in these patients. Patients may remain undiagnosed for long periods of their life [2]. Multiple fractures can be present. In some cases (such as the second patient we describe in the present report) tumors may never be identified. The first patient reported here expired due to a tumor which was diagnosed late in the patient's course, but in the second patient, no tumor was identified after following the patient for 7.6 years.

Materials and Methods

Bone biopsies were obtained from the anterior iliac crests with the Bordier trephine with the trans

Table 1: Summary of Initial Clinical Features.

	Case #1	Case #2	Normal range
Serum calcium (mg/dl)	9.0 – 9.7	8.6 – 9.6	8.6 – 10.3
Serum phosphorus (mg/dl)	1.7 – 2.3	1.7 – 2.4	2.3 – 4.1
Serum potassium (mEq/l)	3.0 – 4.3	3.6 – 3.8	3.7 – 5.1
Serum chloride (mEq/l)	108 - 116	104 - 105	96 – 105
Serum magnesium (mEq/l)	2.0*	1.9**	* 1.4 – 1.9 **1.3 – 2.1
Serum CO_2 (mEq/l)	21 – 25	27 - 30	21 – 29
Serum uric acid (mg/dl)	1.4 – 1.8	6.0 – 7.4	<7.5
Alkaline phosphatase (IU/l)	253 - 274	303 - 323	35 – 110
PTH (pg eq/ml)	1390	730	430 – 1860
1,25(OH)$_2$vitamin D (pg/ml) [a]	23	34	20 – 76
25(OH)vitamin D ng/ml)	9.4	27	10-55
24-hour urine calcium	84	80	<250
T_m phosphate	1.6	1.7	2.5 – 4.2
Creatinine clearance (ml/min)	82	152	

*And**: For appropriate normal range, see relevant superscript in column 4 normal ranges.

[a] Note that the 1,25(OH)$_2$vitamin D normal range listed here was appropriate for the time at which specimens were assessed. The absence of an elevated PTH level indicates that there is no significant vitamin D deficiency in the study patients.

orientation. Second biopsies were obtained from the contralateral iliac crest. In order to expedite treatment of her severe muscle pain, only one course of tetracycline for two days preceded the biopsy of Patient 1. Tetracycline labelling of Patient 2 utilized the following regime: Acromycin, 250 mg q.i.d., two days; 11 days without label; declomycin, 150 mg q.i.d., one day prior to the first bone biopsy.

Bone biopsies were fixed in 10% neutral buffered formalin dehydrated and embedded in methacrylate. Serial sections were cut using a Reichert/Jung 2050 microtome. Five µm sections were stained with Goldner's stain [8] for quantitation of structural features. Unstained serial 7 µm sections were examined with fluorescence microscopy. Quantitative morphometry was performed using a Zeiss microscope, camera lucida and Summagraphics Bit Pad One interfaced with an IBM-XT computer. Bone morphometry software was obtained from BioMed Stats, Inc., (Tacoma, WA). Histochemical evaluation for the presence of aluminum used the aurin tricarboxylic acid method [9]. Serum and urine parameters were determined with standard laboratory methods. PTH was determined by the carboxy-terminal assay of BioScience Laboratories. Serum 25-OHD concentrations were measured using the method of Preece et al. [10] after chromatography on Sep-Paks. 1, 25-$(OH)_2$ - vitamin D_3 concentrations were measured by the method of Reinhardt et al. [11].

Case Presentation

Case 1: The patient was a 36-year-old black female admitted to Los Angeles County/USC Medical Center for right hip pain preceded by a 10-year history of recurrent pelvic and hip fractures. Ten years prior to admission she experienced a pelvic fracture after falling out of a chair. A second pelvic fracture occurred after another fall one year before admission. 1-1/2 years prior to admission a muscle biopsy was performed because of complaints of weakness; it showed type II atrophy. Two years prior to admission, the patient had undergone a

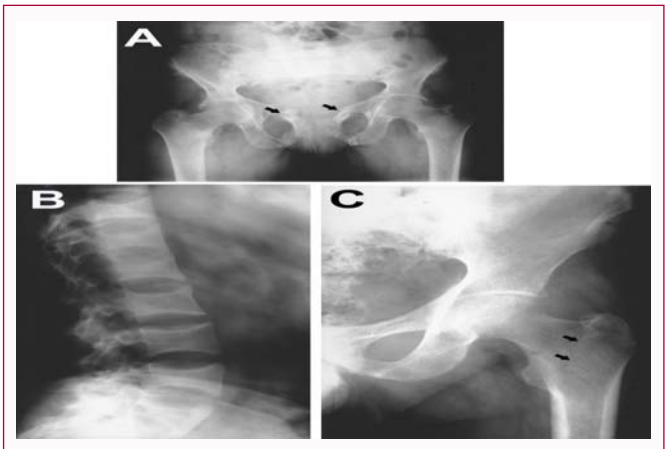

Figure 1: A and B, Patient 1: Pelvic radiograph shows several fracture sites(Figure 1A); lumbar spine films show osteopenia and marked expansion of intervertebral disc space (Figure 1B). C, Patient 2: A pseudofracture is present in the left femoral neck. (Arrows mark facture sites).

total abdominal hysterectomy. There was no family history of bone disease. No history of alcohol abuse or antacid or anticonvulsant therapy was obtained. The patient experienced increasing disability over the year prior to admission, progressively requiring from one to two canes for ambulation. The patient continued her duties as a clerk and a mother with difficulty until admission. On the day of admission she had fallen and experienced severe right hip pain. Roentgenographic examination of the pelvis was interpreted as showing multiple fractures. On physical examination her height was 5'5" and her weight was 130 lbs. The thorax was tender to palpation at multiple costochondral junctions and over the right posterior 11th and 12th ribs. Proximal muscle strength in the lower extremities appeared mildly decreased. A roentgenographic survey of the skeleton revealed multiple unhealed pelvic fractures bilaterally (Figure 1A) and severe osteopenia of the lumbar spine with considerable expansion of the intervertebral disc spaces (Figure 1B). Her serum chemistries are summarized in Table 1. In addition to hypophosphatemia and hyperphosphatasemia, mild hypokalemia and mild hyperchloremic acidosis were noted. Four years after presentation the patient experienced mid-epigastric pain associated with anorexia, weight loss of 25 pounds over two months and nausea and vomiting. She was admitted to a local cancer hospital. Abdominal CT scan showed diffuse low density lesions throughout the liver in a heterogeneous pattern with irregularity of the liver surface. Chest CT scan showed an abnormal internal mammary node, possible anterior mediastinal lymphadenopathy and multiple bilateral small pulmonary nodules. Ultrasound examination showed that the left portal vein appeared to be compressed by tumor. A bone scan showed no focal lesions. A fine needle aspirate was given a cytopathologic diagnosis of "probably clear cell adenocarcinoma". The histopathologic findings were believed to be more consistent with a metastatic clear cell carcinoma than a primary hepatoma, but there was no way to differentiate between the two possibilities. The patient expired in another hospital under another physician's care; no autopsy was performed.

Case 2: The patient was a 53-year-old male auto mechanic born in Guatemala. Three weeks before admission to Los Angeles County/USC Medical Center the patient had undergone surgery at Orthopaedic Hospital for a stress fracture of the femoral neck. A biopsy was taken which revealed no specific diagnosis. Internal fixation of the femoral neck was accomplished with threaded pins.

Table 2: Bone Biopsy Quantitative Histomorphometry Data.

	Patient 1	Patient 2	Normal Values[a]
Indices of Bone Formation			
Osteoid volume (OV/BV, %)	40.9	53.8	2.8 ±0.4 [b]
Osteoid seam thickness (Oth, µm)	114.1	90.8	9.4 ±0.4
Osteoblast number (Nob/BPm)	10.2	6.4	4.3 ±0.7 [b]
Osteoblast surface (%)	5.8	5.6	3.4 ±0.2
Indices of Bone Resorption and Fibrosis			
Eroded surface (ES/BS, %)	0.7	2.3	4.4 ±0.4 [b]
Osteoclast surface (OcS/BS, %)	0.2	0.8	1.0 ±0.2 [b]
Osteoclast number (Noc/BPm)	0.2	0.3	0.3 ±0.01
Fibrotic volume (%)	0.2	0.003	-0-

a.Values are means ±s.e.m from reference [25] unless otherwise marked asb. which denotes values from reference [26].

A pseudofracture of the femoral neck was present at the time the patient was initially examined (Figure 1C), and the patient complained of almost incapacitating bone pain and muscle weakness. The patient had experienced progressive generalized weakness, difficulty walking and worsening pains in the right hip, back, ribs and feet for eight months and he required a cane. No history of alcohol abuse or use of antacids or anticonvulsants was obtained. There was no family history of bone disease. On physical examination, his height was 5'4-3/4" and his weight was 175 lbs. He had tenderness on palpation of the posterior pelvis, several ribs, the metatarsals and the left humerus.

A roentgenographic survey of the skeleton revealed mild osteopenia of the vertebrae with slight expansion of several intervertebral disc spaces. A radiolucent cortical lesion as seen on the medial aspect of the left femoral neck (Figure 1C) and on the lateral aspect of the left scapula (data not shown). These were typical pseudofractures; one rib fracture with a callus was also noted. A bone scan revealed multiple focal areas of uptake in the cervical and thoracic spines, the ribs, the left humerus and the right femoral neck. His serum chemistries are also summarized in Table 1.

Results and Discussion

At presentation, both patients had serum phosphorus levels which were consistently low (1.7 mg/dl - 2.4 mg/dl), alkaline phosphatase levels consistently elevated (253-303 IU/I) and T_m phosphorus (1.6 - 1.7). Other serum data for the two patients presents in Table 1. Heavy metal screening was negative and thyroid function tests were normal.

Initial bone biopsy values were markedly abnormal for both patients. Percent osteoid volume, surface and osteoid thickness were markedly increased (Table 2; Figure 2A and 2C). Osteoblast number was also increased (Table 2). Mild marrow fibrosis was present. Although double labelling was not successful in these patients, single label incorporation was diffuse and very smeared (Figure 2B) Shane et al. [3] were also not able to measure tetracycline-based parameters in their patient. It is interesting that in some patients tetracycline labeling can form distinct labels when osteoid seams are not as wide as those reported here; Siris et al. [4] measured a Mineralization Lag Time (MLT) <0.2 µm/day in a patient with osteoid seams 59 µm in width; Gods all et al. [5] reported a similar MLT finding in a patient with thin osteoid seams (18 µm). Patients studied here showed extremely wide osteoid seams (90 and 114 µm (Table 2)). Hogan et al. [6] were unable to measure MLT in their patient with wide osteoid seams (81.9 µm); this patient had hypophosphatemic osteomalacia and neurofibromatosis. Histochemical staining for aluminum was negative for the patients studied here (data not shown). Indices of bone resorption were not elevated. Other quantitative histomorphometric bone features are summarized in Table 2.

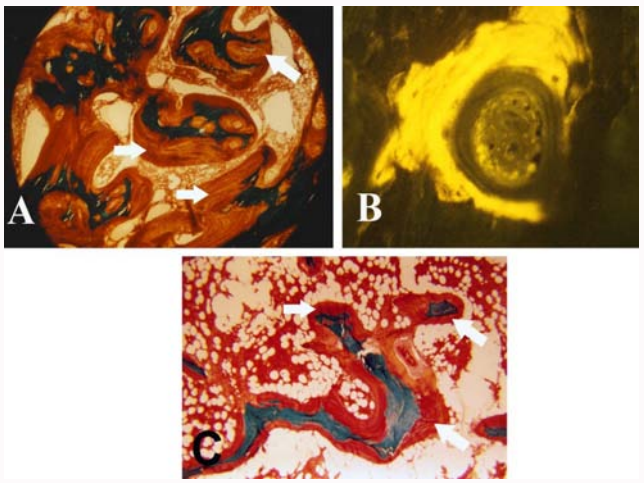

Figure 2: Representative light micrographs illustrating extremely widened osteoid seams (stained red, arrows) and thin inner trabecular core of mineralized bone matrix (stained dark green) in Patient 1 (Figure 2A) and Patient 2 (Figure 2C), (Goldner's stain). Figure 2B shows wide, diffuse tetracycline labeling in Patient 1. (Unstained section viewed with UV microscopy). (Original magnification x150).

Previous reports of adult onset hypophosphatemic osteomalacia have documented associations with numerous reports of tumor-induced osteomalacia [4,12], neurofibromatosis [6,13,14], with treatment with antacid and/or sucralfate [5,15,16], and in several reports, with idiopathic occurrence [17-20]. In Patient 1 it is possible that the serum and bone changes at initial presentation were tumor-related. After 7.6 years, no tumor was identified in Patient 2.

It is interesting that in tumor-induced osteomalacia, it was the investigation of these tumors which resulted in identification and isolation of FGF23 [21,22]. This finding has expanded our understanding of heritable hypophosphatemic disorders and regulatory systems affecting Pi homeostasis [1]. Unfortunately, the present two patients were studied prior to discovery and clinical implementation of FGF23 serum assays. We also were not able to utilize newer powerful scanning modalities which, when combined, can often be of great utility in tumor identification [7,23,24].

In summary, we present here clinical data and bone histomorphometry analyses on two patients; this work expands the study of the interesting and rare condition of adult acquired hypophosphatemic osteomalacia.

References

1. Carpenter TO. Primary disorders of phosphate metabolism. In. www.endotext.org. South Dartmouth. 2014.
2. Chong WH, Molinolo AA, Chen CC, Collins MT. Tumor-induced osteomalacia. Endocrine-Related Cancer. 2011;18(3):R53-R77.
3. Shane E, Parisien M, Henderson JE, Dempster DW, Feldman F, Hardy MA, et al. Tumor-induced osteomalacia: Clinical and basic studies. J Bone Miner Res. 1997;12(9):1502-11.
4. Siris ES, Clements TL, Dempster DW, Shane E, Segre GV, Lindsay R, et

al. Tumor-induced osteomalacia. Kinetics of calcium, phosphorus, and vitamin D metabolism and characterixtics of bone histomorphometry. Am J Med. 1987;82(2):307-12.

5. Godsall JW, Baron R, Insogna KL. Vitamin D metabolism and bone histomorphometry in a patient with antacid-induced osteomalacia. Am J Med. 1984;77(4):747-50.
6. Hogan DB, Anderson C, MacKenzie RA, Crilly RG. Hypophosphatemic osteomalacia complicating von Recklinghausen's neurofibromatosis: increase in spinal density on treatment. Bone. 1986;7(1):9-12.
7. Geller JL, Khosravi A, Kelly MH, Riminucci M, Adams JS, Collins MT. Cinacalcet in the management of tumor-induced osteomalacia. J Bone Miner Res. 2007;22(6):931-7.
8. Gruber HE. Adaptations of Goldner's masson trichrome stain for the study of undecalcified plastic embedded bone. Biotech Histochem. 1992;67(1):30-4.
9. Buchanan M, Ihle BU, Dunn CM. Hemodialysis related osteomalacia: a staining method to demonstrate aluminum. J Clin Pathol. 1981;34(12):1352-4.
10. Preece MA, O'Ruirdabm JLH, Lawson DEM, Kodiced E. An assay for 25-hydroxy-cholecalciferol and 25-hydroxy=ergocalciferol in serum. Clin Chem ACTA. 1971;54:235-42.
11. Reinhardt TA, Horst RL, Orf JW, Hollis BW. A microassay for 1,25 dihydroxy vitamin D not requiring high performance liquid chromatography. Application to clinical studies. J Clin Endo Metabol. 1984;58(1):91-8.
12. Rao DS, Parfitt AM, Villanueva AR, Dorman PJ, Kleerekoper M. Hypophosphatemic osteomalacia and adult Fanconi syndrome due to light-chain nephropathy. Another form of oncogenous osteomalacia. Am J Med. 1987;82(2):333-8.
13. Konishi K, Nakamura M, Yamakawa H, Suzuki H, Saruta T, Hanaoka H, et al. Hypophosphatemic osteomalacia in von Recklinghausen neurofibromatosis. Am J Med Sci. 1991;301(5):322-8.
14. Weinstein RS, Harris RL. Hypercalcemic hyperparathyroidism and hypophosphatemic osteomalacia complicating neurofibromatosis. Calcif Tissue Int. 1990;46(6):361-6.
15. Levy Y, Bansal M, zackson DA, Lane J, Shike M. Phosphate depletion syndrome: case report with bone and muscle histology findings and review of the literature. JPEN J Parenter Enteral Nutr. 1988;12(3):313-7.
16. Chines A, Pacifici R. Antacid and sucralfate-induced hypophosphatemic osteomalacia: a case report and review of the literature. Calcif Tissue Int. 1990;47(5):291-5.
17. Silverton SF, Haddad JG. Medical reversal of acquired hypophosphatemic osteomalacia. Am J Med. 1987;82(5):1077-82.
18. Weiss M, Schechter P, Bab I, Mekhmandarov S, Bank H, Eisenstein Z. Metabolic studies in a patient with idiopathic hypophosphatemic osteomalacia. Isr J Med Sci. 1988;24(1):46-50.
19. Rico H, Gomez-Castresana F, Hernandez ER, Matute JA, Torrubiano J, Nunez-Torron M. Adult hypophosphatemic osteomalacia: report of two cases. Clin Rheumatol. 1985;4(3):325-34.
20. Dent CE, Stamp TCB. Hypophosphatemic osteomalacia presenting in adults. Quart J Med. 1071;40:303-29.
21. Shimada T, Mizutani S, Muto T, Yoneya T, Hino R, Takeda S, et al. Cloning and characterization of FGF-23 as a causative factor of tumor-induced osteomalacia. Proc Natl Acad Sci USA. 2001;98(11):6500-5.
22. Bowe AE, Finnegan R, Jan de Beur SM, Cho J, Levine MA, Kumar R, et al. FGF-23 inhibits renal tubular P transport and is a PHEX substrate. Biochem Biophys Res Commun. 2001;284(4):977-81.
23. Hesse E, Moessinger E, Rosenthal H, Laenger F, Brabant G, Petrich T, et al. Oncogenic osteomalacie: Exact tumor localization by co-registration of positiron emission and computed tomography. J Bone Miner Res. 2007;22(1):158-62.
24. Jiang Y, Xia WB, Xing XP, Silva BC, Li M, Wang O, et al. Tumor-induced osteomalacia: an important cause of adult-onset hypophosphatemic osteomalacia in China: Report of 39 cases and review of the literature. J Bone Miner Res. 2012;27(9):1967-75.
25. Malluche HH, Meyer W, Sherman D, Massry SG. Quantitative bone histology in 84 normal American subjects. Micromorphometric analysis and evaluation of variance in iliac bone. Calcif Tissue Int. 1982;34(5):449-55.
26. Gruber HE, Gutteridge DH, Baylink DJ. Osteoporosis associated with pregnancy and lactation: Bone biopsy and skeletal features in three patients. Metabol Bone Dis Relat Res. 1984;5(4):159-65.