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A Case of Osteomalacia: The Pivotal role of the Non-Decalcified Bone Biopsy

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A postmenopausal osteopenic woman presented with recurrent stress fractures of the feet and normal parameters of mineral homeostasis. Despite the absence of biochemical or radiographic evidence, severe osteomalacia was documented by histomorphometric analysis of a tetracycline labeled, non-decalcified bone biopsy. This observation underscores the need for specific bone biopsy confirmation of skeletal disease in patients with fracture-prone osteopenia.

Key Words: *Osteopenia, Osteomalacia, Bone Biopsy*

INTRODUCTION

Most patients with generalized osteopenia are evaluated by radiographic and biochemical means. As informative as this approach may be, it often fails to define the specific skeletal lesion. This difficulty has led to development of the non-decalcified bone biopsy, a relatively new technique which offers precise delineation of generalized bone diseases. Under these circumstances, the biopsy material is generally obtained from the iliac crest by atraumatic and safe procedures.[1] Sequential biopsies can be performed in the same patient and, therefore, subsequent response to the therapeutic trials can be directly assessed. This technique, particularly when used in conjunction with tetracycline "labeling," often provides critical information in patients with metabolic bone disease, particularly when clinical findings are subtle and radiological and biochemical parameters are normal. In this report we underscore the pivotal role of the non-decalcified bone biopsy in the management of osteopenic patients.

CASE REPORT

This 54-year-old Caucasian woman was well until 3 years ago, when she developed extreme pain localized to the right distal tibia. Despite extensive laboratory investigation which included a decalcified bone biopsy of the distal tibia, no specific cause of her discomfort was discovered, but the pain gradually subsided without treatment.

Several months prior to her admission to the clinical Research Center at Barnes Hospital, the patient developed bilateral foot pain. X-ray examination was reproted as normal, but a 99Tc-pyrophosphate bone scan revealed multiple "hot spots" in her feet. A diagnosis of "stress fractures" was made and she was fitted with orthopedic shoes to minimize the stress while walking. Despite these measures the same symptoms reappeared in her left foot, and she was referred to our service for further evaluation.

The patient had undergone a hysterectomy and bilateral oophorectomy at age 34, and she had never received estrogen replacement therapy. Her calcium and vitamin D intake was adequate and included three 8 oz. glasses of milk daily. She had never received dilantin, phenobarbital, antacids, glucocorticoids, heparin, vitamin D, calcium supplements, or fluoride, all of which could potentially affect her skeletal status. Similarly, she experienced no prolonged food intolerance, diarrhea or steatorrhea.

The patient appeared well nourished but walked with a slight limp because of foot pain. There was edema of the left ankle and tenderness about the internal malleolus. Her routine laboratory evaluation was normal and those values which pertain to bone

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are listed in Table 1. Radiographs showed diffuse osteopenia and minimal degenerative changes in the spine and feet and there were no pseudofractures.

A transiliac bone biopsy specimen was obtained following two three-day courses of tetracycline, separated by 14 days. The specimen was fixed in neutral phosphate-buffered formaldehyde solution, embedded in methyl methacrylate[2] and sectioned at 5mm using a Jung Model K Sledge Microtome (Heidelberg, Germany). Sections were stained with modified Masson, and Goldner, and histomorphometric analysis was performed with a Merz-Schenk Integrating Eyepiece.[3] The following parameters were measured in trabecular bone as previously described:

(a) % total bone volume, or % of medullary space occupied by bone matrix;

(b) % relative osteoid volume, or % of bone matrix composed of osteoid(unmineralized matrix);

(c) % total osteoid surface, or % of trabecular surface covered by osteoid;

(d) % osteoblastic osteoid surface, or % of trabecular surface covered by osteoid lined by characteristic osteoblasts;

(e) mean osteoid seam width;

(f) number of osteoclasts/mm medullary space;

(g) % total resorptive surface, or % of trabecular surface containing scalloped resorptive bays (Howship's lacunae);

(h) % osteoclastic resorptive surface, or % of trabecular surface in apposition to osteoclasts; and

(i) % fibrotic surface, or % trabecular surface in apposition to marrow fibrosis.

Special stains for aluminum intoxication were also performed.[4] Tetracycline-based parameters included the percentage of osteoid seams assuming a fluorescent label and the cellular rate of mineralization, or the mean distance between double labels divided by the interdose duration.

Table 1. Biochemical Data

Calcium	9.7 mg/dl	(9-10.3)
Phosphate	3.5 mg/dl	(2.5 - 4.5)
Albumin	3.8 mg/dl	(3.5 - 4.5)
Alkaline Phosphatase	80 IU/L	(35- 95)
Magnesium	1.7 mEq/l	(1.5 - 2.4)
25 OHD	25 ng/ml	(8- 40)
iPTH	7 μleq/ml	(6- 10)
24 UCa/Cr	125 mg/gmCr	(100-300)
TRP	88 %	(78- 90)

* 25 OHD = 25-OH vitamin D, iPTH = immunoreactive parathyroid hormone, 24 UCa/Cr = 24 hour urinary calcium excretion per gm creatinine, TRP = tubular reabsorption of phosphorus.

*Normal values are in parenthesis.

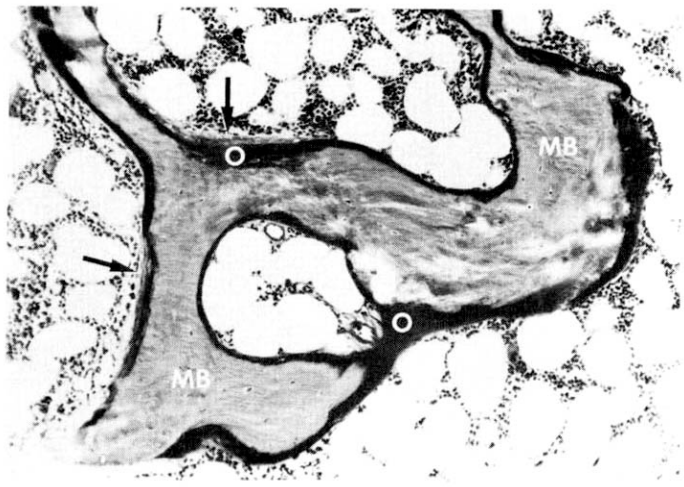

Fig. 1. *Trabecular bone of patient. Virtually all bone surfaces are covered by darkly staining, wide osteoid seams (non-decalcified, Goldner stain, 160X). O:osteoid, MB: mineralized bone, Arrows:osteoid covered with osteoblasts.*

Table 2. Histomorphometric Assessment of Trabecular Bone.

Total bone volume	21.81%	(23.72 ± 7.15)
Relative osteoid volume	8.14%	(0.97 ± 0.42)
Total osteoid surface	80.12%	(6.46 ± 8.34)
Mean osteoid seam width	12.14μm	(9.67 ± 9.50)
Total resorptive surface	3.02%	(2.22 ± 1.40)
Osteoclastic resorptive surface	0.39%	(0.07 ± 0.23)
Fibrotic surface	0.03%	(0)
Total surface covered by tetracycline	6.25%	(>65)
Appositional rate	1.0 μ/day	(0.70 ± 0.16)

*Normal values are in parenthesis (mean ± SD)

The patient's biopsy contained approximately ten times the normal quantity of osteoid (Fig. 1, Table 2). While some osteoid seams were thick, the predominant cause of the hyperosteoidosis was an increase in the percentage of trabecular surface covered by unmineralized matrix. There was also a slight proliferation of osteoclasts and mild peritrabecular marrow fibrosis. The tetracycline-based parameters confirmed the impression of severe osteomalacia. Less than 8% of osteoid seams (% total surface covered by tetracycline/total osteoid surface) assumed a fluorescent label, whereas under normal circumstances, such fluorescent bans should be present in apposition to at least 65% of these seams.[5] On the other hand, of those few foci where double label formation had occurred, the cellular rate of mineralization was normal.

In summary, osteomalacia was diagnosed in this case by the non-decalcified bone biopsy. However, the etiology was unclear, since the patient's routine laboratory findings and bone parameters were completely normal.

DISCUSSION

Post-menopausal osteopenia is a common yet poorly understood syndrome. It has become clear, however, that consistent with the variety of possible pathogenetic mechanisms, the histological appearance of the bone of patients with clinically significant, age-related osteopenia is heterogeneous.[6] The importance of these observations relates to differences in therapeutic approaches to patients with various forms of bone disease. In particular, patients with osteomalacia are especially important to identify as this family of disorders is often amenable to treatment.

Osteomalacia is the presence of excess unmineralized bone matrix due to defective skeletal mineralization. In most centers, the diagnosis is made intuitively on the basis of clinical, biochemical and radiological studies. Affected patients may complain of bone pain and tenderness, muscle weakness and spontaneous fractures. Their biochemical studies are often characterized by hypocalcemia, hypophosphatemia, increased serum alkaline phosphatase activity, and low levels of circulating 25-hydroxyvitamin D. Hypocalciuria is believed to be particularly useful in identifying osteomalacic individuals.

Pseudofractures (Looser's zones, Milkman fractures) have for some time been considered the pathognomonic radiological sign of osteomalacia.[7] These are symmetrically distributed lesions which characteristically occur perpendicular to the bone surface and do not transverse both cortices. Unfortunately, from the diagnostic point of view, most osteomalacic patients do not have pseudofractures, and a recent study has shown that the presence of these lesions is not pathognomonic of a mineralization defect.[8]

We have found that osteomalacic patients, as documented by bone biopsy, often fail to demonstrate the classical clinical features of their disease. The not infrequent failure to diagnose osteomalacia by non-histological means has contributed to establishing the non-decalcified bone biopsy as an essential tool in the evaluation of generalized disorders of the skeleton. In contrast to decalcified bone sections, non-decalcified material permits easy identification of patients with excess osteoid, a sine qua non for the diagnosis of osteomalacia.[9] On the other hand, osteoid may accummulate in bone by two basic mechanisms: (a) decreased rate of mineralization or (b) enhanced synthesis of bone organic matrix. Distinction between these two events requires the

use of tetracycline as a time-spaced histological marker of mineralization.[10] The present patient's skeleton failed to assume tetracycline in sufficient quantities to produce fluorescence at most osteoid-mineralized bone interfaces. This observation documents a paucity of newly deposited mineral at this location, which is the normal site of bone calcification and establishes the diagnosis of osteomalacia.

Thus, we have demonstrated that patients may have severe osteomalacia without clinical, biochemical or radiological evidence of the disease. Identification of such patients, which presently rests with the properly prepared bone biopsy, is essential because of the potential for successful therapy.

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