The histology of metabolic bone disease

Edward F McCarthy

Abstract

Patients with metabolic bone disease are usually cared for by endocrinologists. Pathologists may examine specimens if fragility fractures occur or if a bone biopsy is required. Some metabolic bone diseases have distinctive histologic features such as tunneling resorption in hyperparathyroidism, wide osteoid seams in osteomalacia, and bone marrow edema in transient osteoporosis. The histologic changes must always be correlated with clinical and radiographic features.

Keywords histomorphometry; osteomalacia; tunneling resorption; undecalcified

Metabolic diseases are disorders of the skeleton resulting from abnormalities in the chemical milieu of the body. With rare exceptions, these diseases cause a generalized decrease in bone mass and a tendency to fracture. The diagnosis and treatment of skeletal fragility is usually the province of endocrinologists. A pathologist is required to help in the diagnosis of specific metabolic disorders when an endocrinologist needs a bone biopsy or when an orthopaedic surgeon removes a portion of bone during stabilization of a fragility fracture. Also, bones retrieved at autopsy may be studied for the presence of metabolic bone disease.

There are four metabolic bone syndromes with distinctive histologic patterns: hyperparathyroidism, osteomalacia, age-related osteoporosis, and transient regional osteoporosis. A fifth pattern, renal osteodystrophy, is a combination of hyperparathyroidism and osteomalacia. Each of these syndromes has identifiable histologic patterns, and they are associated with distinctive clinical and radiographic features.

Hyperparathyroidism

Hyperparathyroidism causes distinctive resorptive changes in bone. Parathyroid hormone stimulates osteoblasts to secrete RANK ligand which causes osteoclast differentiation. Activated osteoclasts cause bone resorption. In the early stages of parathyroid overactivity, there is an increased number in resorption pits. This develops into a very distinctive pattern called tunneling resorption, a pattern diagnostic of hyperparathyroidism (Figure 1). Osteoclasts can penetrate the middle of a bone trabeculae and resorb a central channel. Further progression causes peritrabecular fibrosis (Figure 2). In the late stages of hyperparathyroidism, extensive resorption causes lytic bone lesions with reparative tissue called giant cell reparative granuloma. Because the giant cells are often associated with extravasated red blood cells and their brown hemosiderin breakdown products, these tumors have been known as brown tumors because of their gross pigmented appearance (Figure 3). Giant cell reparative granulomas have a zonal pattern with areas of multinucleated giant cells surrounded by fibrous tissue and reactive bone in a pattern that repeats itself many times in a low power microscopic field (Figure 4). This zonal pattern distinguishes this lesion from other giant cell containing neoplasms. In addition, giant cell reparative granulomas are not localized to the ends of long bones as are conventional giant cell tumors of bone.

These distinctive histologic changes may be seen in both primary and secondary hyperparathyroidism. Primary parathyroidism is almost always caused by a single parathyroid gland adenoma. Rarely four gland hyperplasia may be a cause of primary hyperparathyroidism if the patient has a multiple endocrinopathy syndrome. Even more rarely, a parathyroid carcinoma can cause primary hyperparathyroidism.

Primary hyperparathyroidism is almost always diagnosed early, years before skeletal changes occur. Nowadays only 5% of patients with primary hyperparathyroidism have clinical bone disease.[1] Therefore, the distinctive histologic features of hyperparathyroidism are rarely seen except if the disease is undiagnosed for many years. Early diagnosis is the result of screening of patients for serum calcium abnormalities which is done in almost all routine medical screening practices.[2] The practice of screening for serum calcium has led to the realization that primary hyperparathyroidism is a common disorder, third only to diabetes and hyperthyroidism.

Patients with primary hyperparathyroidism are usual asymptomatic but a few have malaise and GI symptoms. Approximately 20% of patients will develop kidney stones.

Patients with secondary hyperparathyroidism are usually suffering with chronic renal disease. The management of the inevitable skeletal changes that occur in chronic renal disease is a major concern in the clinical management of patients with renal failure.

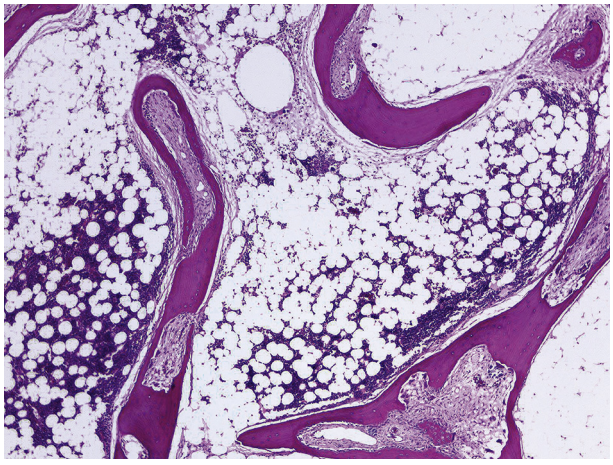

Figure 1 Low power photomicrograph of cancellous bone in hyperparathyroidism. There is tunneling resorption of the trabeculae.

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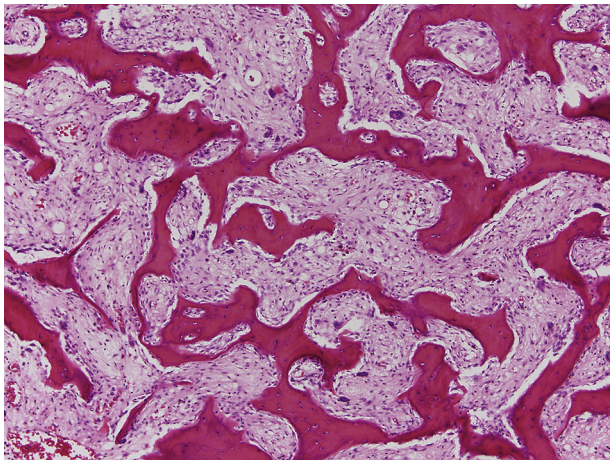

Figure 2 Photomicrograph showing abundant woven bone in a fibrous tissue matrix indicating the reparative phase of renal osteodystrophy.

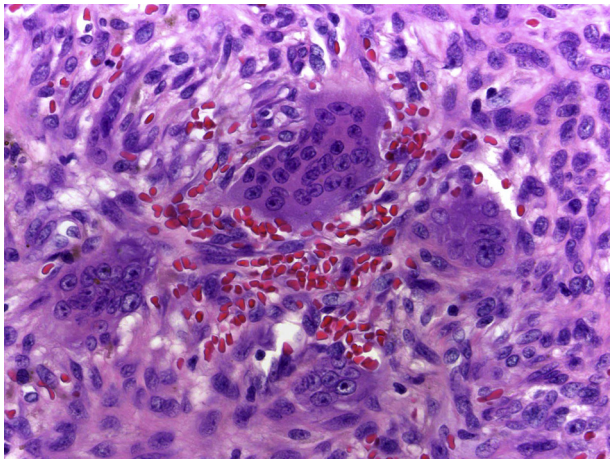

Figure 3 Giant cells clustered around extravasated red blood cells.

The earliest radiologically identifiable skeletal changes of primary and secondary hyperparathyroidism are resorption of the tuffs and margins of the phalanges (Figure 5). More advanced cases show osteopenia and, in long standing cases, multiple lytic lesions are present which represent the giant cell reparative granulomas (Figure 6). This end stage skeletal changes in long standing hyperparathyroidism was historically referred to by Von Recklinghausen as osteitis fibrosa cystica generalisata.[3]

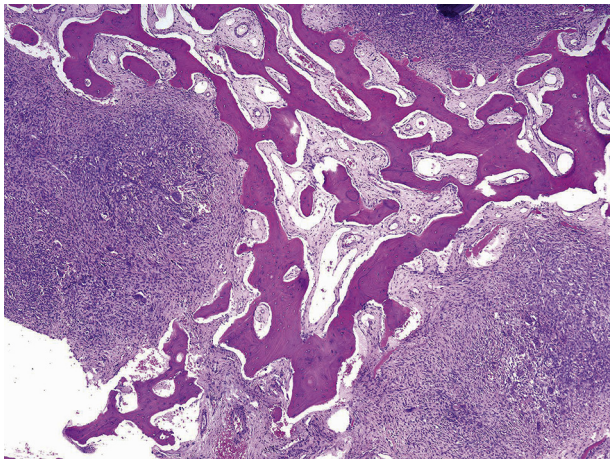

Figure 4 Low power photomicrograph of a brown tumor of hyperparathyroidism, also known as a giant cell reparative granuloma. There is a distinct lobular zonal growth pattern.

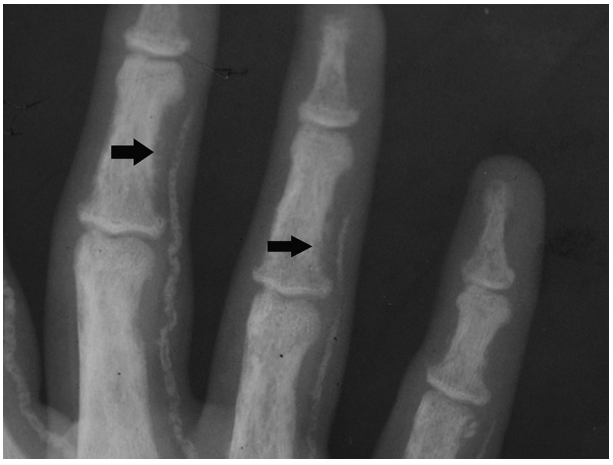

Figure 5 Plain radiograph of the hand and primary hyperparathyroidism. There is subperiosteal resorption along the middle phalanges (arrows).

Osteomalacia

Another metabolic bone syndrome with specific histopathologic features is osteomalacia. Osteomalacia, meaning soft bones, is caused by inadequate mineralization of normally synthesized bone matrix. The poorly mineralized bone results in skeletal fragility in the adults. In children, poor mineralization results in rickets, a syndrome of short stature and skeletal deformities. In both osteomalacia and rickets, the available ambient calcium (or occasionally phosphorus) is not sufficient to form calcium hydroxyapitate crystals which are necessary to mineralize bones.

The degree of bone mineralization cannot be appreciated on a standard decalcified H&E preparation. The special procedure

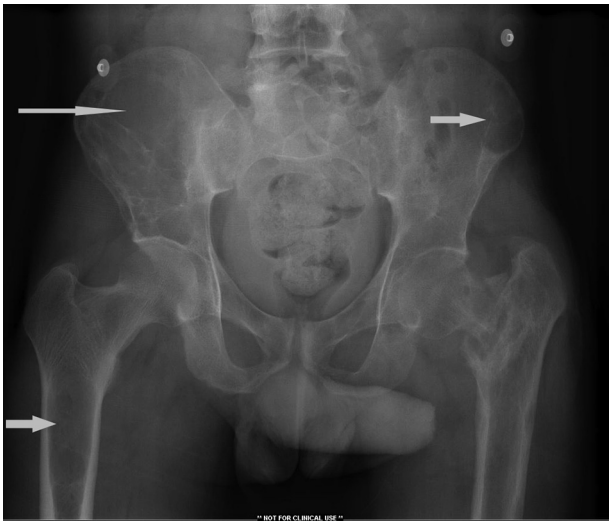

Figure 6 Plain radiograph of the pelvis in advanced hyperparathyroidism. There are multiple lytic lesions throughout the skeleton (arrows).