Bone Involvement in Multiple Myeloma

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The combination of aching bones and pathologic fractures, Bence Jones proteinuria, and progressive cachexia has indicated multiple myeloma since Kahler first emphasized the diagnostic criteria in 1889. Snapper [1] later recognized that pathologic fracture of the sternum is practically pathognomonic of multiple myeloma. Although chemotherapy for multiple myeloma has prolonged the survival period [2], progressive osteolytic lesions, spontaneous fractures, and incapacitating bone pain remain major problems in the clinical management of the disease. Bone pain is the most frequent complaint in patients with multiple myeloma [3] and is the presenting feature in 63% to 90% [1,3,4]. The pain, which nearly always starts in the lower back and ribs, is aggravated by the muscular effort of a mere cough or a sneeze. In the latter stages of the disease, severe pain may occur with the slightest physical motion. The report by Mariette et al [5] in this issue of The American Journal of Medicine addresses the impact of chemotherapy on the bone involvement in multiple myeloma. Before this report can be carefully examined, the pathogenesis, evaluation, and treatment of the bone disease should be briefly reviewed.

The bone disease develops for several reasons. The proliferating B-cell monoclonal can synthesize and release soluble factors that stimulate osteoclasts to resorb bone [6]. These osteoclast-activating factors are primarily composed of interleukin-1β with a smaller contribution from tumor necrosis factor-β (previously known as lymphotoxin) [7–9]. The direct relationship between the extent of skeletal destruction, the tumor-cell burden, and the amount of osteoclast-activating factors produced by cultured myeloma cells indicates that bone involvement in multiple myeloma is due to the production of these bone-resorbing cytokines [11]. Bone biopsies from patients with multiple myeloma show increased numbers of osteoclasts in the areas invaded by plasma cells [12].

Further aggravation of the bone disease occurs because the cytokines produced by myeloma cells also inhibit bone formation [10]. Therefore, the osteolytic lesions lack reactive or compensatory osteoblast proliferation. For this reason, the serum alkaline phosphatase activity is usually normal unless liver damage is present [1]. Advanced osteolytic disease is associated with elevated urinary excretion of hydroxyproline [13] and low levels of serum osteocalcin [14], representing the increase in osteoclasts and decrease in osteoblasts [9,10].

Hypercalcemia develops in at least a third of patients with myeloma and most probably occurs in those with a larger tumor-cell burden and greater release of cytokines [6]. The hypercalcemia is accompanied by subnormal levels of intact parathyroid hormone (PTH), as measured by the new two-site immunoradiometric methodology, which detects only the bioactive, secretory form of the hormone [15]. Low levels of serum 1,25-dihydroxyvitamin D₃ have also been reported [16]. The osteolytic lesions along with the low PTH secretion usually result in high-normal or elevated levels of serum inorganic phosphorus [1]. Renal impairment, which may eventually occur in about 50% of patients, is also associated with hyperphosphatemia. If a carboxyl terminal or middle molecule-specific PTH assay is used in hypercalcemic patients with renal failure, a modestly elevated PTH value may be found. These assays are notoriously unreliable in renal insufficiency because elevated levels are almost always detected and represent decreased renal clearance of PTH fragments rather than increased PTH secretion [17]. When hypercalcemia is found in myelomatous patients, associated bone pain, weight loss, and anemia are expected [3]. Ionized hypercalcemia may be overlooked in patients with advanced disease who have unremarkable serum total calcium concentrations due to concurrent hyperalbuminemia [18] or misdiagnosed in those rare patients with IgG-κ myeloma proteins that abnormally bind calcium and cause misleadingly high serum total calcium levels [19,20].

Therapy of multiple myeloma with prednisone may affect the bone disease. Glucocorticoids inhibit intestinal calcium absorption and increase urinary calcium excretion, resulting in a negative calcium balance [21]. In patients with multiple myeloma, glucocorticoid therapy further decreases osteoblast vigor and bone formation. Bone resorption is enhanced by glucocorticoids, but this is primarily due
to the secondary hyperparathyroidism caused by the negative calcium balance. Nevertheless, it seems unlikely that PTH contributes to bone resorption in patients with multiple myeloma. Glucocorticoids may also paradoxically inhibit bone resorption that has been stimulated by interleukin and tumor necrosis factor [21]. The combined impact of these glucocorticoid effects on the bone mass in multiple myeloma is, therefore, hard to predict. Another possible factor in the bone disease is the decrease in gonadal function that occurs with glucocorticoid treatment [22], chemotherapy [23], or severe systemic disease [24]. Reductions in the secretion of sex hormones may increase the rate of bone loss. Gonadotropin and sex hormone levels should be measured in patients with multiple myeloma because of the potential benefit of gonadal hormone replacement therapy on the skeleton. In addition to these factors, the decreased ambulation of the patient with severe pain may also contribute to the loss of bone mass [21].

Roentgenographic examination of the skeleton yields abnormal findings in approximately 80% of patients [4]. In more than half, there is a combination of lytic lesions, pathologic fractures, and a generalized increase in skeletal radiolucency [3,4]. Multiple myeloma may, however, present with osteopenia alone in 10% of patients and thus masquerade as postmenopausal osteoporosis or senile osteoporosis, if monoclonal gammopathy and marrow plasmacytosis are not discovered [3,4]. Skeletal surveys remain negative in up to 20% of patients [3,4]. The increased sensitivity of computed tomography (CT) may identify focal lytic lesions of the spine in patients with back pain, increased plasma cells in the bone marrow, and a monoclonal protein in the serum but no radiologic changes of myeloma [25]. Magnetic resonance imaging may prove to be even more valuable for the early diagnosis of myeloma bone disease [26]. When lytic lesions are identified, they are most commonly found in the skull, ribs, clavicle, sternum, spine, pelvis, and proximal parts of the extremities [1,3]. The sharply demarcated, punched-out, sieve-like appearance of the calvarium is particularly well known. However, it should be realized that similar radiographic abnormalities may be caused by metastatic carcinoma, especially of the breast [1,3]. With vertebral collapse due to multiple myeloma, the intervertebral disk usually remains intact [1] and the vertebral pedicles are rarely involved, reflecting the relative paucity of red marrow in the pedicles as compared with the vertebral body [27]. Preservation of the pedicles, an intact intervertebral disk, and the more frequent presence of a paraspinal mass are guides that help distinguish multiple myeloma from metastatic carcinoma [1,3]. Because of the defective osteoblast response to the osteolysis, the lytic lesions receive poor uptake of radionuclides [28]. For this reason, bone scans generally underestimate the number of lytic lesions in patients with multiple myeloma. Osteosclerotic lesions occur in only about 3% of patients but can result in positive bone scans [29]. Osteosclerotic myeloma may be associated with chronic progressive polyneuropathy, hepatosplenomegaly, diabetes mellitus, and gynecomastia [30].

A single, particularly painful bone lesion can be palliated with moderate doses of local radiotherapy. Radiotherapy must, however, be limited to a small field and adjunctive chemotherapy delayed until the hematologic impact of the radiation is clear. Lesions usually persist, and radiographic evidence of skeletal repair is rare. Regression of lytic lesions on serial lateral skull roentgenograms has, however, been demonstrated in 30% of patients who respond to melphalan with a reduction in myeloma protein production [31]. Consequently, many attempts have been made to develop adjunctive therapy to treat or prevent widespread bone disease in multiple myeloma. In a large double-blind cooperative study, fluoride therapy was shown to be ineffective and possibly detrimental [32]. Another study examined a regimen of calcium carbonate combined with sodium fluoride, but there were no significant increases in bone density as measured by single-photon absorptiometry of the radial diaphysis, a cortical bone site, or of the distal radius, a primarily cancellous bone site [33]. Dichloromethylene bisphosphonate, a bone-seeking inhibitor of osteoclasts, decreases urinary calcium and hydroxyproline excretion in patients with active myeloma and, in some patients, has diminished bone pain [34,35]. This potentially useful drug is, however, not available in the United States. Even more promising are the reports of inhibition of osteolytic bone lesions with the more potent and longer-lasting agent, (3-amino-1-hydroxypropylidene)-1,1-bisphosphonate or APD, currently available as pamidronate disodium (Aredia, CIBA-GEIGY, Summit, NJ) [36,37]. In one report, the relief of bone pain with pamidronate lasted 10 to 24 months, but evidence of sclerosis within a previously lytic lesion occurred only once [38]. The side effects of this drug are confined to a transient increase in temperature of 1°C to 2°C and infrequent, mild, local irritation at the injection site. In short-term studies, salmon calcitonin has also been shown to decrease bone resorption and hypercalcemia in patients with multiple myeloma [39]. The hypocalcemic response to calcitonin may even be used to estimate the extent of lytic lesions [40]. Further studies are in progress to assess the value of pamidronate and calcitonin in
the prevention and treatment of osteolytic lesions in multiple myeloma. Considerable interest has been focused on recalcification of lytic lesions as proof of a beneficial drug response, although this is not a particularly sensitive assessment of bone healing. Estimates of the amount of bone mineral that must be lost or gained to be evident to the trained radiologist range from 20% to 60%.

Mariette and associates [5] analyzed bone density determinations in 10 patients with stage III myeloma. Stage III myeloma is characterized by a high tumor burden (greater than 1.2 x 10^12 myeloma cells/m^2) with a hemoglobin level less than 8.5 g/dL, a serum calcium level greater than 12 mg/dL, advanced lytic bone disease, or high M-component production rates [41]. The patients were treated with high-dose melphalan, carmustine, cyclophosphamide, and etoposide, total body irradiation, and autologous blood stem cell transplantation. Between stem cell collection by leukopheresis and autograft, the patients received three monthly courses of vincristine, Adriamycin, and methylprednisolone. Bone mineral density was measured at the lumbar spine and femoral neck by dual-energy radiograph absorptiometry (DXA or DEXA) at the time of diagnosis of the myeloma and 8 to 12 months after therapy. DEXA uses a stabilized radiographic tube to generate photons of two different energies (one photon is attenuated by bone, the other by soft tissue) and allows a much greater photon flux than with decay of nuclear sources. This state-of-the-art technique thus increases the image resolution and precision while minimizing the radiation exposure and time required for the measurements. Excluding one patient with profound initial osteopenia and an extraordinary gain in bone density after therapy, the remaining nine patients had a mean increase in lumbar density of 0.057 g/cm^2, representing a gain of 0.074 g/cm^2 or 9.1%, whereas at the femoral neck, density decreased from 0.622 to 0.533 g/cm^2, indicating a loss of 0.089 g/cm^2 or 14.3% (95% confidence limit at the hip, 0.039 g/cm^2). These findings are similar to those reported by Mariette et al [5] and suggest that the improvement in lumbar density is detectable because of the sensitivity of the new DEXA technique, rather than from more aggressive therapy of the myeloma. Furthermore, the simultaneous decrease in bone density at the femoral neck implies an increasing risk of hip fracture and stresses the vital importance of performing bone densitometry at multiple skeletal sites. The axial and appendicular bones respond differently to various systemic conditions and drug treatments. Augmentation of bone density in response to therapy is usually more conspicuous in the spine than in the appendicular skeleton [43].

The last sentence in the paper by Mariette and associates [5] is possibly the most important. Bone densitometry could well become a routinely measured prognostic factor in the treatment of patients with multiple myeloma. Now that the bone involvement can be precisely assessed with DEXA and promising therapeutic options with calcitonin or pamidronate are available [36–39], prevention of skeletal pain and fracture in multiple myeloma should no longer be considered impossible.
REFERENCES


