Myeloma and Bone Disease: "The Dangerous Tango"

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Abstract: Osteolytic bone disease is the most debilitating manifestation of myeloma. However, myeloma-induced effects on the bone-active cells in the bone marrow are more than just a manifestation of disease—the myeloma derives essential support from the changed balance between bone-forming and -resorbing cells. This observation has lead to the notion that effective control of myeloma bone disease by reducing osteoclast activity and restoring osteoblast activity will contribute to long-term control of myeloma progression. Unlike osteolysis associated with other tumors that metastasize to bone, myeloma-associated lytic lesions are unique in that they do not repair even after many years in complete remission, reflecting a total loss of osteoblastic activity in areas of myeloma foci, apparently induced by the myeloma. Advances in imaging technology including positron emission tomography–computed tomography scanning allows accurate detection of lytic lesions and the monitoring of treatment effects. Effective antimyeloma therapy combined with anti-osteoclast drugs can halt the progression of osteolysis; in severe cases with vertebral compression fractures, effective physical support in the form of vertebroplasty or kyphoplasty is required for control of function, pain, and stature. Fractures of the long bones are usually treated by intramedullary rod placement. New approaches to enhance osteoblast activity while controlling osteoclast activity currently under investigation may prove effective in controlling lytic bone disease and myeloma progression.

Keywords
Myeloma, lytic bone disease, imaging

Bone remodeling is a normal process responsible for maintaining skeletal integrity. The process is performed by "teams" of osteoclasts (which resorb bone) and osteoblasts (which lay down new bone in resorbed areas) in response to signals from osteocytes reacting to mechanical stress.[1-3] Normally, all parts of the process—signaling by osteocytes, resorption of damaged bone by osteoclasts, and formation of new bone by osteoblasts—are well balanced, or coupled. The coupling mechanism is mediated by factors released from the bone matrix and cells in the bone marrow, and apparently osteoclasts have an important role in this mechanism.[4] New evidence indicates that damage to any part of this process by affecting the number of osteocytes, osteoclasts, or osteoblasts, results in abnormalities in bone metabolism.[5] Genetic factors, nutritional abuses, hormonal changes, and chemotherapeutic agents (eg, glucocorticoids, bisphosphonates) act to disrupt the functions of different components of this delicately balanced process, resulting in abnormalities in bone turnover and the associated pathologic symptoms.[6-9]

Myeloma's intimate association with lytic bone disease is unique among the hematologic malignancies. Myeloma-associated osteolysis is the most debilitating manifestation of this malignancy, present in at least 80% of all patients as discrete osteolytic lesions and general osteopenia. In contrast to other tumors that metastasize to bone (eg, prostate, breast), myeloma is very seldom associated with osteoblastic lesions[10,11] and myeloma-associated lytic bone lesions do not repair even in patients who are disease-free for years. The relationship between myeloma and bone turnover presents a dynamic continuum, from systemic stimulation of bone turnover at the early stages to severe osteolysis with compression fractures of the spinal column.

Biology of Multiple Myeloma–Associated Lytic Bone Disease

Among the plasma-cell dyscrasias, monoclonal gammopathy of unknown significance (MGUS) is often considered a premalignant syndrome, with an annual conversion rate of 1% to overt myeloma.[12] Among the characteristics of MGUS is the lack of osteolytic bone lesions.[13] In an attempt to clarify the early events of bone involvement in myeloma, Bataille and coworkers reported that, unlike MGUS, in which bone resorption remains within the normal range, osteoclast activity is increased in early myeloma and overt myeloma. In contrast, osteoblast number and activity is significantly elevated in early myeloma but reduced in patients with overt disease.[14] They found that patients who maintained elevated osteoblast activity did not develop lytic bone diseases in spite of significantly elevated osteoclast activity, because the rate of bone loss was matched by the rate of new bone formation.[10] These observations suggest that a systemic increase of osteoblast activity coupled with an increased bone resorption rate is an early event in the progression of myeloma. That myeloma has systemic effects on bone metabolism was also evident in a study reporting that bone mineral density (BMD) of the lumbar spine and femoral neck, areas of hematopoietic activity in which myeloma often resides, was significantly lower in myeloma patients than in age-matched controls. However the BMD at the radial diaphysis, a site devoid of hematopoiesis, was above normal.[15] It thus appears that myeloma affects bone metabolism both systemically and locally: while promoting a coupled systemic increase in bone metabolism in areas remote from myeloma foci, myeloma cells induce uncoupling of osteoblast activity from osteoclast resorption. Because osteoclasts are hematopoietic cells, the myeloma-induced coupled increase in bone turnover rates results in increased BMD in areas devoid of hematopoiesis. In areas with hematopoietic activity, where the environment is hospitable for myeloma cells, a coupled increase in bone turnover rate is observed early in myelomagenesis. With progression, myeloma cells suppress osteoblast activity while promoting osteoclast activity, resulting in osteolytic lesions in areas adjacent to myeloma cells. In contrast, in patients with no lytic bone disease, osteoblast activity remains elevated even in areas adjacent to myeloma cells, thus maintaining the coupling between osteoblast and osteoclast activities. It therefore appears that myeloma-associated lytic bone disease reflects systemic enhancement of bone turnover with local suppression of osteoblast activity.[16]

Mechanisms of Myeloma Lytic Bone Disease

Stimulation of Osteoclastogenesis

A key requirement for the formation of osteoclasts from myeloid progenitors is activation of the transcription factor nuclear factor kappa B (NFκB) by binding of the receptor activator of NFκB (RANK) on the surface of the progenitors to its ligand (RANKL). RANKL is normally expressed by various cells in the bone marrow stroma, which also produces osteoprotegerin (OPG), which binds to RANKL and prevents its binding to the receptor, thus regulating the rate of osteoclast formation and bone resorption.[17-19] Myeloma cells alone and in contact with bone marrow stromal cells have been reported to produce factors known as osteoclast-activating factors.[20] More recently it has been discovered that myeloma cells change the balance between RANKL and OPG production in the bone marrow stroma; RANKL expression is upregulated, while OPG production is turned off.[21,22] Myeloma cells also act to sequester OPG from the environment by binding to the heparin sulfate proteoglycan syndecan-1 on their surface, followed by internalization and degradation.[23] In addition to affecting the balance of RANKL and OPG, myeloma cells express RANKL and can directly affect differentiation of osteoclasts from their progenitors.[24-27]

Although the RANK/RANKL axis has been considered the main pathway responsible for osteoclast differentiation, recent reports invoke macrophage inflammatory protein-1 α as a primary contributor to myeloma-induced osteoclastogenesis, although its function, and whether its activity is independent of RANK/RANKL, is still controversial.[28-32]

Figure 1. Classic focal osteolytic lesion (arrows) seen on a standard radiograph in the proximal radius of a patient with newly diagnosed multiple myeloma.

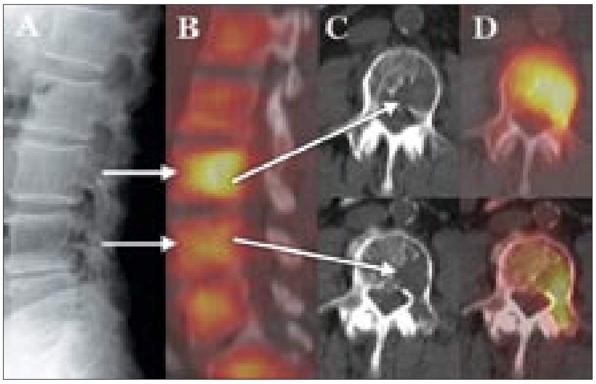

Figure 2. Lateral x-ray of the lumbar spine (**A**) with contemporaneous sagittal fused 18-fluorodeoxyglucose positron emission tomography (PET)–computed tomography (CT); (**B**) with axial CT; (**C**) and fused PET-CT; (**D**) images of L3 (top) and L4 (bottom) vertebral bodies. The x-ray fails to demonstrate the clear-cut focal osteolytic lesions seen on the axial CT images, demonstrated by fused PET-CT to be metabolically active focal lesions from multiple myeloma.

Effects on Osteoblasts

As discussed above, myeloma-induced changes in bone metabolism leading to lytic bone disease are believed to be more a reflection of inactivation of the osteoblastic response to osteolysis than of the activation of bone resorption by osteoclasts. Osteoblasts are differentiated from their progenitors, the bone marrow mesenchymal stem cells, in response to stimulation by the bone morphogenic protein-2. Signaling through the canonical wingless (Wnt) pathway is critical for this process.[33,34] Myeloma cells disrupt the process of osteoblast differentiation by secreting the Wnt signaling inhibitor Dikkopf-1 (DKK-1)[35,36] and possibly also soluble frizzled related protein-2 (sFRP-2).[37] Interleukin-3, a cytokine elevated in myeloma, has also been proposed as an inhibitor of osteoblast differentiation while supporting osteoclastogenesis.[38] The net result is a lack of osteoblasts and the absence of regeneration of osteoblast activity in bone areas infiltrated with myeloma cells.

Clinical Considerations

Diagnosis

Lytic bone disease in multiple myeloma is seen as both a diffuse loss of bone mass (osteoporosis) and well-circumscribed or “focal” bone lesions. Markers for bone formation/resorption are present and can be used to study systemic changes in bone metabolism.[39-45] Still, the standard for diagnosis of diffuse osteoporotic bone loss in multiple myeloma is via radiographic means, such as dual x-ray absorptiometry or routine radiographs with visualization of an osteoporotic appearance and/or the presence of complications from the diffuse bone loss (eg, osteoporotic or insufficiency fractures, including the sometimes debilitating compression fractures of the vertebral column).

In addition to the diffuse bone loss associated with multiple myeloma, focal growth of myeloma cells often produces focal lytic bone lesions. Diffuse bone loss is seen in areas of diffuse tumor infiltration of the marrow and also occurs systemically due to various cytokines released by the myeloma cells and/or the microenvironment interactions between myeloma and bone marrow. The mechanism of focal bone loss, which is associated with active focal nodules or masses of myeloma cell, is poorly understood. The original Durie-Salmon staging of myeloma uses the presence and number of focal lytic bone lesions.[46] On standard radiographs, focal lesions are areas of well-circumscribed defects in the bone architecture where loss of bone density occurs, specifically appearing as “holes” in the bone. Loss of at least 30% of the bone matrix is needed before such lytic changes are seen in radiographs; thus, focal lesions seen on radiographs are late changes that imply permanent loss of bone structure (Figure 1). Furthermore, air

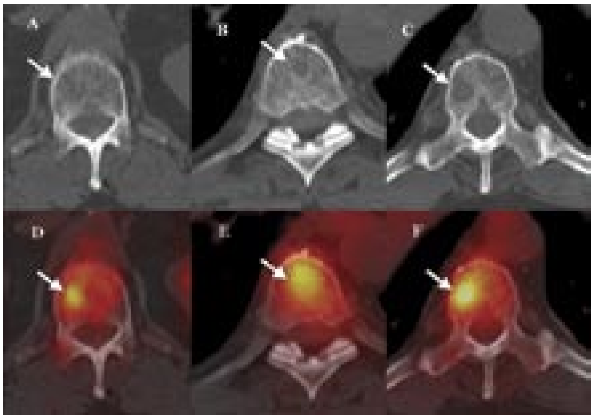

Figure 3. Series of axial computed tomography (CT) (**A–C**) and fused 18-fluorodeoxyglucose positron emission tomography (FDG PET)-CT (**D–F**) images in a patient with newly diagnosed multiple myeloma. These images are from the same FDG PET-CT scan, demonstrating different stages of evolution of focal lesions occurring simultaneously in the same patient. Figures 3A and 3D demonstrate a focal plasmacytoma with FDG PET imaging that has not yet produced focal osteolysis. Figures 3B and 3E demonstrate a focal plasmacytoma with early permeative lytic changes. Figures 3C and 3F demonstrate a focal plasmacytoma with clear-cut focal-associated osteolysis.

in the lungs, gastrointestinal tract, overlying soft tissues such as the visceral organs, and other skeletal structures can obscure focal bone loss on radiographs until it is relatively extreme.[9] Helical computed tomography (CT) can visualize focal bone loss much earlier because of its superior contrast resolution compared to plain x-ray, as well as its ability to image the marrow space of the skeletal system, the location where most focal bone disease occurs as a result of multiple myeloma. Thus, helical CT is a very powerful means to diagnose focal lytic bone disease and is currently the modality of choice (Figure 2).[47,48] When CT is combined with positron emission tomography (PET), using an ^{18}F-labeled deoxyglucose, a powerful medical imaging modality is formed, allowing fusion of both anatomy (CT) and physiology as demonstrated by quantitative glucose metabolism (PET), which provides visual representation and quantitative measurement of form and function. These techniques are more sensitive than standard x-rays, can demonstrate focal growth of multiple myeloma before focal osteolysis occurs, and can accurately follow the development of focal osteolytic bone lesions and the effects of treatment (Figure 3). Indeed, if treatment is successful, focal osteolysis is prevented. Combined PET-CT imaging clearly demonstrates that myeloma-associated osteolytic lesions are not repaired even in patients in complete remission and with no tumor activity even after many years (Figure 4).

Treatment

The treatment for bone disease has two goals: prevention of osteolysis or halting its progress and repair of osteolytic damage. Successful treatment of myeloma is the most effective method of preventing further changes in bone turnover. However, because successful treatment cannot be guaranteed, the use of inhibitors of osteoclast activity has become the standard of care in myeloma.[49] To this end, the bisphosphonates have become a mainstay in effective treatment of multiple myeloma bone loss.[49,50]

Although bisphosphonates block osteoclast activity and can lead to their apoptosis, these agents do not stimulate osteoblast differentiation or function. However, they protect osteoblasts and osteocytes from dexamethasone-induced apoptosis.[9,51] Inhibition of osteoclast function would generally be sufficient to produce a net increase in osteoblast activity relative to resorption by osteoclasts[12,52]; however, due to the myeloma-induced loss of osteoblast differentiation and function, increased BMD occurs only in uninvolved bones[15] and never in focal osteolytic lesions.[1-3]

Recent insight into the biology of bone presents new opportunities for the treatment of myeloma-associated lytic bone disease. The RANK/RANKL axis, responsible for differentiation of osteoclasts, presents an attractive target for therapy.[27,53,54]

A relatively new treatment for vertebral compression fractures resulting from diffuse or focal bone lesions from multiple myeloma is the use of vertebroplasty or kyphoplasty, a technique whereby a large-bore cannula is placed into the bone in question and “cement” is injected into the bony defect. The heated, liquefied material (methyl methacrylate) rapidly hardens to the consistency of cement, stabilizing the weakened bone and leading often to dramatic and essentially instant pain relief.[55-57] Fractures of the long bones are usually treated by intramedullary rod placement.

Does Treatment Contribute to Osteolysis?

Glucocorticoids have been a mainstay in myeloma therapy for over 40 years,[58] and high-dose prednisone pulsing has been used for over 35 years.[59] Glucocorticoids are known to adversely affect bone metabolism.[60-64] Recently it has been reported that glucocorticoids induce apoptosis of osteoblasts and osteocytes, thus preventing repair of damage to bone.[7] It has also been reported that the bisphosphonate pamidronate can prevent glucocorticoid-induced apoptosis of osteoblasts and osteocytes, while inducing apoptosis of osteoclasts.[51] Glucocorticoids, in turn, protect osteoclasts from pamidronate-induced apoptosis.[51,65] It is thus possible that by counteracting each other in the context of lytic bone disease, two of the most widely used

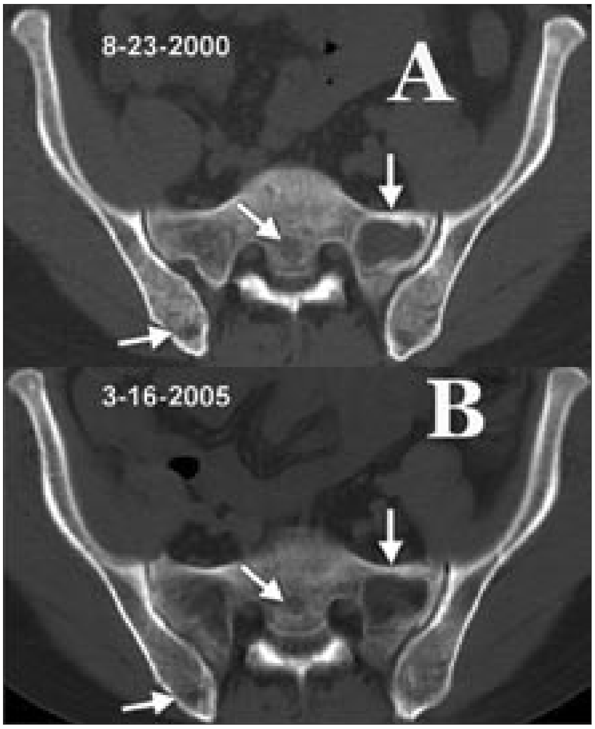

Figure 4. Axial computed tomography image through the upper pelvis of a patient with multiple myeloma. (**A**) image taken at diagnosis in August 2000, showing distinct lytic bone lesions (arrows). (**B**) Image taken in March 2005, when the patient has been in continuous complete remission since January 2001, demonstrating the lack of repair of myeloma-associated lytic bone lesions.

drugs in myeloma therapy may contribute to complications in the course and therapy of myeloma bone disease.

Effects of Osteoclasts and Osteoblasts on Myeloma Cells

As discussed above, myeloma is intimately (by frequency and spacial relation) associated with disruption of bone metabolism. Progression from MGUS to overt myeloma is preceded by increased bone turnover rate, and with progression at least 80% of patients lose the coupling between bone formation and resorption, leading to osteolysis. In the 20% or so of patients in whom osteoblast numbers and activity are maintained, no evidence of osteolysis can be detected. These observations lead one to wonder if the development of myeloma actually requires shifting the balance between osteoclast and osteoblast numbers and activities. In other words, is myeloma lytic bone disease merely a manifestation of myeloma, or is there a symbiotic relationship between the two?

Role of Osteoclasts

Several investigators reported that inhibition of osteoclast formation or activity in the SCID-hu[21,27] and 5T murine[66,67] myeloma models was associated with reduction in myeloma tumor burden. In vitro, osteoclasts were reported to support long-term survival and sustained proliferation of primary human myeloma cells.[68,69] Clinically, an anecdotal report suggested that treatment with pamidronate reduced myeloma tumor burden in 2 patients with progressive myeloma[70] and that a single infusion of pamidronate increased the proportion of apoptotic myeloma plasma cells in newly diagnosed patients.[71]

Role of Osteoblasts

While there has been much research into the effects of myeloma cells on osteoblasts and their mesenchymal progenitors, little is known of the effects osteoblasts might have on myeloma cells. Recently published data exist suggesting that increasing osteoblast numbers and activity may inhibit myeloma growth in vitro and in the SCID-hu model.[72] Inhibitors of proteasome activity stimulate osteoblast differentiation and bone formation in vitro and in vivo.[73,74] Clinical observations indicate that response to the proteasome inhibitor bortezomib (Velcade, Millennium Pharmaceuticals), shown to increase osteoblast activity in vitro, is associated with increased serum bone alkaline phosphatase levels and activation of osteoblasts.[75,76] Although not definitive, these studies may suggest that, at least in some patients, increasing osteoblast activity may have a suppressive effect on myeloma.

Taken together, these data on the relationship between myeloma cells and bone-active cells indicate that myeloma-induced changes in osteoclast and osteoblast activities are essential for myeloma survival and progression, and that normalization of bone turnover may prevent progression of myeloma and even suppress advanced myeloma, thus presenting new challenges and opportunities for novel therapies.

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