Monoclonal Gammopathies in a Fracture Liaison Service

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ABSTRACT

Monoclonal gammopathies are a spectrum of disorders characterized by the overproduction of plasma B-cells and immunoglobulin. Monoclonal gammopathy of uncertain significance (MGUS), a pre-malignant form of multiple myeloma, is defined by relatively low bone marrow concentration of clonal plasma cells and asymptomatic clinical presentation. New evidence, however, points to an association of MGUS with osteoporosis, microarchitectural bone deficiency, and fractures, and it has been suggested that it be renamed "Monoclonal Gammopathy of Skeletal Significance." The prevalence of MGUS in the general geriatric population is estimated to be 3–8%, while the prevalence in geriatric vertebral fracture patients is 15%, and the prevalence in all fracture patients within the Rhode Island Fracture Liaison Service is 10%. Therefore, MGUS and other monoclonal gammopathies should be suspected in all patients diagnosed with osteoporosis or an osteoporotic fracture, and patients diagnosed with monoclonal gammopathies should be evaluated for osteoporosis and fracture risk and treated appropriately.

KEYWORDS: monoclonal gammopathy of undetermined significance; multiple myeloma; plasma cell neoplasms; fractures

INTRODUCTION

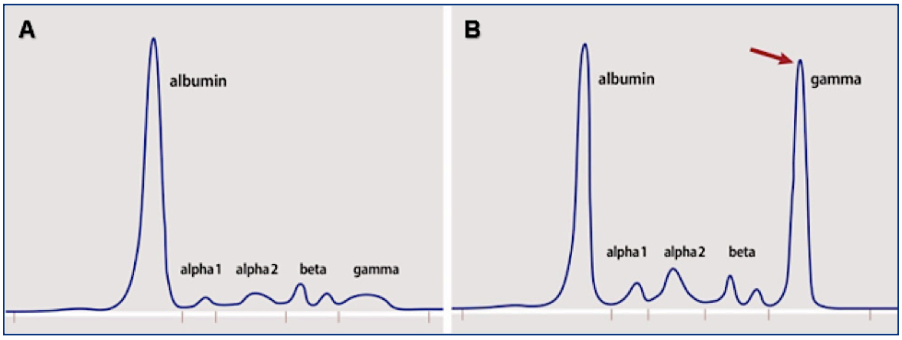
Monoclonal gammopathies represent a spectrum of bone marrow disorders caused by clonal expansion of plasma B-cells that overproduce an immunoglobulin, or monoclonal paraprotein, with consequences that are similarly variable. The most common resulting malignancy is multiple myeloma (MM), which is characterized by >10% of these plasma cells in the bone marrow with end-organ dysfunction such as hypercalcemia, renal dysfunction, anemia, and bone lesions, also known as "CRAB" signs. Multiple myeloma is the second most common hematologic malignancy, and will likely be diagnosed in over 30,000 Americans this year. At the other end of the monoclonal gammopathy continuum is monoclonal gammopathy of unknown significance (MGUS), a pre-malignant condition defined by low bone marrow concentrations of clonal plasma cells (<10%) and thus low circulating serum monoclonal protein. It is characterized by clinically asymptomatic disease without constitutional symptoms, anemia, lymphadenopathy or hepatosplenomegaly. It is becoming clearer that, despite its name, MGUS is rarely of no clinical significance, with subcategories including monoclonal gammopathy of renal significance (MGRS)[1], monoclonal gammopathy of neurological significance[2], and the proposed monoclonal gammopathy of skeletal significance, indicating that low circulating monoclonal protein concentrations may still have limited but important end-organ effects.[3,4] Blurring the line between the two extremes is smoldering multiple myeloma (SMM). Monoclonal gammopathies can also result in the development of solitary plasmacytoma of bone, solitary extramedullary plasmacytoma, light chain (AL) amyloidosis, or Waldenström Macroglobulinemia.

CLINICAL FEATURES OF MGUS

MGUS is the most common monoclonal gammopathy, found in approximately 3% of adults over age 50 and in 5% of adults older than the age of 70.[5] Interestingly, one study found the risk of MGUS to be 3.6% in patients with osteoporosis and 2% in those patients without osteoporosis.[6] Another study of patients with acute osteoporotic vertebral fractures found the risk of MGUS to be up to 15%.[7] The rate of progression from MGUS to MM over a lifetime varies, based on the amount of monoclonal paraprotein, the involved to uninvolved free light chain ratio, and the immunoglobulin isotype.[8] The average risk of progression is approximately 1% each year.[9] This is a linear risk as long as significant growth of the plasma cell clone does not move patients from the diagnosis of MGUS to smoldering multiple myeloma. Lifetime risk depends upon age at diagnosis. For a 65-year-old individual with an estimated life expectancy of 20 years, the risk can be considerable and justifies close follow-up.

Screening laboratory studies for monoclonal gammopathies should include serum protein electrophoresis (SPEP) with immunofixation (IFE), kappa and lambda free light chains with ratio, and quantitative immunoglobulins (IgG, IgA, IgM). If a patient has a non-IgG paraprotein, an abnormal serum free light chain ratio, a serum monoclonal protein of 1.5 g/dL or more, or a symptom concerning for multiple

Figure 1. Serum protein electrophoresis
A: Normal. **B**: M-spike in the gamma region (arrow).



myeloma, bone marrow assessment is recommended.[10] M protein spikes of over 3g/dL are more likely to be associated with malignancy while spikes under 3g/dL are usually not. However, a significant number of patients with myeloma may have a low M spike and, therefore, all patients with M spikes need oncologic evaluation. Most of the clinical interest is focused on the gamma region of the SPEP which contains primarily IgG immunoglobulins. **Figure 1** displays an SPEP with a large M spike in the gamma region representing a monoclonal gammopathy. Approximately 70% of MGUS is comprised of IgG, 15% of IgM and 12% of IgA.

MGUS, OSTEOPOROSIS AND FRACTURE

A consensus panel identified MGUS as a "non-malignant B-cell disorder (that) is the most common plasma cell dyscrasia and is associated with an increased risk of developing serious B-cell disorders."[11] This group pointed out that, from the perspective of the skeleton, individuals with MGUS have an increased risk of osteoporosis and osteopenia and an increased likelihood of developing fractures, especially in the vertebrae. Because of the prevalence of vertebral compression fractures, MGUS patients with significant back pain should be evaluated by MRI to rule out both vertebral fractures and myeloma. Given that MGUS is associated with a higher risk of osteoporosis/osteopenia and associated skeletal complications, especially fractures, it was recommended in the consensus statement that anyone with age-inappropriate or atypical bone loss undergo screening for the presence of a monoclonal gammopathy.[11] It was further recommended that MGUS patients who have evidence of vertebral compression fractures or who are osteoporotic be initiated on anti-resorptive therapy, and that MGUS patients with osteopenia be strongly considered for treatment as well. Bisphosphonates have been shown to improve bone density in the setting of monoclonal gammopathies. Other studies have confirmed that MGUS is a risk factor for fracture, particularly in the vertebrae, and have reported that vertebral compression fractures in patients with MGUS may be asymptomatic and may occur in patients without osteoporosis but still may be predictors of subsequent fractures. In one report, 18.4% of MGUS patients had at least one vertebral compression fracture and none were traumatic in nature.[12] Concordant data from US and European studies in largely Caucasian populations have suggested that overall fracture rates are increased approximately 1.7-fold, and vertebral fractures are increased up to approximately 6.3-fold in MGUS subjects when compared to the general population.[3] The observations that MGUS is associated with an increased risk of fractures has been supported by other studies showing that the risk of fracture at any anatomic site is 1.4–2.5 times greater in MGUS than in control populations.[13,14] Because of the propensity to fracture, the International Myeloma Working Group has recommended bisphosphonates for all MGUS patients with either osteopenia or osteoporosis.[15]

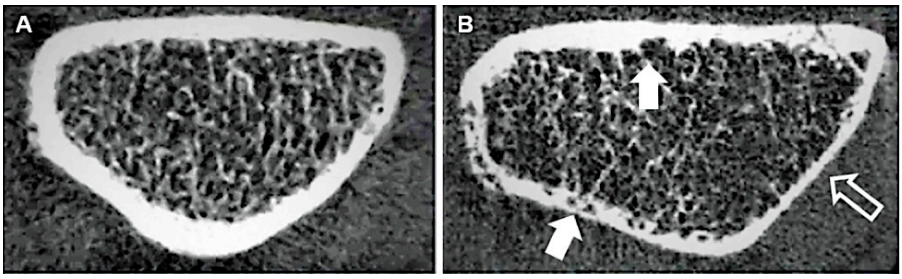
Having established the increased prevalence of fractures in MGUS patients, it is of substantial importance to examine the inverse: the prevalence of MGUS in the fracture population. Previously unrecognized MGUS is a relatively common finding in patients with fractures, as evidenced by a recent study which demonstrated that 6% of otherwise healthy subjects aged 50 years and older who sustained a hip fracture had MGUS.[16]

Understanding the mechanisms of bone loss in MGUS is of importance since the majority of these patients do not receive any therapy to increase bone density despite a substantially higher tendency to fracture. Monoclonal gammopathies are associated with excess bone resorption as assessed by increased levels of N-telopeptide of type I collagen. In one study of bone biopsies in 87 patients evaluated for MGUS, 45% of MGUS patients had criteria for excess bone resorption compared to 79% patients with indolent multiple myeloma and 93% of patients with overt myeloma.[17] Bone resorption was more frequent (52%) in MGUS patients that had progressive disease and subsequently developed myeloma. This study concluded that excessive bone resorption in MGUS is associated with progression and is an early sign of malignancy.

It has also been shown that MGUS patients have increased osteoclastogenesis and abnormally high bone resorption producing deterioration of skeletal microarchitecture and reduction in bone strength and ability to resist stress, leading to fracture.[3] Two studies have shown that patients with MGUS exhibit decreased bone mineral density at the proximal femur. High-resolution QCT has demonstrated decreased cortical and trabecular thickness, widening of the endosteal canal, increased cortical porosity, and increased bone width,

Figure 2. Distal radius showing trabecular and cortical bone

A: Normal. **B**: MGUS showing widening of the medullary canal, thinning of trabeculae, thinning of the cortex (open arrow), and porosity of the cortex (solid arrows).



all typical features of osteoporosis.[18,19] (**Figure 2**) The trabecular number and separation did not differ between the different groups. Micro-finite element analysis revealed that these microarchitectural alterations contributed to decreased biomechanical strength with an 8.9% reduction in the apparent modulus of elasticity.[3] Together, these observations characterize structural abnormalities in cortical and trabecular bone that result in decreased bone strength and contribute to the reduced ability of bone in MGUS to withstand applied stress and a heightened susceptibility to fracture.

Although over 20 cytokines that suppress osteoblast function or enhance osteoclast activity have been identified in multiple myeloma, few have been studied in MGUS. Two that are active in both myeloma and MGUS are macrophage inflammatory protein-1 alpha (CCL3/MIP-1α), a macrophage chemokine that, among other things, activates osteoclasts and is seen in inflammatory conditions associated with bone resorption (i.e., rheumatoid arthritis), and dickkopf-related protein 1 (DKK1) that inhibits the Wnt/β-catenin signaling pathway by blocking LRP6 receptor interactions and is seen in both myeloma and osteolysis. Circulating levels of the osteoclast activating factor, CCL3/MIP-1α, have been shown to be increased nearly 6-fold and circulating levels of the osteoblast-suppressive factor DKK1 are increased approximately 2-fold in MGUS patients compared to age, sex, and body mass matched control subjects.[18] These cytokines contribute to producing osteoporosis in monoclonal gammopathies. Since so few of the cytokines active in bone destruction in myeloma have been studied in MGUS, it may be that cytokines other than those described may also participate in reducing bone density and increasing fracture risk in MGUS.

MGUS IN THE RHODE ISLAND FRACTURE LIAISON SERVICE

The National Osteoporosis Foundation has reported that over 60% of American adults over the age of 50 will sustain fragility fractures.[20] Frequently, it is in the treatment of these fractures that monoclonal gammopathies are diagnosed. Accordingly, laboratory evaluation of low bone mass in our FLS will occasionally detect conditions that require further evaluation. SPEP is a useful screening test for identifying monoclonal gammopathies and is performed on patients evaluated for decreased bone mass and osteoporotic fractures. In our FLS, of 265 consecutive patients with osteoporosis and fracture, we diagnosed 27/265 (10%) with MGUS. This is compared to a report of 6% of fracture patients with MGUS.[16] Since about 1%/year of patients with MGUS develop multiple myeloma or other malignant monoclonal gammopathies, depending upon the patient's age at diagnosis, the lifetime cumulative risk can be substantial. The finding of MGUS requires oncologic evaluation and lifelong follow-up. Since MGUS has a higher risk of fractures than do age- and gender-matched cohorts without gammopathies, it is not surprising to find a higher prevalence of MGUS in fracture patients and in an FLS than in the general population. In addition to MGUS, the FLS has found 10 patients with a variety of hematologic malignancies including multiple myeloma, Waldenström macroglobulinemia, chronic lymphocytic leukemia, mast cell leukemia, and lymphomas.

MULTIPLE MYELOMA, OSTEOPOROSIS, AND FRACTURE

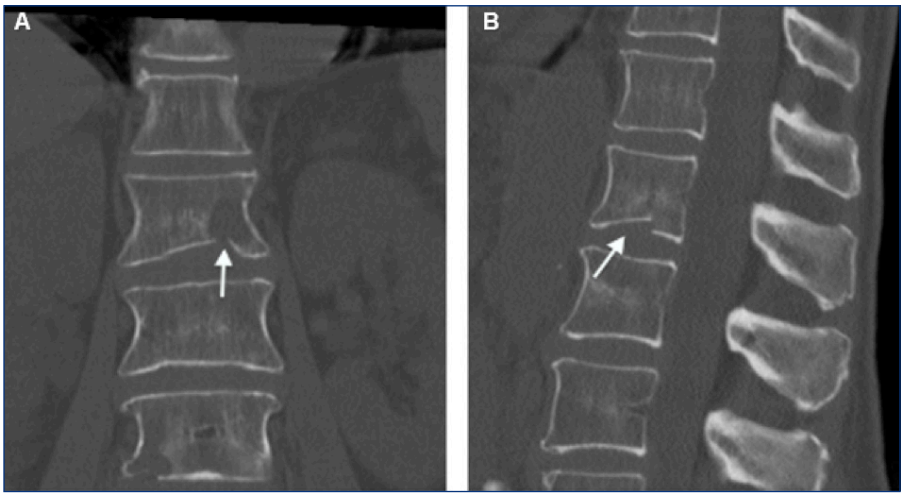
Multiple myeloma is one of several hematologic malignancies associated with decreased bone density, including lymphoproliferative diseases and Waldenström macroglobulinemia. Myeloma is a malignancy of plasma cells, which develop from B lymphocytes, and is characterized by IgG paraprotein. Decreased bone density can be diffuse in myelomatosis or localized in plasmacytomas. In a fracture liaison service, evaluation of decreased bone density by SPEP will usually detect abnormalities in the IgG region which can be explored in more detail with immunoelectrophoresis.

A typical antibody is characterized by 2 IgG heavy chains and 2 IgG light chains. Two types of light chains exist, kappa and lambda, each encoded by a separate gene. Monoclonal IgG light chains produced by malignant plasma cells are called Bence-Jones proteins and are associated with myeloma. Abnormal IgG proteins can be further characterized by immunoelectrophoresis and the concentration of kappa and lambda light chains can be quantified. The typical ratio of free kappa to lambda is 0.26:1.65. Alterations in this ratio are associated with malignancies.

Of the potential end malignancies associated with monoclonal gammopathies, the best studied for bone disease is MM. The complex pathophysiologic effects can be distilled into bone destruction and failure of bone formation.

Figure 3. CT of the spine in multiple myeloma

A: A lytic lesion can be seen on the AP view of the spine (arrow) and **B**: end-plate fracture on the lateral view (arrow).



Numerous factors have been described in this dynamic imbalance in bone homeostasis. The Notch signaling pathway influences the receptor activator of nuclear factor kappa-B ligand (RANKL) and the osteoprotegerin (OPG) system, activating osteoclasts and inhibiting osteoblasts. This signal is amplified by tumor necrosis factor (TNF) secreted by malignant plasma cells.[21] CCL3 (MIP-1α) has also been implicated as a chemokine that influences osteoclast differentiation and inhibition of osteoblast activity.[22] More recently, extracellular vesicles have been implicated in promoting this osteoblast/osteoclast imbalance, and represents a potential therapeutic target.[23] The results may include osteopenia, osteoporosis, lytic bony lesions, and fractures (**Figure 3**). These can be widespread but often have a predilection for the spine, skull, and long bones. Lytic lesions rarely appear in patients below the elbow or below the knee.

For adults in the United States over 50 years of age, the prevalence of osteoporosis and osteopenia is approximately 12% and 43%, respectively.[24] By comparison, bone lesions and bone density changes occur in 80% of patients with MM.[25] While there is a demonstrated increased fracture risk in MGUS, up to 74% in one study, the mechanism is not well understood, and recent studies have not found an associated decrease in bone mineral density or higher rate of progression to MM in patients with MGUS and fracture.[26]

Skeletal events have an important effect on mortality for patients with MM. One study found that patients diagnosed with MM at the time of a fracture have a 28% higher risk of death than patients with new MM and no fractures.[27] Another study found that patients requiring up-front radiation therapy for treatment of painful bony lesions have an increased risk of death compared to those patients who do not require radiation at diagnosis.[28] Even after MM diagnosis, patients who develop a fracture have a 2-fold increased risk of death compared to those without fractures, highlighting the importance of bone health in patients with monoclonal gammopathies.[27] The treatment of MM often involves bone strengthening measures including supplemental calcium and vitamin D. Aggressive use of bisphosphonates or RANKL inhibitors are recommended for patients with multiple myeloma to reduce risk of fracture.[29] Currently, there are no guidelines advocating for bone-modifying agents in patients with MGUS without concurrent fracture or reduced bone density.[30]

WALDENSTRÖM MACROGLOBULINEMIA

Waldenström macroglobulinemia is one of a closely related group of plasma cell malignancies that can present with osteoporosis and fractures. Plasma cells develop from B lymphocytes in bone marrow and lymph nodes and produce diverse groups of antibodies. Dysregulated plasma cell multiplication produces clonal expansion and the production of incomplete antibodies or, M-proteins (IgM), related to multiple myeloma and monoclonal gammopathies. Men are affected more than women and the average age of onset is 65 years. The etiology is unknown.

In addition to osteoporosis and fractures, patients with macroglobulinemia may have anemia, hyperviscosity syndrome, cryoglobulinemia, hepatosplenomegaly, lymphadenopathy, hemorrhage, and recurrent bacterial infections. In one study, 1/3 of patients' DEXA scans had hip T-scores of <–2.0 and 15/45 (33%) of patients had a vertebral compression fracture. In a study of 45 bone biopsies in patients with elevated IgM (36 men and 9 women), 2/3 of the abnormal antibodies were composed of kappa chains. Structurally, the bone abnormalities were comprised of both reduced formation and excessive resorption. Bone formation rates and mineralization surfaces were decreased and microresorptive osteoclastic surfaces were increased, contributing to bone fragility and inability to repair microdamage.

The initial diagnosis of Waldenström macroglobulinemia is suggested by an abnormal SPEP. Immunofixation studies will characterize the abnormal immunoglobulin. Treatment of Waldenström macroglobulinemia is with one of several chemotherapeutic agents, such as ibrutinib and rituximab, often in combination with corticosteroids. While helpful in controlling the clonal expansion of plasma cells, the treatment may not help, or even worsen, the osteoporosis.

CONCLUSIONS

Despite the original characterization of MGUS as a condition of "undetermined significance," there is now clear epidemiologic evidence that patients with MGUS have a significantly increased fracture risk and that the prevalence of MGUS is increased in patients with osteoporosis and fractures.[3] Because MGUS is associated with a significant prevalence of microarchitectural bone deficiency and a greater risk of fracture than age and gender-matched cohorts without gammopathies, it has been proposed that the term "MGUS" be replaced by the term, "monoclonal gammopathy of skeletal significance."[3] (1) The prevalence of MGUS in the geriatric population has been reported to be 3–8%; 15% in vertebral fractures, 6% in hip fractures, and, in our FLS, 10% of all fractures. (2) The prevalence of fractures in MGUS is 18% in vertebral fractures. Concordant data suggest that overall fracture rates are increased approximately 1.7-fold, and vertebral fractures are increased to approximately 6-fold.[3] (3) MGUS should be suspected in patients referred to an FLS, or those with osteoporosis on DEXA, and patients should not just be given treatment for osteoporosis without an evaluation including for MGUS. (4) Orthopedic surgeons, and FLS programs, are in unique positions to screen for and identify metabolic bone diseases that have substantial implications for appropriate skeletal therapy. Identification of MGUS is a contribution to bone health, and even longevity, that evaluation of osteoporosis and fractures should not ignore.

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