Monoclonal Gammopathy of Undetermined Significance: Why Identification of These Patients and Assessment of Their Skeletons Is Important

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Abstract

Monoclonal gammopathy of undetermined significance (MGUS) is a plasma cell disorder characterized by the presence of a serum monoclonal immunoglobulin (M-protein) at ≤ 3 g/dL. It is an asymptomatic premalignant disorder that can progress to multiple myeloma and related B-cell disorders. Recent studies have suggested the association of MGUS with enhanced bone loss and debilitating skeletal complications, particularly vertebral compression fractures (VCFs) often leading to back pain. Early identification of MGUS and evaluation of bone status will facilitate prophylactic treatment with bisphosphonates to increase bone density and likely reduce the risk of fractures as well as identify patients with VCFs who might benefit from early surgical intervention. With proper diagnostic and treatment strategies, these patients will experience improved outcomes and quality of life.

Clinical Lymphoma & Myeloma, Vol. 9, No. 4, 311-315, 2009; DOI: 10.3816/CLM.2009.n.061
Keywords: Bisphosphonates, Bone mineral density, Kyphoplasty, M-protein, Vertebral compression fractures

Introduction

It has been recently shown that patients with monoclonal gammopathy of undetermined significance (MGUS) have enhanced bone loss and a higher risk for fractures, especially of the axial skeleton, than individuals without the condition.[1,2] Patients with vertebral compression fractures (VCFs) often have acute and chronic pain, which can eventually progress to additional disabilities. The incidence of fractures can be reduced by 40%-60% with pharmacotherapy to reduce bone turnover.[3,4] Moreover, recent advances in minimally invasive surgical procedures such as vertebroplasty and kyphoplasty have resulted in marked and rapid palliation of bone pain for patients with VCFs from benign and malignant causes.[5,6] Thus, identification of patients with MGUS who are at high risk for bone loss and VCFs is important in order to implement prophylactic therapies to reduce bone loss that results in fractures, as well as surgical procedures that rapidly improve their bone pain and overall quality of life.

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Submitted: Sep 5, 2008; Revised: Jan 29, 2009; Accepted: Mar 3, 2009

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Monoclonal Gammopathy of Undetermined Significance

Monoclonal gammopathy of undetermined significance was first designated as benign monoclonal gammopathy based on the identification of a small serum M-protein without evidence of multiple myeloma (MM) or a related B-cell disorder.[7] The disorder was renamed MGUS after recognition that some patients eventually develop MM and related B-cell disorders.[8] Progression to these disorders occurs at a rate of approximately 1% per year, and as a result, these patients require indefinite follow-up visits.[9,10] Although specific factors that increase this risk have been described,[10] no interventions have proven useful to decrease the development of these disorders, which have been markedly underdiagnosed. Early estimates of MGUS prevalence were compromised by study designs that lacked geographically defined populations, testing of specific periods, and screening methods of adequate sensitivity.[9] However, a recent population-based study that used highly sensitive laboratory procedures (agarose gel electrophoresis and immunofixation of individual sera) to determine the prevalence of MGUS in Olmsted County, Minnesota, revealed that this disorder occurred in > 5% of persons aged > 70 years and > 3% of persons aged > 50 years[11] in contrast to previous studies that suggested the prevalence was approximately half of these levels.[12,13] A Turkish study found the prevalence to be approximately 2% in persons aged > 65 years, but this study did not examine an entire geographic population.[14]

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Elevated bone resorption resulting in osteoporosis, lytic bone lesions, and pathologic fractures is a hallmark of MM. Recent studies have shown that MGUS patients have increased osteoclastogenesis, leading to increased bone resorption.[15,16] This was confirmed by elevation in the levels of N-telopeptide of collagen type-I and serum levels of soluble RANKL among these individuals when compared with matched controls, as well as increased levels of carboxy-terminal telopeptide of type-I collagen and deoxypyridinoline that correlate with the extent of the overall disease among patients with MGUS and MM.[15,16] A European study demonstrated that these individuals show decreased bone mineral density (BMD) and higher risk of VCFs.[2] Similarly, in an age- and sex-matched control group comparison with patients with MGUS in Olmsted County, MGUS patients showed a nearly 3-fold increased risk for axial fractures, the majority of which were VCFs.[1] Thus, it is becoming increasingly clear that these patients need to be identified and evaluated for bone disease so that they may receive both preventive and therapeutic modalities.

Vertebral Compression Fractures

Fracture is the most common result of osteoporotic bone disease, and VCF is the most common fragility fracture in the United States, with 700,000 new fractures occurring each year.[17,18] Vertebral compression fracture is characterized by kyphotic deformity, postural changes, and severe back pain. Left untreated, it can lead to compressive spine disease with significant loss of height, which can, in turn, decrease truncal strength and compromise pulmonary and digestive functions, placing these individuals at increased risk for hospitalization and death.[19,20] Notably, a 15% higher risk of mortality is observed for osteoporosis patients with VCF within the first 5 years of fracture.[21]

Because patients with MGUS show increased risk of bone loss and developing fractures, there is a clear need for early identification, assessment, and treatment of persons in this high-risk population. Patients could benefit from therapeutic interventions that both prevent and treat the deleterious skeletal problems.

Prophylactic Treatment for Patients With MGUS With Bone Loss

Diagnosis of MGUS has been a challenge because of its asymptomatic nature, and screening for the disease is currently not routine in clinical practice. Most individuals are identified because of elevated total protein or, less frequently, from detection of a potentially associated condition, such as peripheral neuropathy.[22] MGUS is currently diagnosed by the identification of a small serum M-protein as measured by serum protein electrophoresis (SPEP) on agarose gel[23,24] and shows plasma cells of < 10% on bone marrow examination and no evidence of bone lesions, anemia, hypercalcemia, or renal insufficiency related to the M-protein.

Orally administered bisphosphonates are currently used for the treatment of osteoporosis, having shown efficacy in reducing skeletal complications.[25-27] Recently, intravenous zoledronic acid administered yearly has also shown efficacy in this setting.[28-32] In a placebo-controlled trial, yearly zoledronic acid (5 mg) significantly increased BMD in the spine of osteoporotic patients (4.3%-5.1% higher than the mean value for the placebo group)[28] and produced a 35% reduction in the development of new fractures when administered within 3 months of an initial hip fracture.[33] Monthly administration of zoledronic acid is currently recommended for MM patients who have lytic bone destruction, osteoporosis, or osteopenia in order to reduce skeletal complications including fractures.[34-38]

Among cancer patients without metastatic bone disease but exhibiting bone loss from antineoplastic therapies, zoledronic acid administered every 3 months has markedly improved BMD for men with prostate cancer receiving treatment with androgen deprivation therapy[29,30] and, given every 6 months, showed a similar benefit for women with breast cancer receiving adjuvant endocrine therapy with aromatase inhibitors.[31,32]

We conducted a open-label phase I/II study of 54 patients with MGUS and evidence of osteopenia or osteoporosis (T-score ≤ –1), as measured by reduced BMD. The mean age of these patients was 67 years, mean lumbar-spine T-score at baseline was –1.70, mean hip T-score was –1.65, and mean serum M-protein was 0.65 g/dL. These patients were treated with zoledronic acid 4 mg at 0, 6, and 12 months. Treatment increased BMD by 22% and 8% at 13 months in the posteroanterior lumbar spine and nondominant proximal femur, respectively.[39] A recent study showed that 18 months of treatment with oral alendronate 70 mg/week, in addition to oral calcium and vitamin D, for MGUS patients with evidence of either osteoporosis or VCF increased BMD,[40] but the increases were more modest (6.1% and 1.5% in the lumbar spine and hip, respectively) than those observed with zoledronic acid in these patients.

Bisphosphonates possess a multitude of antitumor effects in the laboratory[41-44] and might reduce the risk of development of MM and other B-cell malignancies in the high-risk MGUS population. Recent studies support these preclinical findings. Studies have shown that zoledronic acid administered at the same dose and schedule as in the MGUS study reduces the development of metastatic bone disease and delays progression of the disease among premenopausal, nonmetastatic breast cancer patients receiving adjuvant hormonal therapy, compared with placebo.[32] Compared with pamidronate, zoledronic acid has been shown to improve overall survival in MM patients with elevated serum bone alkaline phosphatase levels.[41] Given the slow rate (1% per year) of progression to serious B-cell disorders, large trials with long follow-up would be required to evaluate this potential additional benefit of treatment with zoledronic acid.

Surgical Management of Vertebral Compression Factors in Patients With MGUS

The treatment of VCFs involves the use of 2 minimally invasive procedures. First, vertebroplasty[45] is a procedure in which polymethyl methacrylate cement is percutaneously injected into a fractured vertebral body, providing reinforcement and stabilization of the fracture. Although vertebroplasty is effective in reducing pain, rare but serious complications associated with the procedure have occurred, such as cement extravasation or leakage, which can result in epidural compression of nerve roots and embolization to the pulmonary vessels[46] resulting in cardiopulmonary complications.[47-49]

The second procedure, kyphoplasty, is a modification of vertebroplasty developed within the past 10 years to treat painful VCFs.[6]

Kyphoplasty involves the inflation of a balloon within the collapsed vertebral body to facilitate restoration of height before cement injection. Kyphoplasty has some advantages over vertebroplasty because it (1) facilitates height restoration, which corrects altered biomechanics, and (2) creates a low-pressure void with the kyphoplasty balloon before injection, which allows cement of higher viscosity to be injected, resulting in a lower risk of cement leakage.[17,50] The incidence of cement extravasation ranges from 30% to 70% after vertebroplasty compared with < 10% after kyphoplasty,[51-53] and the more serious complications are observed less frequently with kyphoplasty.[54] Kyphoplasty rapidly reduces bone pain and analgesic requirements in 60%-97% of patients,[6,55-57] resulting in improved quality of life for patients with VCFs regardless of whether these fractures occur among patients with or without cancer.[58,59] In a randomized trial among cancer patients with VCFs, a marked improvement was shown in mean Roland-Morris Disability scores and pain scores between patients randomized to receive immediate kyphoplasty compared with those who received nonsurgical care.[5]

Identification of MGUS and Identifying and Treating Its Associated Bone Loss and Fractures

Recognition of the deleterious sequelae associated with MGUS will lead treating physicians to perform BMD assessments for these individuals and also evaluate them for fractures. These assessments should result in prophylactic administration of bisphosphonates for those with bone loss, as well as procedures that may reduce the morbidity associated with VCFs. Thus, a proactive stance toward diagnosis and treatment in this patient group should significantly improve their quality of life. Consequently, we herein propose a 3-pronged approach toward the identification and treatment of patients with potential MGUS: (1) diagnosis of MGUS, (2) intervention and prevention of bone mineral loss, and (3) identification and treatment of fractures.

Diagnosis of MGUS

We propose that screening for MGUS be conducted among all individuals with unexplained osteopenia or osteoporosis using both SPEP and urine PEP. For example, men aged < 65 years with these bone disorders without an obvious etiology should be assessed for the presence of a monoclonal gammopathy. These relatively simple and inexpensive tests will result in the identification of patients with a high risk for bone loss and fractures, which may then be specifically assessed, as well as patients with more serious B-cell disorders such as MM. For individuals with a monoclonal gammopathy, a more serious B-cell disorder must be ruled out, including assessment with a skeletal survey with complete spine films. The latter assessment will also allow evaluation for possible fractures that may require orthopedic intervention in this at-risk population.[1] Conversely, all patients with MGUS should be further evaluated by dual-energy x-ray absorptiometry to assess BMD in order to identify individuals with bone loss who might benefit from treatment with bisphosphonates.

Intervention and Prevention of Bone Mineral Loss

A reduction in BMD is associated with increased risk of fracture.[18] Similar to other individuals with low T-scores, MGUS patients demonstrating T-scores ≤ –1 are likely to be at risk for development of fractures. Vitamin D_2 and D_3 levels should be assessed in the elderly population because this age group has demonstrated frequent deficiency of this vitamin.[60] Regardless of vitamin D levels, routine supplementation with oral vitamin D 800 IU/day and calcium 1 g/day should be administered, with greater supplementation for patients in which vitamin D deficiency has been identified. MGUS patients with T-scores ≤ –1 should also be considered for chronic bisphosphonate therapy. Intravenous zoledronic acid 4 mg every 6 months or oral alendronate administered 70 mg weekly has improved BMD for patients with MGUS,[39,40] and both are reasonable options for these individuals, though greater improvement of BMD was observed among patients treated with zoledronic acid. Less intensive interventions might be effective for other types of patients with osteopenia or osteoporosis, but these treatments might not provide adequate protection for MGUS patients with their high risk of bone loss and fracture compared with age- and sex-matched controls.[1,61] For example, yearly administration of zoledronic acid improved BMD in the spine and hip only up to 5.1% and 3.5%, respectively, among women with osteoporosis without cancer,[28] whereas twice-yearly administration of zoledronic acid to MGUS patients with osteoporosis or osteopenia increased BMD in the spine and hip by 22% and 8%, respectively.[39] Whether more frequent dosing of 4 mg of zoledronic acid for MGUS patients with its greater positive effect on BMD also results in a significantly greater reduction in fracture risk compared with yearly administration of 5 mg remains to be determined. In addition, the potential increased risk of renal impairment and osteonecrosis of the jaw (ONJ) from more frequent chronic administration of zoledronic acid must be weighed against the possible benefit of increased BMD. However, the every-6-month dosing schedule of zoledronic acid 4 mg has not been associated with either ONJ or renal impairment in MGUS or other cancer patients.[31,39] Nevertheless, preventative measures and careful monitoring for ONJ are recommended.[62]

Identification and Treatment of Vertebral Compression Factors

Because of the high risk of fractures among MGUS patients,[1,61] we recommend careful screening for the presence of any skeletal deformities. Skeletal survey by x-ray that also encompasses the spine should be performed for individuals with MGUS to identify any possible signs of malignant disease, including the presence of osteolytic bone lesions, as well as possible fractures that occur with increased frequency in this population.[1] Among patients considered at high risk for VCFs, MRI with sagittal short τ inversion recovery sequences to image osseous edema should be conducted. Because of the recent proven benefit of kyphoplasty for both patients with cancer, including MM, and patients with VCFs without cancer,[5,6] we recommend that MGUS patients with symptomatic VCFs be assessed for possible kyphoplasty or vertebroplasty procedures to reduce their bone pain and improve their quality of life.

Conclusion

Although MGUS is a common condition in individuals aged > 50 years, it is infrequently identified because routine screening with simple serum and urine electrophoretic studies are not gener-

ally performed without additional indications. These patients are at risk to develop MM and related B-cell disorders, but because of the low rate of progression to malignant disorders in these individuals, as well as the lack of studies showing that intervening with any treatment can reduce this risk, it has not been considered important to identify the condition. However, recent studies demonstrate that this patient group is also at high risk for enhanced bone loss and fractures, especially VCFs. Early identification of MGUS and evaluation of bone status will facilitate prophylactic treatment with bisphosphonates such as zoledronic acid to increase bone density and likely reduce the risk of fractures, as well as identify patients with VCFs who may benefit from early surgical intervention. Overall, the diagnostic and treatment strategies recommended in this article should improve the outcome and quality of life for individuals with this common condition that remains largely unrecognized today.

Acknowledgements

Third-party writing support was provided by Medtronic Researched by Helix based on guidance received from the authors September 5, 2008.

Disclosures

James R. Berenson is a consultant for and/or has received grant/research support from Novartis Pharmaceuticals, Medtronic, and Sebia, Inc. and is on the Speaker's Bureau for Novartis Pharmaceuticals. Ori Yellin has no relevant potential conflicts of interest to report.

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