Open Journal of
Clinical & Medical
Case Reports

Volume 3 (2017)
Issue 16

ISSN 2379-1039

The missing M protein: An unusual cause of severe osteoporosis

Christine D Uy, MD; Faryal S Mirza, MD*

***Faryal S Mirza, MD**

Division of Endocrinology and Metabolism, University of Connecticut, 263 Farmington Avenue, Farmington, CT 06030, USA.
Phone: 860-679-2160, Email: fmirza@uchc.edu

Abstract

Multiple myeloma is a hematological malignancy where immunoglobulin-producing plasma cells undergo clonal expansion. Classically, monoclonal protein or M spike is detectable in serum or urine by protein electrophoresis [1]. Rarely, M spike may be absent causing difficulty in diagnosis [2].

We report an unusual case of a 56-year-old Caucasian female who initially presented to orthopedics for evaluation of back pain. She was noted to have several vertebral compression fractures and was referred for osteoporosis evaluation. History was significant for 9-inch height loss over 6 months and severe low back pain. Although hematological malignancy was considered in initial evaluation, initial workup was unremarkable except for very mild elevation of calcium. Hemoglobin was normal and serum and urine protein electrophoresis and immunoelectrophoresis were both negative for monoclonal gammopathy. Bone marrow aspiration biopsy was pursued to evaluate for malignancy due to her unusual presentation and remarkable fractures. Findings revealed a rare form of monoclonal gammopathy with more than 50% plasma cell, consistent with the diagnosis of non-secretory multiple myeloma. Patient was referred to oncology service for further care and was initiated on zoledronic acid for multiple myeloma that also treated her for osteoporosis.

This case highlights the need to be vigilant in pursuing the secondary causes for osteoporosis and fractures in unusual disease presentations.

Keywords

osteoporosis; height loss; nonsecretory multiple myeloma

Introduction

Multiple myeloma (MM) is a relatively rare malignancy representing 1.8% of all cancer diagnoses [3], with 6.5/100,000 new cases reported yearly in the US [3]. MM is the fourteenth leading cause of cancer death in the United States [3]. It is an important differential diagnosis in patients with suspected osteoporosis as it affects patients of the same age and causes bone fragility. One in twenty patients with newly diagnosed osteoporosis had MM or monoclonal gammopathy of undetermined significance [4]. The most important diagnostic finding in MM is the demonstration of a monoclonal (M) protein in the serum and/or urine. This report highlights the need to be vigilant and persistent in evaluation for secondary causes of osteoporosis when patients present with unusual findings. Our patient's initial

workup and imaging studies were negative for monoclonal gammopathy. A bone marrow biopsy was pursued due to her presentation with multiple vertebral compression fractures which confirmed the diagnosis of non- secretory multiple myeloma (NSMM). Although MM is relatively common malignancy, this case represents a rare form of MM and aims to increase awareness of such entity as NSMM and emphasize the importance of maintaining a high index of suspicion in considering it in the differential for unexplained osteoporosis, even when initial workup for monoclonal gammopathy is negative.

Case Presentation

A 56-year old Caucasian menopausal female was referred for evaluation of osteoporosis due to multiple compression fractures by her orthopedic physician. She developed severe low back pain with nausea, vomiting, anorexia and 15-pounds weight loss in a span of 4 months. MRI of the thoracolumbar spine revealed multiple compression fractures involving thoracic 8^{th} to 11^{th} vertebrae. Bone densitometry was consistent with osteopenia at the spine (T-score of L1-L4 = -1.8) and normal bone density at the hip (T-score of left femoral neck = -0.9; total hip T-score = -0.7). Physical therapy and narcotics did not afford any relief of the low back pain. She was started on alendronate by her primary care physician but stopped after 3 weeks due to severe retching. History at presentation to us was also significant for a 9-inch height loss over the past 6 months (tallest height being 5 feet 6 inches and present height of 4 feet 9 inches), which was confirmed in family pictures brought in by the patient. There was no history of eating disorder, immobilization, malabsorption, thyroid disease, kidney stones, or family history of osteoporosis.

Physical examination was significant for a disproportionately short upper trunk relative to the lower extremities along with moderate kyphosis and diffuse paraspinal tenderness along the thoracic and lumbar spine. Heart rate was 108 beats/minute and blood pressure was 142/98 mm Hg. Lung and abdominal exam were normal. There was no pedal edema. Investigations revealed normal hemoglobin and hematocrit at 15 g/dl and 45.7% respectively, mild hypercalcemia with ionized calcium at 1.42 mmol/L (1.12-1.33 mmol/L) and normal renal function with creatinine of 0.8 mg/dl. No paraprotein was detected on serum protein electrophoresis and immunofixation. Her IgG and IgA levels were normal; IgM levels are low at 48 mg/dl (reference range: 60-292 mg/dl). Chest x-ray revealed normal lung fields and the presence of compression fractures from T8-L2. She also had several X-rays of the thoracic and lumbar spine and CT scan of the thoracic spine by her orthopedic physician, which confirmed the fractures. No lytic lesions were identified in the reports. She was scheduled to have zoledronic acid IV infusion at this point.

Upon follow-up three weeks later, she had further height loss of about an inch, worsening back pain, now wheelchair bound with new rib pain in the right anterior chest. X-ray of the ribs showed new onset diffuse bone lucencies involving the ribs, scapula and humerus. CT scan showed multiple osteolytic lesions seen in all the visualized bones of chest, abdomen and pelvis. No lymphadenopathy was noted. Older imaging studies were again determined to be negative for lytic lesions. Repeat serum electrophoresis and urine immunofixation electrophoresis including assay for urinary Bence Jones protein were negative. Quantitative serum free light chain (SFLC) assay showed mild elevation in kappa free light chain at 2.34 mg/L (upper normal range at 1.94 mg/L), with normal Kappa/Lambda ratio. Due to progressive height loss, fractures and worsening pain, hematologic malignancies and metastatic disease were considered in the differential. She was referred to the Hematology-Oncology service for

bone marrow aspiration and biopsy, which revealed more than 50% plasma cells, consistent with MM. She was diagnosed with NSMM and started on treatment for MM with zoledronic acid along with other medications.

Discussion

MM is a neoplasm characterized by proliferation of a single clone of plasma cells in the bone marrow frequently invading adjacent bone and producing skeletal destruction in the process, resulting in bone pain and fractures [5]. MM is the second most common hematologic neoplasm in the US, with approximately 30,000 new cases annually [3]. The most common symptoms on presentation are fatigue, bone pain and recurrent infections [6]. Diagnostic criteria require the presence of at least 10 percent plasma cells on examination of the bone marrow, monoclonal protein in the serum or urine and evidence of end-organ damage that consists of a group of findings referred to as CRAB – hypercalcemia, renal insufficiency, anemia, and bone lesions [6,7].

As illustrated by this case, NSMM enters into the differential diagnosis when serum and urine protein electrophoresis studies do not detect a monoclonal protein, but the clinical picture is consistent with features of plasma cell dyscrasia [8]. NSMM is a rare variant of the classic MM [5] and is characterized by the absence of detectable monoclonal (M) protein in both serum and urine [9]. The International Myeloma Working Group defines NSMM as MM lacking monoclonal protein by serum or urine immunofixation, which can include light-chain MM with quite high levels of monoclonal FLCs detected solely by the SFLC assay [10,11]. The condition remains nonsecretory in the majority of patients, even with extended follow-up. The subset of NSMM has become smaller over time, with the availability of the SFLC assay [12]. Hence our case is unusual in that it represents are very rare presentation of multiple myeloma that is difficult to diagnose with the conventional methods. Hence a high index of suspicion is needed to warrant bone biopsy which also helps in distinguishing other differential diagnoses of this condition, including other hematologic malignancies and metastatic disease.

Two types of NSMM have been described: the “producer type”, which is characterized by producing immunoglobulin but not secreting them out of the cell (nonsecretory), and the “nonproducer type”, in which the plasma cells are unable to produce immunoglobulins [5]. A variety of hypotheses have been proposed to explain the absence of abnormal proteins in NSMM. The lack of M-protein in serum and urine of patients with NSMM may be explained by the incapacity of plasma cells to excrete the immunoglobulin, the low synthetic capacity of immunoglobulin, increased intracellular degradation, or (4) rapid extracellular degradation of abnormal immunoglobulin chains [6,9]. A high frequency of translocation t(11;14) (q13;q32) has been reported in NSMM [13]. Coriu et al. have reported the molecular basis for NSMM (with a normal serum FLC assay) due to the presence of abnormal κ light chains that resulted from a frame shift mutation that led to the absence of cysteine required for disulfide bonds [14]. The misfolded κ light chains were presumably retained within the plasma cell cytosol and then underwent proteolysis [8,14]. The mechanisms that could result in nonproducer myeloma are a defective gene with true nonsynthetic capability, synthesis of an antigenically unrecognized immunoglobulin or its fragments, or very rapid intracellular degradation [1,5,9]. Another cause of negative electrophoresis could be intermittent immunoglobulin excretion, possibly due to variations in tumor mass. These cases have been referred to as “pseudo-nonsecretory myeloma” [2,16]. Finally, free

light chains may sometimes be present as a series of polymers of differing molecular weights, and may not form visible bands on electrophoresis [17]. The serum free light chain assay is a more sensitive assay for the detection of monoclonal free light chains [18] and can help in establishing the diagnosis of MM in these cases. Overall, with the routine use of the ELISA-based SFLC assay, the proportion of true NSMM, meaning MM that secretes no measurable monoclonal heavy or light chain at all, is closer to <1%–2% of all MM [19]. Hence our patient represents a very unusual presentation of multiple myeloma that was diagnosed as she was undergoing workup for secondary causes for osteoporosis.

Clinical presentation of NSMM is similar to classic MM, with bone pain being the most common symptom [20]. Renal function impairment [9,15] is rare as long as light chains cannot be detected in the urine. Lytic bone lesions and/or hypogammaglobulinemia are seen in nearly all cases [8,9]. Regardless of age, patients with MM benefit from early diagnosis to minimize renal and skeletal complications [4]. The absence of an M band delays the diagnosis, and can adversely affect the outcome [2,15]. Bone lesions in myeloma occur through the stimulation of osteoclastic activity and inhibition of osteoblastic activity. There is increased expression of the receptor activator of nuclear factor-κβ ligand (RANKL) and a reduced level of its decoy receptor, osteoprotegerin. RANKL stimulates the differentiation, activation, and function of osteoclasts [1]. Overexpression of dickkopf1 (DKK1) by myeloma cells is also involved in the generation and maintenance of the focal osteolytic lesions of multiple myeloma which inhibits the Wnt signaling pathway, important for osteoblast differentiation [1].

Following response to treatment and relapse in patients with NSMM also poses a problem as one cannot assess the changes in the M-protein levels because of the lack of measurable M-protein. The serum FLC assay also can be a useful adjunct in monitoring therapy and disease activity in these patients [8,11,19].

Conclusion

Although multiple myeloma is a relatively common hematologic malignancy, NSMM represents less than 1-2% of all multiple myeloma presentations. Hence our patient is extremely unusual in that she had a rare presentation of multiple myeloma which was discovered as she was worked up for severe osteoporosis. The take home message of this report is to understand the importance of considering other differential as workup is being pursued, including hematologic malignancies, connective tissue disease and metastatic disease. Maintaining a high index of suspicion for the diagnosis of NSMM is essential, especially in patients who present with severe osteoporosis, unusual fractures or significant height loss with vertebral fractures.

References

1. Glass DA, 2nd, Patel MS, Karsenty G. A new insight into the formation of osteolytic lesions in multiple myeloma. N Engl J Med. 2003; 349(26): 2479-2480.

2. Kumar SK, Sohal PM, Kohli HS, et al. Acute renal failure due to cast nephropathy in nonsecretory myeloma: a case report and review of the literature. Int Urol Nephrol. 2005; 37(2): 351-353.

3. NIH Myeloma – SEER Stat Fact Sheets. [Accessed April 4].

4. Abrahamsen B, Andersen I, Christensen SS, Skov Madsen J, Brixen K. Utility of testing for monoclonal bands in serum of patients with suspected osteoporosis: retrospective, cross sectional study. BMJ. 2005; 330(7495): 818.

5. Gafumbegete E, Richter S, Jonas L, Nizze H, Makovitzky J. Nonsecretory multiple myeloma with amyloidosis. A case report and review of the literature. Virchows Arch. 2004; 445(5): 531-536.

6. Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med. 2004; 351(18): 1860-1873.

7. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia. 2009; 23(1): 3-9.

8. Shaw GR. Nonsecretory plasma cell myeloma--becoming even more rare with serum free light-chain assay: a brief review. Arch Pathol Lab Med. 2006; 130(8): 1212-1215.

9. Blade J, Kyle RA. Nonsecretory myeloma, immunoglobulin D myeloma, and plasma cell leukemia. Hematol Oncol Clin North Am. 1999; 13(6): 1259-1272.

10. International Myeloma Working G. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol. 2003; 121(5): 749-757.

11. Drayson M, Tang LX, Drew R, Mead GP, Carr-Smith H, Bradwell AR. Serum free light-chain measurements for identifying and monitoring patients with nonsecretory multiple myeloma. Blood. 2001; 97(9): 2900-2902.

12. Dupuis MM, Tuchman SA. Non-secretory multiple myeloma: from biology to clinical management. Onco Targets Ther. 2016; 9: 7583-7590.

13. Avet-Loiseau H, Garand R, Lode L, Harousseau JL, Bataille R, Intergroupe Francophone du M. Translocation t(11;14)(q13;q32) is the hallmark of IgM, IgE, and nonsecretory multiple myeloma variants. Blood. 2003; 101(4): 1570-1571.

14. Coriu D, Weaver K, Schell M, et al. A molecular basis for nonsecretory myeloma. Blood. 2004; 104(3): 829-831.

15. Rubio-Felix D, Giralt M, Giraldo MP, et al. Nonsecretory multiple myeloma. Cancer. 1987; 59(10): 1847-1852.

16. Matsuzaki H, Yoshida M, Akahoshi Y, Kuwahara K, Satou T, Takatsuki K. Pseudo-nonsecretory multiple myeloma with light chain deposition disease. Acta Haematol. 1991; 85(3): 164-168.

17. Joyner MV, Cassuto JP, Dujardin P, et al. Non-excretory multiple myeloma. Br J Haematol. 1979; 43(4): 559-566.

18. Tate JR, Gill D, Cobcroft R, Hickman PE. Practical considerations for the measurement of free light chains in serum. Clin Chem. 2003; 49(8): 1252-1257.

19. Chawla SS, Kumar SK, Dispenzieri A, et al. Clinical course and prognosis of non-secretory multiple myeloma. Eur J Haematol. 2015; 95(1): 57-64.

20. Abdalla IA, Tabbara IA. Nonsecretory multiple myeloma. South Med J. 2002; 95(7): 761-764.

Manuscript Information: Received: April 04, 2017; Accepted: June 23, 2017; Published: June 30, 2017

Authors Information: Christine D Uy, MD[1]; Faryal S Mirza, MD[2]*

[1]The Cotton O'Neil Diabetes & Endocrinology Center, Stormont Vail Health, Topeka, Kansas USA 66606
[2]Division of Endocrinology and Metabolism, University of Connecticut, 263 Farmington Avenue, Farmington, CT 06030, USA

Citation: Christine DU, Mirza FS. The missing M protein: An unusual cause of severe Osteoporosis. Open J Clin Med Case Rep. 2017; 1297.

Journal: Open Journal of Clinical and Medical Case Reports is an international, open access, peer reviewed Journal focusing exclusively on case reports covering all areas of clinical & medical sciences.

Visit the journal website at **www.jclinmedcasereports.com**
For reprints and other information, contact editorial office at **info@jclinmedcasereports.com**