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IgM Multiple Myeloma: A Rare Clinical Entity and Diagnostic Dilemma

IgM Multiple Myeloma: A Rare Clinical Entity and Diagnostic Dilemma

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ABSTRACT

IgM multiple myeloma is a rare disease that shares many common features with Waldenström macroglobulinemia and lymphoplasmacytic lymphoma. It has been described in the literature as having unique diagnostic findings that separate it from the more common IgG and IgA myelomas. It is important for physicians to be able to differentiate between IgM multiple myeloma, Waldenström macroglobulinemia and lymphoplasmacytic lymphoma as their treatments vastly differ. This case report describes the clinical presentation of a patient with IgM lambda multiple myeloma and highlights the pathologic and clinical findings that are specific to this rare entity. We aim to provide further evidence for the previously reported diagnostic criteria for IgM multiple myeloma.

Keywords: IgM Multiple Myeloma, Waldenstrom Macroglobulinemia, Lymphoplasmacytic lymphoma, Fluorescent In Situ Hybridization, Molecular testing

INTRODUCTION:

Multiple myeloma (MM) is a hematologic malignancy characterized as a plasma cell dyscrasia marked by elevation of monoclonal immunoglobulins.[1] IgM MM is an extremely rare entity representing less than 0.5% of all myeloma diagnoses.[2] Distinguishing between IgM MM and Waldenström macroglobulinemia (WM) – a condition marked by a clonal lymphoplasmacytic population in the bone marrow and a monoclonal IgM gammopathy in the peripheral blood – can be challenging. Distinguishing these entities has clinical importance, as the treatments are different. The International Myeloma Working Group (IMWG) criterion is used to diagnose the more common IgG and IgA myelomas,[3] however, this distinct entity is suggested to have unique diagnostic criteria by Schuster et al.[4]

They describe IgM MM as a symptomatic clonal plasma cell proliferative disorder, regardless of IgM monoclonal protein size, with 10% or more plasma cells in the bone marrow, lytic bone lesions and a t(11;14) translocation. Some groups have proposed also using molecular testing to assist with diagnosis of IgM MM including CXCR4 and MYD88 negativity.[4–7] Here, we present the case of a patient diagnosed with the extremely rare entity of IgM multiple myeloma, while highlighting several key features that are utilized to distinguish IgM MM from WM.

Case:

An 88 year old male with history of smoldering myeloma, and neuropathy presented with complaints of midsternal chest pain and back pain for 2 months. He was first diagnosed with smoldering myeloma in 2012, when SPEP showed an M-spike of 0.2 g/dL with immunofixation revealing an IgM lambda monoclonal gammopathy. Free kappa/lambda ratio was 0.14. Bone marrow biopsy showed 15% plasma cells. The patient was diagnosed with smoldering myeloma and followed with active surveillance. His most recent skeletal survey was 17 months prior to this hospitalization and was negative for lytic lesions. Labs at that time did not reveal any anemia, hypercalcemia, or renal dysfunction. M-spike was stable at 0.3g/dL with free kappa/lambda ratio of 0.13. With regards to his neuropathy, anti-MAG IgM testing was performed in 2013 and showed a titer of <1:1600 making it very unlikely that his neuropathy was related to his IgM paraprotein.

In June 2021, he developed 2 months of midsternal chest and back pain. On presentation to the emergency room, vital signs were stable. Acute coronary syndrome was ruled out with normal troponins, and EKG without any ischemic patterns. Labs on admission were notable for mild anemia with hemoglobin of 11.5 g/dL, which was 13.5 g/dL one year prior, and an elevated calcium of 11.5 mg/dL. Renal function was stable with a creatinine of 0.99 mg/dL. Computed tomography angiography chest was negative for acute pulmonary embolism; however, it did show diffuse osteopenia with multiple lytic lesions throughout the osseous structures of the chest, abdomen, and pelvis, which were suspicious for multiple myeloma (MM). Additionally, there were acute/subacute appearing manubrial and sternal pathologic fractures. CT brain revealed patchy lucent lesions in the calvarium and skull base, consistent with MM. CT abdomen was negative for any organomegaly or lymphadenopathy. His SPEP revealed an M-spike of 1.7g/dL with immunofixation showing an IgM lambda monoclonal band, consistent with his prior smoldering myeloma phenotype (Figure 1). Free kappa/lambda ratio was 0.03.

Immunoglobulin panel showed an elevated IgM level of 3,060 mg/dL and decreased levels of IgA and IgG, <5mg/dL and 367 mg/dL, respectively. He had elevated beta-2 microglobulin, 5.69 mg/L, and low albumin, 2.9g/dL. Lactate dehydrogenase (LDH) was 282 U/L. To confirm the diagnosis of multiple myeloma and formally rule out WM, a bone marrow biopsy was performed revealing a hypercellular bone

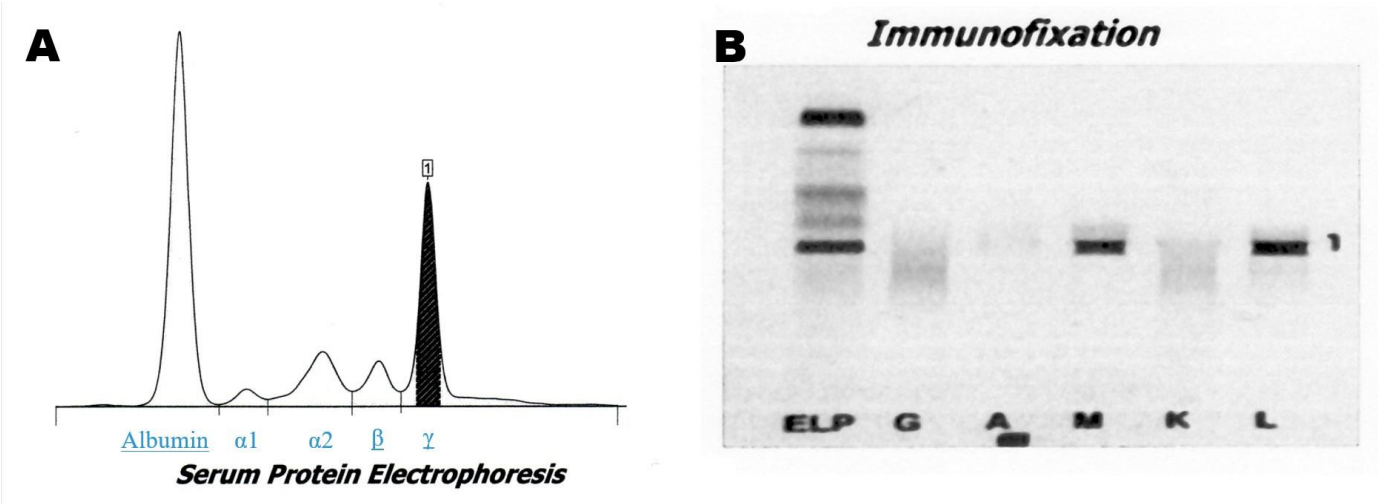

Figure 1 (A) Serum protein electrophoresisdemonstrates a prominent M-spike [1] in the gamma region which is quantitatedat 1.7 g/dL. (B) Immunofixationcharacterizes the M-spike as IgM lambda.

marrow with 70-80% plasmacytosis (Figure 2). Importantly, immunohistochemical staining for B-lymphocytes was negative. Congo red staining was negative for amyloid. MM fluorescence in situ hybridization (FISH) panel was positive for t(11;14) and trisomy 15, and with these findings he had a hyper-diploid MM. Chemokine receptor type 4 (CXCR4) and MYD88 mutations were not detected.

In light of his overall deconditioned state, poor prognosis, and in efforts to preserve his quality of life at the age of 88, goals of care discussion was initiated with the patient and family. Ultimately, the decision was made to attempt myeloma directed therapy inpatient and he received 5 days of steroids and 1 day of bortezomib. His clinical condition continued to deteriorate and per family wishes in discussion with the hematology team, he was transitioned to inpatient hospice. The patient passed away on day 12 of hospitalization.

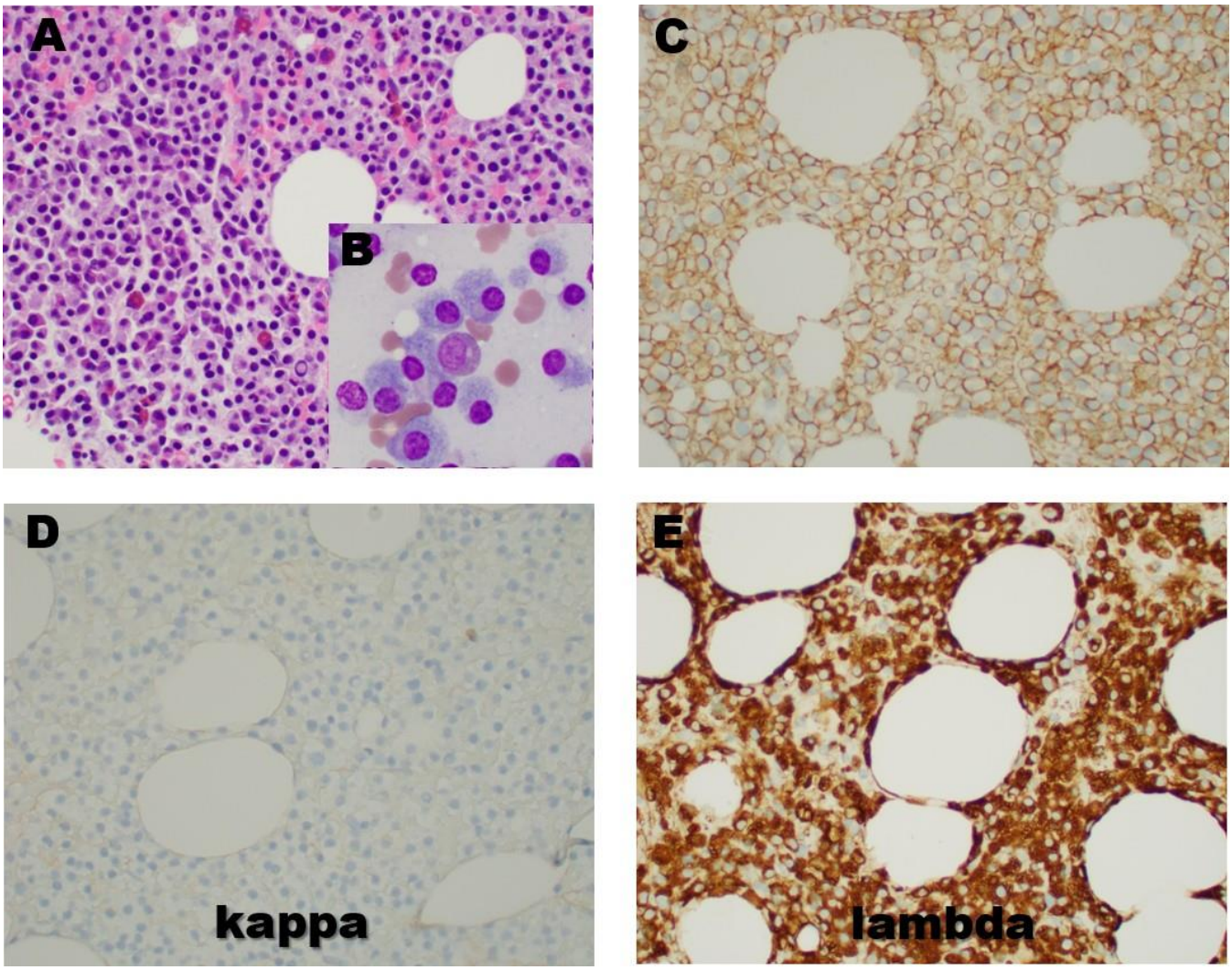

Figure 2 Bone marrow involvedby multiple myeloma: (A) Bone marrow core biopsy showing complete effacement bysheets of plasma cells (H&E x400). (B, inset) Bone marrow aspirate smearwith marked plasmacytosis (Wright Giemsa x1000). (C-E) The neoplastic plasmacells are diffusely positive for CD138 and show lambda light chain restrictionby immunohistochemistry (x400).

DISCUSSION & CONCLUSION:

IgM MM is an extremely rare entity and comprises less than 0.5% of all reported MM cases.[2] It has been characterized as a clonal plasma cell infiltration of the bone marrow of 10% or greater plus lytic bone lesions and a t(11;14) translocation.[4] WM, by contrast, is characterized by a clonal lymphoplasmacytic infiltration of the bone marrow of any quantity as well as a monoclonal IgM paraprotein in the peripheral blood.[6] Given that IgM monoclonal gammopathy is a common feature of both IgM MM and WM, distinguishing between the two entities is often challenging. Whereas mostMost cases of MM have anemia, renal insufficiency, and lytic osseous lesions as the major features, in contrast, WM is often characterized by hyperviscosity, lymphadenopathy, organomegaly, and peripheral neuropathy.[2] From a

pathological perspective, bone marrow biopsies in WM will show an infiltration of clonal lymphoplasmacytic cells, whereas pure plasmacytic morphology is seen in IgM MM (Table 1).[8] Although not pathognomonic for WM, the MYD88 gene, which is a myeloid differentiation primary response gene, is mutated in 80-95% of WM cases and is highly characteristic of WM.[5–7] The absence of an MYD88 mutation does not rule out WM, however, this mutation has not been reported in any IgM MM cases.[5,6] It is also important to note that 20-40% of WM patients have activating mutations in the C-terminal domain of the C-X-C chemokine receptor type 4 (CXCR4) gene.[6] Initial testing for both MYD88 and CXCR4 gene mutations has been suggested as a potential tool to assess tumor burden in WM patients.[9] Another helpful marker to help aid in the diagnosis of IgM MM is Cyclin D1 expression and detection of translocation t(11;14), which usually favors a diagnosis of MM over WM.[6]

In our patient, the lytic lesions, hypercalcemia, and anemia present on admission was pathognomonic for MM, however given the rarity of IgM MM, extensive testing on bone marrow biopsy was performed. Bone marrow biopsy revealed a total absence of B-lymphocytes, both by flow cytometry and immunohistochemical staining. This was highly suggestive of MM however it is important to note that CD20 positivity is seen in IgM MM and is not a reliable marker.[10] The expression of CD56 by plasma cells essentially eliminated lymphoplasmacytic lymphoma and other B-cell lymphomas from the differential diagnosis. In a study involving 55 MM patients, it was concluded that strong CD56 expression is common in MM and that CD56 expression is near absent in polyclonal plasma cells from non-neoplastic tissue sites.[11] Additionally, t(11,14) seen on FISH analysis and absence of MYD88 and CXCR4 mutations supported the diagnosis of MM.

Table 1 Clinical,laboratory and pathologic findings of IgM MM vs WM

IgM Multiple Myeloma	**Waldenström Macroglobinemia**
Clinical Findings Bone pain and lytic lesions Neuropathy	Clinical Findings Organomegaly Lymphadenopathy Neuropathy
Laboratory Findings Hyperviscosity Serum IgM clonal paraprotein Abnormal K/L ratio Anemia Hypercalcemia Elevated creatinine	Laboratory Findings Hyperviscosity Serum IgM clonal paraprotein
Common IHC, FISH and Molecular Findings Bone marrow >10% plasma cells CD5- CD20+/- CD56+ CD117+/- CD138+ t(11;14)	Common IHC, FISH and Molecular Findings CD20+ 6q deletion (55%)[12] MYD88 mutation CXCR4 mutation

Despite the similarities between MM and WM, it is crucial for clinicians to have the tools to differentiate between the two diagnoses as their management is different. MM is typically managed with induction therapy consisting of triple or even quadruple therapy with steroids, proteasome inhibitors, immunomodulators and monoclonal antibodies, followed by hematopoietic stem cell (HSC) transplant depending on cytogenetic findings, minimal residual disease, and transplant eligibility. Following transplant, there is a subsequent maintenance therapy phase.[12] In contrast, WM management is driven by symptom severity, in which emergent plasmapheresis is utilized for symptoms of hyperviscosity, usually when serum IgM levels >4000 mg/dL, in addition to therapy aimed at the malignant clone. Rituximab based therapies or BTK inhibitors are utilized in the first line setting, further highlighting the difference between WM and MM, given the presence of CD20+ B-lymphocytes seen in WM.[13]

Unfortunately, our patient presented with severe sternal and rib fractures leading to significant atelectasis and eventual respiratory failure. Despite initiation of treatment with bortezomib and steroids, his clinical condition deteriorated. Interestingly, following initiation of MM directed therapy, his IgM level dropped from 3,060mg/dL to 1,620mg/dL, however, he was too clinically unstable to pursue further therapy.

This paper provides a discussion of a case of IgM MM, a rare clinical entity. It explores the key features of the diagnostic workup for MM, in addition to highlighting the unique clinical and pathologic features that can help physicians distinguish IgM MM from WM.

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