

Case Report of IgM Multiple Myeloma: Diagnosing a Rare Hematologic Entity

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Abstract

IgM multiple myeloma is an exceedingly rare hematologic entity comprising only less than 0.5% of multiple myeloma cases. Given the rarity of this disorder, it makes it a challenge to differentiate from other more prevalent hematologic disorders like Waldenstrom macroglobulinemia. These 2 diseases have the common finding of an IgM monoclonal gammopathy and distinguishing between these 2 diagnoses is of great importance given that therapy and prognosis differ significantly. This report illustrates the case of a 64-year-old man who presented with IgM lambda monoclonal gammopathy in whom signs, symptoms, laboratories, and imaging were initially thought to be consistent with Waldenstrom macroglobulinemia. Upon further analysis, which included bone marrow biopsy, flow cytometry, immunohistochemistry, fluorescence in situ hybridization, and MYD88 (L265P) gene mutation analysis, the rare diagnosis of IgM multiple myeloma was confirmed. As highlighted by this patient's case, reaching the diagnosis of IgM multiple myeloma can be a difficult task which requires a high index of suspicion and accurate diagnostic methods. By using the approach detailed in this report, more cases of IgM multiple myeloma can be diagnosed early, which in turn may lead to earlier treatment and better outcomes.

Keywords

multiple myeloma, Waldenstrom macroglobulinemia, monoclonal gammopathy, anemia

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Introduction

IgM multiple myeloma (MM) is an extremely rare hematologic entity comprising only less than 0.5% of MM cases.¹ Differentiating from other more prevalent but still uncommon hematologic disorders like Waldenstrom macroglobulinemia (WM) creates a very difficult challenge due to the rarity of this disease. The presence of an IgM monoclonal gammopathy is a common finding in these 2 diseases, and since therapy and prognosis greatly differ, differentiating between them is of great importance.² Multiple myeloma is characterized by the neoplastic proliferation of plasma cells preferentially in the bone marrow producing a monoclonal immunoglobulin in the blood and/or urine. The abnormal immunoglobulin can be IgG (52%), IgA (21%), IgD (2%), kappa or lambda light chains only (16%), biclonal (2%), or IgM (0.5%). Multiple myeloma is associated with end-organ damage and 10% or more plasma cells on bone marrow biopsy which are distinguished from

normal plasma cells by exhibiting a kappa/lambda ratio more than 4:1 or less than 1:2, and in contrast to normal plasma cells, myeloma cells infrequently express CD19 and 70% will express CD56. The most common signs of MM include hypercalcemia, renal insufficiency, anemia, and lytic bone disease. Uncommon presentations may also include paresthesias (5%),

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hepatomegaly (4%), splenomegaly (1%), lymphadenopathy (1%), and fever (0.7%). However, in addition to these, the diagnosis of IgM MM is made based on the presence of a serum IgM monoclonal protein, which is usually found on approximately 0.5% of cases. First-line therapy in eligible candidates with MM is based on 3 drug combination, which usually include a proteasome inhibitor and immunomodulatory drug and steroids, followed by autologous stem cell transplant, followed by maintenance.²

Waldenstrom macroglobulinemia is an IgM-secreting lymphoplasmacytic lymphoma that usually presents with signs and symptoms related to bone marrow and lymph node infiltration of lymphoplasmacytic cells leading to anemia, lymphadenopathy, hepatosplenomegaly, and/or symptoms related to the IgM monoclonal protein in serum, like hyperviscosity and peripheral neuropathy.^{3,4} This infiltrate usually expresses a typical immunophenotype (eg, IgM⁺, CD5⁻, CD10⁻, CD11c⁻, CD19⁺, CD20⁺, CD22⁺, CD23⁻, CD25⁺, CD27⁺, FMC7⁺, CD103⁻, CD138⁻). In addition, the plasmacytic component will be CD138⁺, CD38⁺, and CD45⁻.

First-line therapy includes rituximab, which is a monoclonal antibody directed against the CD20 antigen present in B lymphocytes.^{1,2} The combination of rituximab plus chemotherapy is the preferred regimen especially in patients with symptomatic WM. Combinations of rituximab-based therapy include the addition of bendamustine alone, dexamethasone and cyclophosphamide, and bortezomib with or without dexamethasone. Ibrutinib is a Bruton's tyrosine kinase inhibitor which also has activity in WM.³ The choice of regimen is often based on toxicity profile, as well as patient and provider preference.

What makes the differentiation of diagnosis between these 2 entities so challenging is that patients often do not present with all the signs and symptoms mentioned above and there may also be overlap between them. However, there have been recent advances in cytogenetics that can help further distinguish between IgM MM and WM. The presence of t(11;14) which leads to cyclin D1 dysregulation has been shown to be present in IgM MM according to recent studies, but absent in WM.^{2,5} On the other hand, research has revealed the presence of a somatic mutation (MYD88 L265P) in patients with WM, identified by means of whole-genome sequencing and confirmed by Sanger sequencing. In contrast, MYD88 L265P mutation is absent in cases of myeloma, including IgM-secreting myeloma, making it useful as a distinguishing feature between WM and IgM MM.²

Because of the overlapping clinical presentations, the disparities in management and the need for early identification for treatment and to improve prognosis establish the need for a more accurate diagnostic approach and techniques to differentiate between these 2 diseases. In this case report, we observe the importance of the use of cytogenetics and gene mutation analysis in differentiating between the diagnosis of IgM MM and WM. Also we see that in the clinical presentation, the presence of IgM monoclonal gammopathy and bone marrow biopsy alone is not enough to make an accurate diagnosis.

Case Presentation

A 64-year-old male veteran with a medical history of hypothyroidism was evaluated at VACHS primary care clinic in September 2015 with the primary complaint of low-back pain of approximately 2-week duration. Pain was localized to the midline of the lower lumbar spine, radiating to the left flank, described as stabbing, constant, 7/10 in intensity, aggravated by movement, and only mild decrease in pain when applying an ice pack. Patient denied recent trauma, abrupt sudden movement, or recent heavy lifting. He also denied pain radiating to lower extremities, lower extremity weakness, loss of sensation, gait, urinary retention, urinary incontinence, fecal incontinence, fatigue, fever, night sweats, weight loss, or any other symptoms. The patient was a chronic smoker of 1 pack/day for 40 years and had no significant family history, and the only medication taken at the time was levothyroxine for hypothyroidism. On physical examination, patient was alert, active, oriented to person, place, time, and in acute pain. Vital signs at initial office evaluation were the following: blood pressure of 107/70 mm Hg, heart rate of 82 beats/min (regular), respiratory rate of 18 breaths/min, and temperature of 36.5 C. Back examination revealed tenderness to palpation at the lower lumbar area. There was no paraspinal muscles tenderness, no superficial lesions noted, no costovertebral angle tenderness, and negative straight leg raise test. There was normal bilateral lower extremity reflexes (2⁺) and strength (5/5), and sensation was intact. No lymphadenopathy or hepatosplenomegaly was noted on examination. Remainder of physical examination was unremarkable. Initial laboratories after symptoms started were remarkable for unexplained normocytic/normochromic anemia (12.3 g/dL), and white blood cells and platelets were within normal limits. There was a mild increase in serum creatinine concentration compared to baseline, elevated total protein (8.6 g/dL), and decreased high-density lipoprotein cholesterol (34 mg/dL). Urinalysis showed proteinuria (100 mg/dL) and he had elevated erythrocyte sedimentation rate (114 mm/1 h). Lumbosacral X-rays and magnetic resonance imaging (MRI) showed L1-L3 compression fractures.

Given the combination of this patient's bone pain, unexplained anemia, increased total serum protein, and vertebral compression fractures, additional laboratory tests were performed for further evaluation; these included serum and urine protein electrophoresis with immunofixation and quantitation of immunoglobulins. Protein electrophoresis revealed an elevated β -globulin and M-spike of 2.1 g/dL. Immunotyping results showed monoclonal gammopathy with IgM lambda (2.1). Up to this point although the clinical presentation was typical of MM as evidenced by the combination of anemia, elevated total protein, and bone disease, the fact that the patient presented with IgM monoclonal gammopathy leads to the consideration of other entities, especially WM. For further evaluation and confirmation of diagnosis, a bone marrow biopsy with flow cytometry and immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), positron emission tomography (PET) scan, viscosity index, and MYD88 (L265P) gene

mutation analysis were performed. Bone marrow biopsy results revealed increased number of plasma cells (24%) and lymphocytes (25%). Dutcher bodies (intranuclear vacuoles containing IgM monoclonal protein within cells) were also observed. Flow cytometry and IHC analysis revealed CD20(−) CD56(−) CD117(−). Fluorescence in situ hybridization revealed t(11;14). PET scan revealed no lymphadenopathy or organomegaly and did not disclose bone disease. Viscosity index was elevated (4.1). MYD88 (L265P) mutation was not detected.

The results of flow cytometry, IHC, and FISH; the negative MYD88 (L265P) mutation; and the absence of organomegaly on PET scan argue against a diagnosis of WM, which usually includes MYD88 gene mutation (+), CD20(+), organomegaly, and absence of t(11;14). Instead, the findings support the rare diagnosis of IgM MM as evidenced by symptoms of bone pain, unexplained anemia and acute kidney injury on laboratory analysis, IgM monoclonal protein on immunotyping, more than 10% plasma cells on bone marrow biopsy, the presence of lytic bone lesions, and the presence of t(11;14). In addition, the immunophenotype CD20(−) CD56(−) CD117(−) is also consistent with IgM MM. Repeated imaging demonstrated diffuse lytic bone lesions involving the ribs, femoral head, and vertebral bodies.

During this period of evaluation and confirmation of diagnosis, the patient developed acute renal failure, worsening anemia, and pathologic rib fractures after a fall with minor trauma to the chest. He also developed severe constipation leading to adynamic ileus secondary to hypercalcemia, which required hospitalization. During this hospitalization, the patient was started on induction therapy for his IgM MM, which consisted of lenalidomide, bortezomib, and dexamethasone (RVD). In addition, during this hospital stay, while on therapy, the patient continued with constipation secondary to refractory hypercalcemia as well as hospital-acquired pneumonia requiring the need of antibiotic therapy. After 11 days of RVD therapy, the patient developed hypercapnic respiratory failure requiring endotracheal intubation and mechanical ventilation at the medical intensive care unit (MICU). The possible precipitant of the respiratory failure was the hospital-acquired pneumonia and development of heart failure (despite a baseline normal cardiac function) according to signs and symptoms presented prior to intubation. The patient spent 5 days in the MICU and was extubated successfully at the third day and transferred back to the general ward 2 days after extubation. However, patient's renal function continued to deteriorate, hypercalcemia persisted, and developed hemodynamic instability, respiratory distress, and hypoxemia. Patient died 22 days after admission to the hospital despite therapeutic measures taken.

Discussion

Establishing a diagnosis of IgM MM is a challenging task, given rarity of the disease and the small number of reported cases in the literature. Given the difference in treatment and

prognosis between IgM MM and WM, being able to distinguish between these 2 clinical entities is of great importance. However, the degree of some overlap in clinical presentation and the difficulty to distinguish based on clinical features and biopsy alone make it a very difficult challenge. In addition, signs and symptoms that usually distinguish them may overlap. For example, a subset of patients with IgM MM have presented with organomegaly, a finding most commonly observed in patients with WM.² Also, as seen in this case and other studied cases, the serum viscosity can also be elevated in IgM MM, indicating that hyperviscosity is not unique to WM and is most likely related to the large structure of IgM immunoglobulin.² Plasma cell immunophenotype may also overlap as even though IgM MM is usually CD20(−), there have been cases in which an unusual CD20 (partial) and CD20(+) was present in MM cells, which is the immunophenotype most commonly seen in WM.²

IgM MM presents as any other type of MM, and the diagnosis of IgM MM requires the presence of an IgM monoclonal gammopathy and 10% or more of clonal plasma cells on bone marrow biopsy, along with at least 1 CRAB criteria or myeloma defining event, such as light chain ratio over 100, 60% or more plasma cells in marrow, or bone lesion greater than 1 cm by MRI.^{1,2} All CRAB criteria were present in the patient described in this case report confirming the diagnosis of IgM MM. The lytic bone lesions developed by this patient are a result of end-organ damage and considered specific to MM and usually not a feature of WM. This patient exhibited the typical immunophenotype of IgM MM which includes CD20(−) CD56(−) CD117(−). In addition, there is a strong association of IgM MM with (11;14), and even though recent studies have shown that this finding is not sensitive or will capture all cases with this disease, its presence is specific for IgM MM.^{2,6} Louiseau and others described presence of t(11;14)(q13q32) as the most common cytogenetic abnormality of IgM, IgE, and nonsecretory myeloma present in up to 83% of cases.⁷ Waldenström macroglobulinemia usually is CD20(+) and exhibits the somatic mutation (MYD88 L265P), which was absent in this patient.^{2,6} The absence of organomegaly in this patient also makes WM less likely.

Once the diagnosis of IgM MM is made, the treatment for transplant eligible patients includes induction therapy with a 3 drug regime which usually includes lenalidomide, bortezomib (or another proteasome inhibitor), and decadron followed by autologous stem cell transplantation, followed by maintenance therapy.⁸ Nontransplant candidates with good performance status can be treated with different regimes such as melphalan, prednisone, thalidomide; melphalan, prednisone, and bortezomib; modified revlimid, velcade, decadron (mRVD); cytoxan, bortezomib, decadron (CyborD); or the same regime described above. In this case, the patient was a transplant candidate and was started on induction therapy with lenalidomide, bortezomib, and dexamethasone (RVD).

As we can observe from this case and the review of literature, there are a number of similarities and overlap in clinical presentation and features between these 2 diseases and

that is when the use of more accurate diagnostic methods plays a significant role. In this patient, what ultimately helped in making the final diagnosis of IgM MM was the use of cytogenetics and gene mutation analysis. Waldenstrom macroglobulinemia has been found to have a homogenous gene expression and clusters with chronic lymphocytic leukemia and normal B cells on unsupervised clustering with very similar expression profiles. Only a small gene set has expression profiles unique to WM compared to chronic lymphocytic leukemia and MM. The most significantly upregulated gene is interleukin 6 (IL-6) and the most significantly associated pathway for this set of genes is Mitogen-activated protein kinases signaling. Thus, IL-6 and its downstream signaling may be of biologic importance in WM. Further elucidation of the role of IL-6 in WM is warranted as this may offer a potential therapeutic avenue.⁹ This shows that patients presenting with IgM monoclonal gammopathy should undergo a thorough diagnostic approach in order to correctly identify patients with IgM MM; this will in turn lead to early treatment and improvement of prognosis.

Declaration of Conflicting Interests

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