Case Report

A Rare Presentation of Biclonal Gammopathy in Multiple Myeloma with Simultaneous Extramedullary Involvement: A Case Report

Pragnan Kancharla^a Eshan Patel^a Kenneth Hennrick^a Sherif Ibrahim^b
Mendel Goldfinger^a

^aNew York-Presbyterian Brooklyn Methodist Hospital, Brooklyn, NY, USA; ^bWest Plains Hospital, White Plains, NY, USA

Keywords

Biclonal gammopathy · Extra medullary myeloma · Multiple myeloma

Abstract

Multiple myeloma is characterized by an abnormal clone of plasma cell infiltration in the bone marrow and presence of a high level monoclonal immunoglobulin (M-protein) in the serum or urine in most cases. The monoclonal protein is usually detected as a discrete band in the gamma globulin region by serum protein electrophoresis. Rarely, it may show a simultaneous presence of two distinct bands, which could be either from a single clone, or two separate clones. We report a very unusual presentation of biclonality with lambda restricted IgG predominant cells from cervical lymph node and kappa restricted IgA cells from the bone marrow simultaneously.

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Introduction

Multiple myeloma is characterized by a clone of abnormal plasma cell infiltration in the bone marrow and presence of a high level monoclonal immunoglobulin (M-protein) in the serum or urine in most cases. The typical clinical manifestations are anemia, bone pain, renal

insufficiency, hypercalcemia and recurrent infections. It is diagnosed by having a monoclonal protein spike in serum or urine, clonal plasma cells >10% on bone marrow aspiration/biopsy and evidence of related end organ damage. The monoclonal protein is detected by serum protein electrophoresis as a single discrete band (M-band) most often in the gamma globulin region. However, it may rarely show a simultaneous presence of two distinct M-bands as seen in 2–6% of cases [1]. We report an unusual presentation of multiple myeloma with double M-bands from likely true biclonality.

Clinical Summary

An 81-year-old man with past medical history of hypertension, distant history of Prostate adenocarcinoma treated with radiation presented with a slowly progressive painless left neck mass. He further reported a 5-pound unintentional weight loss over two months. The patient denied B-symptoms (i.e fevers, chills or night sweats). Physical examination affirmed a large left neck mass that was non-tender. He was referred to a PET scan after failing a trial of antibiotics which showed a 4 × 2.8 × 2.6 cm left parapharyngeal mass (SUV 28), multiple enlarged left cervical nodes at level II and level III measuring up to 3 cm with max SUV of 34. He underwent a left neck node excisional biopsy. (Fig. 1a–c). Pathology demonstrated an atypical population of interfollicular plasma cells. These atypical plasma cells had a lambda light chain restriction. Immunohistochemically the plasma cells were positive for CD20, CD43, PAX5, CD138, and CD56 and negative for BCL-1.

A bone marrow biopsy done approximately one month later showed a bone marrow with 30% kappa restricted plasma cells (Fig. 2a–e). Serum laboratory studies demonstrated a hemoglobin, calcium and creatinine within normal limits. There was an elevated IgA of 619 mg/dL, IgG of 1,300 mg/dL, free kappa 279.9 mg/L and free lambda 35.2 mg/L with a kappa/lambda ratio of 7.95. Serum protein electrophoresis showed two monoclonal spikes of 0.7 and 0.4 gm/dL in the gamma region with similar findings in the urine electrophoresis (Fig. 3). Serum immunofixation confirmed two monoclonal bands in gamma region with one being IgG / lambda and the other having an IgA/Kappa identity.

The patient was started on Velcade, Revlimid and Decadron with significant reduction in size of the nodes after one cycle and downtrending IgA 259, IgG 642 mg/dL, free kappa 36.8 mg/L and free lambda 17 mg/L with further intent to continue chemotherapy.

Discussion

Multiple myeloma is a hematological malignancy with a global annual incidence of approximately 114,500 and an annual mortality of approximately 80,000. Men are usually affected more than woman with incidence increasing with age [2]. Extramedullary disease is an uncommon manifestation of multiple myeloma. Usmani et al. [3] reported that lymph node was the primary site amongst 6% of extramedullary cases in their study and that extramedullary diseases were associated with poor prognosis regardless of treatment.

The clinical manifestations of multiple myeloma are based on the presence of one or more markers of end organ damage such as anemia, bone pain, renal insufficiency, hypercalcemia and recurrent infections. Protein manifestations characteristic of multiple myeloma include increase of monoclonal (M) protein concentrations (IgG, IgA, IgM, IgD) and/or light chain concentrations (kappa or lambda) identified by protein electrophoresis of serum or urine. A bone

marrow biopsy is done to substantiate the abnormal findings. In current practice, fluorescence in situ hybridization (FISH) and cytogenetics are routinely performed on samples diagnosed with multiple myeloma. Biological classification of multiple myeloma into two categories, hyperdiploid multiple myeloma (harboring numerous chromosomal trisomies and low prevalence of IgH translocations) and non-hyperdiploid multiple myeloma (encompassing hyperdiploid, pseudodiploid and near tetraploid multiple myeloma and highly enriched IgH for translocations) play an important role in predicting prognosis and guiding therapy. Patients with hyperdiploid myeloma have a more favourable outcome [4].

Several groups have shown that $t(4;14)$ (p16;q32) and $t(14;16)$ (q32;q23) are associated with poor survival, irrespective of the treatment modality. In multiple series tested, 17p13 deletions confer an aggressive disease with high prevalence of extramedullary disease and hypercalcemia prompting an overall shorter survival [4, 5]. Performing FISH in unsorted samples carries a significant risk of low sensitivity for detection of chromosomal abnormalities. Based on multiple series, the minimum panel required for prognostic estimation should include $t(4;14)$ (p16;q32), $t(14;16)$ (q32;q23) and 17p13 deletions and a further comprehensive panel should include testing for $t(11;14)$ (q13;q32), chromosome 13 deletion, ploidy category and chromosome 1 abnormalities. The utility of this information not only helps determine biological subtype but has a significant prognostic value and assists in guiding treatment [4, 5].

Biclonal gammopathies are a vanishingly rare group characterized by the production of two distinct monoclonal proteins. This rare finding can result for example from either a proliferation of two clones of plasma cells with each producing an unrelated monoclonal spike or from the production of two monoclonal spikes by a single clone of plasma cells. Approximately 1.5% of multiple myeloma cases present with biclonal paraproteinemia [6]. Mullikin et al. [7] reported that 23 out of 393 patients with biclonal gammopathy of unknown significance in their study had progression to either multiple myeloma, smoldering myeloma, light chain amyloidosis or Waldenstrom macroglobulinemia with the dominant clone being the principal player through the course of the disease in 21 patients [7]. Several cases of isotype switching have been reported in myeloma patients with biclonal spikes. A case exhibited a shift from primarily IgG with a minor IgD component to a predominant IgD immunoglobulin production after chemotherapy with findings revealing neoplastic origin from a single clone of B-cells [8]. Franck et al. [9] reported another case with shift from a single paraprotein IgG Kappa to a biclonal paraprotein IgG kappa and IgD kappa. It is not uncommon to see biclonal bands with isotype switching on serum immunofixation of post stem cell transplant patients and those receiving immunosuppressive therapy. They are more likely to be transient phenomena as opposed to a neoplastic recurrence and are not associated with adverse prognosis [10].

Kyle et al. [6] reported no difference in prognosis between biclonal and monoclonal gammopathy. However, recognition of this existence increases the credibility and helps in assessing treatment response during follow-up [1]. To our knowledge, this is the first ever-reported case with biclonal gammopathy with simultaneous extramedullary involvement.

Conclusion

Our case report highlights an extremely rare clinical presentation of lymph node and bone marrow involved by biclonal multiple myeloma. Biclonal gammopathy can have its origin from either a single clone or two clones of plasma cells. Given the simultaneous presentation it is unclear in our case as to which originated first. Nevertheless, identification of biclinality

not only helps us to be precise but also will be helpful in guiding treatment and to follow up response.

Statement of Ethics

The authors have no ethical conflicts to declare. The authors have provided informed consent to publish the manuscript.

Disclosure Statement

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

The authors do not have any conflicts of interest to disclose.

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Fig. 1. **a** Low-medium power H&E stained sections demonstrate residual follicles with an interfollicular expansion by numerous atypical plasma cells. **b** High power H&E stained sections demonstrate numerous atypical plasma cells with classic eccentric nuclei mild to moderate pleomorphism, round to slightly irregular nuclei, and moderately clumped chromatin. **c** High power in situ hybridization studies demonstrate lambda restriction of the atypical plasma cell population in the excisional biopsy of neck lymph node.

Fig. 2. **a** Aspirate smear (100×): Atypical plasma cells. **b** Bone marrow (40×): Mildly Hypercellular marrow for age with increased plasma cells. **c** CD138 stain (40×): CD138+ Plasma Cells. **d** Lambda stain (40×): Lambda negative plasma cells. **e** Kappa stain (40×): Kappa restricted plasma cells.

Fig. 3. Biclonal spike on urine electrophoresis.