A Rare Case of Acute Hemolytic Anemia in a Patient with Newly Diagnosed Multiple Myeloma: Maintaining a Fine Balance between Occam’s Razor and Hickam’s Dictum

Jerin Ovett¹ Parathan Karunakaran¹ Jayachandran Perumal Kalaiyarasi¹ Deepa Devi² Karthik Bommannan³ Gopal Gopisetty⁴ Nikita Mehra¹,⁴

¹Department of Medical Oncology, Cancer Institute (WIA), Chennai, Tamil Nadu, India
²Department of Transfusion Medicine, Cancer Institute (WIA), Chennai, Tamil Nadu, India
³Department of Onco-Pathology, Cancer Institute (WIA), Chennai, Tamil Nadu, India
⁴Department of Molecular Oncology, Cancer Institute (WIA), Chennai, Tamil Nadu, India

Address for correspondence: Nikita Mehra, MD, DM, Department of Medical Oncology, Department of Molecular Oncology, Cancer Institute (WIA), Dr. S. Krishnamurthy Campus, 38 Sardar Patel Road, Chennai-600036, Tamil Nadu, India (e-mail: m.nikita@cancerinstitutewia.org).

Abstract

Anemia is a common feature in multiple myeloma and is multifactorial. A 52-year-old lady was admitted to our hospital with complaints of fatigue, exertional dyspnea, paresthesia, and a recent-onset confusion state. Fundus examination revealed features of hyperviscosity. The patient received 2 units of packed red blood cell transfusion (PRBC) before the present hospital admission. Laboratory investigations revealed severe anemia and thrombocytopenia. The M-protein was 5.8 g/dL. Bone marrow showed sheets of plasma cells. Immunofixation electrophoresis confirmed the presence of an IgA band. FISH was positive for IgH-FGFR3 fusion. The investigations confirmed multiple myeloma R-ISS stage III. The patient was immediately started on CyBorD chemotherapy regimen. The patient had indirect hyperbilirubinemia and symptomatic anemia. Initial testing of the patient’s sample showed blood grouping discrepancy with DCT, ICT, and auto control positive. The symptomatic anemia persisted requiring PRC transfusions. Further antibody study revealed the presence of anti-Jka antibody—a warm IgG antibody and cold antibody. Subsequently, the patient received Jka antigen-negative B-positive compatible PRBC transfusions and the hemoglobin normalized. Our patient had transfusion-associated alloimmunization along with hyperviscosity. The timely recognition and early institution of plasmapheresis and myeloma-directed therapy along with transfusion of compatible Jka antigen-negative PRBC lead to rapid improvement.

ISSN 0971-5851.

© 2022. The Author(s).
This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (https://creativecommons.org/licenses/by/4.0/)
Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India
Introduction

Multiple myeloma (MM) is a plasma cell neoplastic disorder characterized by the clonal proliferation of malignant plasma cells. Symptomatic patients present with myeloma-defining events, i.e., CRAB features (hypercalcemia, renal insufficiency, anemia, and bone lytic lesions). Herein, we report a case of IgA MM presenting with hyperviscosity and hemolytic anemia.

Case Report

A 52-year-old lady, a resident of Southern India, was admitted to our hospital with complaints of fatigue, exertional dyspnea, and paresthesia involving both her lower limbs for the past month. The patient’s past medical history was unremarkable. The patient’s son reported that she was confused and had an irrelevant speech for 1 week before the hospital admission. On admission, the patient was conscious, disoriented, and irrational. Her vitals were stable, and she was afebrile. Clinical examination revealed severe pallor, peripheral neuropathy, and skin petechiae over the lower extremities. Fundus examination by ophthalmoscope revealed dilated and tortuous retinal veins, and disc edema bilaterally suggestive of hyperviscosity. The patient did not have acrocyanosis, Raynaud’s phenomenon, or skin changes. The patient received 2 units of packed red cell (PRC) transfusion before the current hospital admission. Laboratory investigations revealed hemoglobin 3.5 g/dL (normal range: 12–17), WBC 7000/mm^3 (normal range, 4000–10000), platelet count of 31,000/mm^3 (normal range, 150,000–400,000/mm^3), blood urea 71 mg/dL (normal range, 15–45), serum creatinine 1.4 mg/dL (normal range, 0.7–1.5), and raised serum calcium 12.7 meq/L (normal range, 8.4–10.2). The peripheral smear revealed normocytic normochromic RBCs, reduced RBC density, occasional plasma cells, and reduced platelets. There was no evidence of hemolysis, viz., RBC fragments or spherocytes. CT of the chest revealed extensive skeletal lytic lesions. Further assessment of monoclonal fragments or spherocytes. CT of the chest revealed extensive skeletal lytic lesions. Further assessment of monoclonal gammopathy revealed total protein: 10.4 g/L (normal range, 6–8), serum albumin: 1.8 g/dL (normal range, 3.5–5), and M-protein of 5.8 g/dL by serum protein electrophoresis (SPEP). Bone marrow showed sheets of plasma cells with suppressed trilineage hematopoiesis (Fig. 1). Flow cytometry revealed 73% clonal plasma cells with lambda light chain restriction. Serum immunoglobulins showed elevated IgA 41 g/L (normal range, 1.03–5.91), IgG 4.91 g/L (normal range, 6.6–16.9), and IgM < 0.19 g/L (normal range, 0.37–2.58). Serum immunofixation (IFE) confirmed the presence of IgA band; serum-free light chains (sFLC): λ>35.1 mg/L (normal range, 5.71–26.3), κ<2.20 mg/L (normal range, 3.3–19.4), and λ/κ ratio of 0.063. MALDI-TOF mass spectrometry revealed a Lambda monoclonal peak (Fig. 2). Fluorescence in situ hybridization was positive for IgH translocation and IgH-FGFR3 fusion, β2 microglobulin was 9.9 mg/L, and serum LDH was 1163 U/L (normal range, 200–400). The investigations confirmed multiple myeloma R-ISS stage III. The nerve conduction study revealed mixed axonal and demyelinating motor-sensory neuropathy of the distal nerves in the lower limb—common peroneal and sural nerves. The patient was immediately started on CyBorD chemotherapy regimen—bortezomib, cyclophosphamide, and dexamethasone. Intravenous dexamethasone was initiated at 40 mg daily for 4 days. The patient had hyperbilirubinemia—6 mg/dL (normal range, 0.2–1.3) with predominant indirect bilirubin elevation of 4.2 mg/dL and normal liver enzymes. Imaging of the liver was within normal limits. Further workup for hemolysis was negative: reticulocyte index 0.45% (normal range, 0.5–2.5) and normal haptoglobin: 40 mg/dL (normal range, 30–200). The indirect Coombs test (ICT) and direct Coombs test (DCT) were strongly positive. The patient had symptomatic anemia for which PRC transfusion was requested. Initial testing of the patient’s sample showed blood grouping discrepancy with DCT, ICT, and autocontrol positive. Because the blood bank team could not resolve the blood group, one unit of O-negative best compatible packed red cell unit was issued for emergency use. Subsequently, a B-positive blood group was confirmed; however, the presence of autoantibodies or an alloantibody could not be ruled out. Therefore, two additional units of least incompatible B-positive packed red cell units were transfused, following which the patient had worsening pulmonary congestion and altered sensorium. CSF analysis was not done as the patient had thrombocytopenia with bleeding diathesis—skin petechiae and hematuria. As there was no improvement in the patient’s sensorium after initiating anti-myeloma therapy, the patient underwent plasmapheresis. Her clinical status dramatically improved, and she was continued on anti-myeloma therapy. The patient’s sensorium, renal dysfunction, hypercalcemia, and thrombocytopenia gradually normalized. However, the symptomatic anemia continued to persist, requiring PRC transfusions. Hence, the patient was worked up for auto- and allo-incompatibility. Further antibody study was performed that revealed the following:

1. Direct antiglobulin test on patient’s red cells: weakly positive
Anemia is one of the most common presenting features that frequent occurrence of high-risk cytogenetic abnormalities. IgA type has an overall poor prognosis partly due to the higher molecular weights. They can cause severe acute hemolytic transfusion reactions. However, more commonly, they present with delayed hemolytic transfusion reactions even up to 1 week after blood transfusions. Anti-Jka antibody is classically evanescent and difficult to detect because the levels rapidly decline in the plasma. Symptomatic hyperviscosity is much more common with Waldenström’s macroglobulinemia (10–30%) than it is in MM (2–6%). Symptoms of hyperviscosity include mucosal bleeding, ocular neurological, and cardiovascular manifestations. Hyperviscosity is observed in IgA and IgM type paraproteinemia partly due to their higher molecular weights. Immediate treatment is indicated in the presence of hyperviscosity-related symptoms. Plasmapheresis immensely aids in reducing hyperviscosity-related symptoms within 1 to 2 days. Simultaneous anti-myeloma therapy with newer daratumumab-based regimens can hasten the recovery. Despite its aggressive disease biology, IgA MM demonstrates a good response to bortezomib-based regimens. The use of anti-CD38 monoclonal antibodies, viz., daratumumab and isatuximab have implications in immunohematology; panagglutination caused by these
anti-CD38 monoclonal antibodies during indirect antiglobulin testing can mask a clinically significant RBC alloantibody. In the present era where daratumumab is approved for use in the frontline setting in MM, RBC phenotyping or genotyping before daratumumab is recommended. This may prevent immune hemolysis and therefore ensure appropriate transfusion. In our patient, the identification of the anti-Jk<sup>a</sup> antibody and subsequent transfusion of Jk<sup>a</sup>-negative PRCs led to improvement and stabilization of hemoglobin. There was no further drop in hemoglobin, indicating that the presence of cold antibody was a silent bystander, despite requiring multiple transfusions during diagnosis and peri-transplant period.

**Conclusion**

To our knowledge, there is no literature on patients with multiple myeloma presenting with anti-Jk<sup>a</sup> antibody and a cold antibody. This case highlights the value of respecting the fine balance one needs to maintain between Occam’s razor and Hickam’s dictum, especially in plasma cell dyscrasias and their systemic associations.

**Conflict of Interest**

“Rapid and Accurate Detection of M-Protein by MALDI-TOF by Reagent-Based Extraction” Copal Gosipsetnik, Nikita Mehra, Subramani Jayavelu Indian provisional patent application no: 202041099443, filed on March 5, 2020.

**Acknowledgments**

We thank the patient for permitting us to share all her clinical details. We thank Mr. Jayavelu for the technical support for MALDI-TOF MS-M-protein analysis. We thank Dr. Anup Devasia for providing his clinical input. We would like to thank the following Institutes: Department of transfusion Medicine-RELA Institute of Medical Science, Apollo Hospitals, Chennai, and ICMR-National Institute of Immunohematology, Mumbai, for performing the detailed antibody screening.

**References**

