



# 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

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## 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 IgAλ 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 Jk<sup>a</sup> antigen-negative PRBC lead to rapid improvement.

## Keywords

- ▶ alloimmunization
- ▶ anti-Jk<sup>a</sup>
- ▶ cold antibody
- ▶ multiple myeloma

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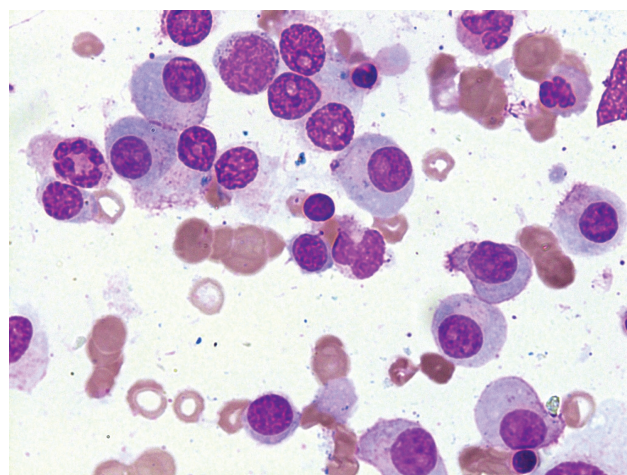
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## Introduction

Multiple myeloma (MM) is a plasma cell neoplastic disorder characterized by the clonal proliferation of malignant plasma cells.<sup>1</sup> Symptomatic patients present with myeloma-defining events, i.e., CRAB features (hypercalcemia, renal insufficiency, anemia, and bone lytic lesions).<sup>2</sup> Herein, we report a case of IgA $\lambda$  MM presenting with hyperviscosity and hemolytic anemia.

## Case Report

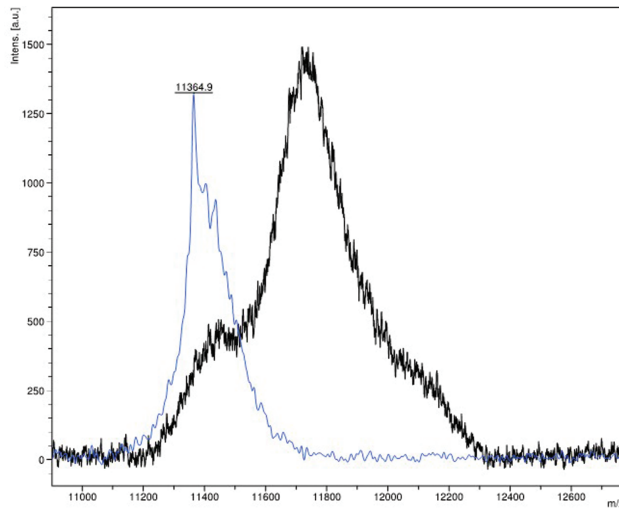
A 52-year-old lady, a resident of Southern India, was admitted to our hospital with complaints of fatigue, exertional dyspnea, and paresthesia involving both her lower limbs for the past month. The patient's past medical history was unremarkable. The patient's son reported that she was confused and had an irrelevant speech for 1 week before the hospital admission. On admission, the patient was conscious, disoriented, and irritable. 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.<sup>3</sup> 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<sup>3</sup> (normal range, 4000–10000), platelet count of 31,000/mm<sup>3</sup> (normal range, 150,000–400,000/mm<sup>3</sup>), 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 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 $\lambda$  band; serum-free light chains (sFLC): $\lambda$ -35.1 mg/L (normal range, 5.71–26.3),  $\kappa$ -2.20 mg/L (normal range, 3.3–19.4), and  $\kappa/\lambda$  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,  $\beta$ 2 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



**Fig. 1** Leishman stain of bone marrow aspirate at 100x magnification showing atypical plasma cells.

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



**Fig. 2** MALDI-TOF mass spectrometry shows a monoclonal spike in the lambda region (blue) against a normal control (black).

2. Atypical antibody in patient's serum using antibody screening cells:
  - by saline technique (IgM phase): negative
  - indirect antiglobulin technique (IgG phase): positive
3. Patient's serum showed the presence of anti-Jk<sup>a</sup> antibody: a warm IgG antibody
4. Presence of cold antibody

Subsequently, the patient received Jk<sup>a</sup> antigen-negative B-positive compatible packed red cell unit transfusion. After that, there was no further hemolysis or drop in hemoglobin. Transfusion with compatible blood products and continuation of anti-myeloma therapy gradually normalized the hemoglobin. Cold antibody was detected; however, there were no clinical features to suggest cold agglutinin disease. The patient was subsequently started on bortezomib, lenalidomide, and dexamethasone (VRd regimen). After four cycles, the patient achieved a very good partial response with normalization of hemoglobin (Hb, 12.2 g/dL) and platelet count. The ICT continued to remain positive. The patient underwent high-dose therapy with melphalan (200 mg/m<sup>2</sup>) followed by autologous hematopoietic stem cell transplantation (ASCT). The transplant and peritransplant periods were uneventful. On subsequent follow-up, SPEP, serum IFE, sFLC, and bone marrow performed on D + 100 were suggestive of stringent complete response (sCR) and an undetectable MRD at 10<sup>-6</sup>. The patient was started on bortezomib maintenance.

## Discussion

IgA type has an overall poor prognosis partly due to the frequent occurrence of high-risk cytogenetic abnormalities.<sup>4</sup> Anemia is one of the most common presenting features that can significantly impact physical functioning and quality of life variables.<sup>5</sup> Several factors can cause anemia in patients

with MM, including abnormal iron utilization, inappropriately low serum erythropoietin levels, a reduction in the bone marrow response to erythropoietin, hemolysis, and bone-marrow involvement.<sup>6</sup> Autoimmune hemolytic anemia and cold agglutination disease are rare presenting manifestations of MM.<sup>7,8</sup> Despite several reports showing the association between autoimmune hemolytic anemia and MM, none have shown conclusive evidence that the myeloma monoclonal protein is responsible, and rarely are they symptomatic due to the same.<sup>9</sup> There was evidence of transfusion-associated alloimmunization in our patient, which was confirmed by the identification of the anti-Jk<sup>a</sup> antibody. Alloimmunization is usually a major concern among patients receiving transfusions over a prolonged duration, which is quite rare with MM.<sup>10</sup> Females who have received multiple transfusions are at a higher risk.<sup>11</sup> The frequency of hemolytic anemia due to alloimmunization is reported in 2 to 6%, of which anti-Jk<sup>a</sup> antibody is the most commonly detected.<sup>12</sup> The reported alloimmunization rate among patients with a hemato-oncological diagnosis was 3.2%. Jk<sup>a</sup> antigen belongs to the Kidd antigen blood group system. The incidence of anti-Jk<sup>a</sup> antibodies in population-based studies varies from 1.3 to 2.5%.<sup>13</sup> In India, routine antibody screening is not done in clinical practice except in a few centers.<sup>14</sup> In patients who have hemolytic anemia due to alloimmunization, screening and antigen matching are recommended to prevent further complications.<sup>15</sup> There are instances of alloimmunization which have occurred in the immediate post-transplant period leading to hemolysis and complicating the management due to the increased transfusion requirement post-ASCT.<sup>16,17</sup> Cold antibody-mediated hemolysis is usually IgM, and RBC hemolysis occurs at 3 to 4°C.<sup>18</sup> Therefore, cold agglutinin disease usually presents with Raynaud's phenomenon and acrocyanosis. The anti-Jk<sup>a</sup> antibody-associated hemolysis is IgG-mediated. Anti-Jk<sup>a</sup> antibodies are usually IgG1 and IgG3; however, some are partly IgG2, IgG4, or IgM.<sup>13,19</sup> 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-Jk<sup>a</sup> antibody is classically evanescent and difficult to detect because the levels rapidly decline in the plasma.<sup>20,21</sup> 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<sup>22,23</sup>. 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.<sup>24,25</sup> Despite its aggressive disease biology, IgA MM demonstrates a good response to bortezomib-based regimens.<sup>26</sup> 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.<sup>27,28</sup> 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.<sup>27,28</sup> 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,<sup>29</sup> 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" Gopal Gopisetty, Nikita Mehra, Subramani Jayavelu Indian provisional patent application no: 202041009443, filed on March 5, 2020.

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