A Curious Case of Multiple Myeloma Hidden in a Cloud of Severe Cryoglobulinemia

Naomi Fei, MD
West Virginia University Hospital, Department of Internal Medicine

Abraham S. Kanate, MD
West Virginia University, Osborn Hematopoietic Malignancy and Transplantation Program, MBRCC

Corresponding Author: Fei, Naomi, WVU SOM, Health Science Center South, Dept. Internal Medicine, 1 Medical Center Dr., Morgantown, WV 26505. Email: naomi.fei@gmail.com.

Abstract
Cryoglobulins are proteins that form ‘cloudy’ precipitates at temperatures <37°C. In type I cryoglobulinemia, the causative protein is a monoclonal immunoglobulin due to an underlying plasma cell dyscrasia. Cryoglobulinemia can present with hyperviscosity syndrome, characterized by headache, fatigue, and blurred vision. In episodes of severe cryoglobulinemia, premature precipitation of proteins can lead to falsely negative diagnostic tests and complications with treatment. The following case exemplifies the complications of diagnosis and treatment of cryoglobulinemia with hyperviscosity syndrome.

Case Report
A 79 year old man presented during the winter months with the chief complaint of syncope with positional lightheadedness. Additional symptoms included 4 months of fatigue, 15 pound unintentional weight loss, and bone pain. Physical exam was significant for cachexia, hypotension with sinus tachycardia. Complete blood count showed anemia (Hgb 11.8 x109/L) with an elevated MCV (102.8 fL). A blood smear with Giemsa stain noted red blood cells in a classic rouleaux formation. Leukocyte count was 6.5 x109/L with normal differential (Neutrophils 73%, Lymphocytes 18%, Monocytes 8%, Eosinophils 1%, Basophils 0%). Differential was without blasts or plasma cells. A basic metabolic panel noted an elevated creatinine (1.5 mg/dL) and elevated calcium (11.52 mg/dL).

Given the high suspicion for multiple myeloma, beta-2-microglobulin was ordered and found to be 4.61 mg/dL. Kappa:lambda free light chain ratio was found to be 0.031 (normal 0.26-1.65). Surprisingly, immunoglobulin levels were found to be within normal limits with IgA 76 mg/dL (normal 85-499mg/dL), IgG 1525 mg/dL (normal 610-1616 mg/dL), and IgM 29 mg/ dL (normal 35-242 mg/dL). A working diagnosis of light chain myeloma was proposed due to the isolated elevation in lambda light chains.

The patient continued to display positional lightheadedness, hypotension, and symptoms of pre-syncope including blurred vision, muscular weakness, and feeling faint. Hyperviscosity syndrome due to type 1 cryoglobulinemia was suggested. Serum viscosity was found to be 3 (normal <1.5 centipoise). Due to the rarity of hyperviscosity syndrome in pure light chain myelomas, repeat immunoglobulin levels were drawn. On inspection of the patient’s serum, the cryoprecipitate was clearly visible at temperatures >37°C (Fig 1), and it was ascertained initial immunoglobulin levels were not appropriately measured. A repeat sample was drawn in a prewarmed tube with caution to prevent premature precipitation of cryoglobulins. Repeat IgG level was found to be 7322 mg/dL. A preliminary diagnosis of IgG lambda multiple myeloma was made with confirmation on bone marrow biopsy.

Treatment of hyperviscosity syndrome secondary to type 1

Figure 1: Photograph of the patient’s serum displaying premature precipitation of immunoglobulins at temperatures greater than 37°C.
Table 1. Type of immunoglobulins, underlying etiologies, and presentations of three types of cryoglobulinemia1,2,3

<table>
<thead>
<tr>
<th>Type of Immunoglobulin</th>
<th>Type I Cryoglobulinemia</th>
<th>Type II Cryoglobulinemia</th>
<th>Type III Cryoglobulinemia</th>
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<tr>
<td>Type</td>
<td>Monoclonal IgG / IgM / IgA</td>
<td>Monoclonal IgM</td>
<td>Polyclonal IgM</td>
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<td>Etiologies</td>
<td>Plasma Cell Dyscrasias</td>
<td>Polyclonal IgG</td>
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<td>Monoclonal Gammopathy of</td>
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<td>Undetermined significance</td>
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<td>Presentation</td>
<td>Asymptomatic</td>
<td>Viral Infection (Hepatitis C Virus)</td>
<td>Arthralgias and Myalgias</td>
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<td></td>
<td>Hyperviscosity Syndrome</td>
<td>Connective Tissue Disease</td>
<td>Cutaneous Vasculitis (palpable purpura)</td>
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<td>Thrombosis</td>
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<td>Peripheral neuropathy</td>
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cryoglobulinemia was initiated with plasmapheresis. Unfortunately, initial attempts at plasmapheresis were unsuccessful due to premature precipitation of cryoglobulins in the catheter. Measures to prevent line occlusion were implemented including infusion of warming fluids, placement of warming blankets, and administration of dexamethasone 10mg IV daily. With these adjunctive therapies, the patient was able to undergo 4 rounds of plasmapheresis with reduction of IgG levels to 10mg/dL. Patient reported resolution of pre-syncopal symptoms and normalization of blood pressure was observed. The patient was started on bortezomib with dexamethasone to treat the underlying multiple myeloma with excellent response. Currently he is alive and disease free approximately 2 years from the initial encounter.

### Discussion

Normal plasma viscosity is dictated by the content and concentration of proteins present. Proteins such as immunoglobulins with higher molecular weight and greater degree of asymmetry result in greater plasma viscosity.4 When increased plasma viscosity results in significant impairment of the microvascular circulation, a combination of symptoms classified as hyperviscosity syndrome occurs. Symptoms include headache, confusion, dizziness, blurred vision, visual loss, epistaxis, and hearing loss.2 Symptoms typically develop when serum viscosity exceeds 4 centipoise, which is usually associated with serum IgM levels of at least 3000 mg/dL, IgG levels of 4000 mg/dL, or IgA levels of 6000 mg/dL.1 This patient’s presentation and findings of IgG levels of 7322 mg/dL perfectly exemplify hyperviscosity syndrome. Thus, the possibility of elevated plasma proteins with a diagnosis of hyperviscosity syndrome should always be considered in the differential of syncope or pre-syncopal symptoms.

The precipitation of immunoglobulins from serum at temperatures below 37°C characterizes cryoglobulinemia. Cryoglobulinemia is categorized into three basic types based on type of immunoglobulins present (Table 1). The presence of monoclonal immunoglobulins, usually either IgM or IgG, secondary to an underlying plasma cell dyscrasia are categorized as type I cryoglobulinemia. A mixed population of monoclonal and polyclonal immunoglobulins are categorized as type II or III cryoglobulinemia. Type II cryoglobulinemia is characterized by monoclonal IgM and polyclonal IgG commonly seen in hepatitis C infections. Type III cryoglobulinemia is defined as polyclonal IgM and polyclonal IgG due to B-cell expansion triggered by a variety of infections and autoimmune disorders.1,2,3

Due to the pathologic levels of immunoglobulins required for symptoms, it is unsurprising that hyperviscosity syndrome is often observed in type I cryoglobulinemia but only in <3% of mixed cryoglobulinemias.4 Of the plasma cell dyscrasias, hyperviscosity syndrome has been noted in 10-30% of Waldenstrom’s Macroglobulinemia (WM) and only 2-6% of multiple myeloma.5,6 This may be explained by the contribution of large, asymmetrical immunoglobulin polymers to increased serum viscosity. WM produces monoclonal IgM that forms large, asymmetric pentamers and would more likely result in higher serum viscosity. When hyperviscosity syndrome is observed in multiple myeloma, it is usually due to the formation of IgA or IgG polymers.7,8 Light chain myeloma is rarely associated with hyperviscosity syndrome, likely due to its smaller molecular size.8,9,10 In case reports of light chain myeloma hyperviscosity syndrome, highly polymerized kappa light chains have been found.10 Though the polymerization status of this patient is unknown, the lambda light chain component of his myeloma makes it less likely that this would present with hyperviscosity syndrome.

Measurement of immunoglobulins involved in hyperviscosity syndrome can be complicated by precipitation as seen in this case. At extremely high concentrations, premature precipitation of immunoglobulins at temperatures greater than 37°C...
is observed with a resultant false negative test for cryoglobulinemia. Therefore, special emphasis must be placed on maintaining a warm sample in order to obtain appropriate measures of immunoglobulin concentration. In this case, a prewarmed tube was used and directly transported to the lab in order to obtain accurate measurements.

Acute treatment of hyperviscosity targets the alleviation of symptoms through plasmapheresis. Viscosity is logarithmically related to protein levels, therefore even a mild decrease in plasma levels of immunoglobulin can result in significant symptom relief. This case reports unique complications to plasmapheresis in the setting of severe cryoglobulinemia due to clotting of the catheter at temperatures >37°C. In such settings, we have found that using warming fluids as well as warming the patient’s core temperature with steroid usage was effective in completing plasmapheresis.

Of note, this patient began to exhibit symptoms of hyperviscosity related to type 1 cryoglobulinemia during the winter months. It may be that colder environmental temperatures precipitated plasma proteins resulting in cryoglobulinemia. Patients at risk for elevated immunoglobulin levels should be counseled on the importance of maintaining a warm environment to avoid symptoms of cryoglobulinemia.

**Conclusion**

This case emphasizes the importance of considering hyperviscosity syndrome secondary to type 1 cryoglobulinemia in the differential diagnosis of pre-syncopal symptoms or syncope. When collecting diagnostic samples for cryoglobulinemia, appropriate warming techniques should be observed to ensure premature precipitation does not occur. Finally, patients with elevated immunoglobulin states should be counseled on the importance of maintaining a warm environment in order to prevent symptoms and aid treatment of cryoglobulinemia.

**Declarations**

Ethics approval and consent to participate

Approval from the WVU Ethics committee regarding the publication of this case report was obtained.

Consent for publication

Approval to submit this case for publication was obtained from the patient. The consent form is available on request for review.

Availability of data and material

Not Applicable

Competing interests

The authors declare that they have no competing interests

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**Authors’ contributions**

NF was a major contributor in writing the manuscript. AK was a major contributor in editing. All authors read and approved the final manuscript.

**References**