CASE REPORT

Immunoglobulin M ‘Flare’ Seen in a Case of Waldenstrom’s Macroglobulinemia: Successfully Managed by Therapeutic Plasma Exchange

Suvro Sankha Datta¹ · Somnath Mukherjee² · Biplabendu Talukder³ ·
Prasun Bhattacharya³

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Abstract Therapeutic plasma exchange (TPE) is a conjunctive modality of treatment along with rituximab to decrease paraproteinemia associated with hyperviscosity. Here we narrate our experience in treating a diagnosed case of Waldenstrom’s macroglobulinemia in 70 years old male patient with moderate anemia and severe features of hyperviscosity syndrome by serial TPE and rituximab combined with bortezomib. The patient was relieved of his symptoms after initial two TPE procedures performed on alternative day. However he again developed signs and symptoms of the disease within 6 weeks following second TPE and starting of rituximab (375 mg/m² weekly for 4 weeks) therapy with bortezomib. His serum IgM level became as high as 9.901 g/dl suggesting immunoglobulin M ‘Flare’ due to rituximab therapy. At the end of third TPE he was relieved symptomatically with low IgM level (3.13 g/dl) and discharged in hemodynamically stable condition. Therefore we concluded that careful monitoring of serum viscosity and IgM level are necessary during treatment with rituximab based chemotherapy and TPE should be promptly initiated to control the treatment related hyperviscosity syndrome.

Keywords Macroglobulinemia · Hyperviscosity · IgM · Rituximab · Therapeutic plasma exchange

Introduction

Waldenstrom macroglobulinemia (WM) is according to the World Health Organization classification, a lymphoplasmacytic lymphoma [1] in which the bone marrow is infiltrated by immunoglobulin M (IgM) producing clonal lymphoplasmacytic cells. The Second International Workshop on WM (IWWM-2) proposed criteria for the clinico-pathological diagnosis and for initiation of therapy in WM patients [2, 3]. The IWWM consensus panels have provided treatment recommendations [4, 5] which were last updated in 2008 (IWWM-4) [6]. It is a rare disorder in people of Asian descent but much more prevalent in western countries and median age at diagnosis is 63 years for blacks and 73 for whites [7]. The clinical manifestations of the disorder are hepatomegaly (20 %), splenomegaly (15 %), and lymphadenopathy (15 %). The most common presenting symptom is fatigue related to a normochromic normocytic anemia [8]. Increased serum IgM levels can lead to blood hyperviscosity-related complications. Peripheral neuropathy has been observed in WM due to autoantibody formation against myelin-associated glycoprotein (MAG) [9]. The IWWM-consensus panels recommended that individual patient considerations should be weighed for the choice of therapy, including the need for rapid disease control, age, candidacy for autologous transplantation, comorbidities, presence of cytopenias, hyperviscosity, lymphadenopathy, IgM-related end-organ damage, and patients’ preferences [6]. Rituximab-based regimens remain a recommended primary therapy for most patients with WM. According to recent consensus

✉ Suvro Sankha Datta
suvro.datta@gmail.com

¹ Department of Transfusion Medicine, The Mission Hospital, Sector-2C, Immon Kalyan Sarani, Bidhannagar, Durgapur, West Bengal 713212, India

² Department of Transfusion Medicine, AIIMS, Bhubaneswar, Odisha 751019, India

³ Department of Immunohematology & Blood Transfusion, MCH, Kolkata, West Bengal 700073, India

combination of bendamustine or bortezomib with rituximab is now a primary treatment option, especially for patients with high tumor bulk [10]. However rituximab is associated with a potentially clinically significant complication, IgM flare; this surge of IgM level mostly observed with single-agent rituximab therapy [11]. Immunoglobulin M flare may require immediate institution of therapeutic plasma exchange (TPE).

Here we report our experience of treating a diagnosed case of WM in 70 years old male with therapeutic plasma exchange who showed IgM flare after initiation of rituximab and bortezomib therapy.

Case Report

A 70 years old male (body weight: 54 kg, height: 161 cm, BSA: 1.56 m²) presented with recurrent syncopal attacks with exertional dyspnea, fatigue and weakness since last 9 months. He had a history of transfusion with two units of red cells during last 3 months. On clinical examination, he had pallor, mild jaundice and bone tenderness. His vitals were normal (BP: 126/82 mm of Hg, pulse: 84/min). There were no lymphadenopathy or hepato-splenomegaly. Cardiovascular, respiratory and neurological evaluations were within normal limits. On laboratory investigations: complete hemogram revealed; Hb: 6.7 g/dl, Hct: 23 %, RBC: $2.6 \times 10^{12}/\text{l}$, MCV: 87 fl, MCHC: 31.1 g/dl, RDW-CV: 22.1 %, TLC: $6.3 \times 10^9/\text{l}$, platelets: $80 \times 10^9/\text{l}$. Laboratory tests for cryoglobulinemia, cold agglutinin disease were negative. Direct antiglobulin test was negative. There was no blood group discrepancy. Patient's blood group was typed as O positive. Coagulation tests were normal (PT: 13 s, control: 12.7–15.4 s; APTT: 29 s, control: 26.3–39.4 s). Serum calcium was 8.8 mg/dl (8.7–10.2 mg/dl). Serum Na⁺/K⁺ were within normal range. Liver function test revealed total serum bilirubin 3.1 mg/dl (0.3–1.9 mg/dl) predominantly conjugated, total serum protein: 15.9 g/dl (6.4–8.3 g/dl), serum albumin: 2 g/dl, serum globulin: 13.1 g/dl with albumin: globulin ratio 1:6.55 (normal 2.2:1.1). Liver enzymes were within normal range. Renal function tests were within normal limit. Infectious markers for HBV, HCV and HIV were negative. ECG and echocardiography were done to rule out any cardiac causes for his repeated syncopes and exertional weakness. Both ECG and echocardiography were normal. Electromyogram (EMG) was also performed and did not reveal any abnormality. Computerized tomography (CT) scan of brain showed diffuse cerebral atrophy related to his age. Considering his age and clinical features serum protein electrophoresis was performed to rule out any form of paraproteinemias. Serum protein electrophoresis combined with immunofixation revealed; IgM monoclonal protein of kappa type. Serum IgM level was 11.3 g/dl (normal

0.4–2.3 g/dl). Bone marrow examination performed subsequently which revealed diffuse infiltration of lymphoplasmacytic cells showing an intertrabecular pattern. All other three lineages were decreased in marrow. Flow cytometric analysis of the bone marrow aspirate were found to be sIgM, CD19, CD20, CD22, CD79, CD5 and CD10 positive; CD23 and TRAP negative. Serum viscosity estimation and cytogenetic diagnosis by analysis of mutation in MYD88 (L265P) could not be possible in this case due to lack of affordability. Therefore it was diagnosed as a case of Waldenstrom's macroglobulinemia.

To provide symptomatic relief to his recurrent syncope and weakness total three therapeutic plasma exchanges (TPE) were performed by intermittent cell separator (Hemonetics, MCS+, USA). Prior to first plasma exchange, he was given four units of concentrated red cells on two consecutive days which raised his Hb level from 6.7 to 12.3 g/dl. His initial two exchanges were done on alternate day with replacement of approximately one plasma volume in each procedure. Albumin along with FFP was used as a replacement fluid due to high cost of human albumin. Approximately 85–90 % of patient's plasma was exchanged with the replacement fluid in each procedure. At the end of second TPE the patient was relieved of his weakness and syncope and his serum IgM was 4.6 g/dl, therefore TPE was discontinued. After second plasma exchange, chemotherapy was started with inj. bortezomib-1.3 mg/m², on day 1, 4, 8 and 11, inj. dexamethasone –4 mg/kg on day 1, 4, 8 and 11 and inj. rituximab 375 mg/m² every week for 4 weeks. The patient again developed recurrent syncope, headache and generalized weakness within 6 weeks of second exchange and starting of rituximab based chemotherapy. His serum IgM became 9.901 g/dl with other laboratory parameters showed Hb: 9.2 g/dl, TLC: $4.5 \times 10^9/\text{l}$, platelet: $156 \times 10^9/\text{l}$, calcium: 9.2 mg/dl, total serum protein: 15.2 g/dl, serum albumin: 3.3 g/dl, globulin: 11.2 g/dl with albumin: globulin ratio 1:3.39 (normal 2.2:1.1). His third plasma exchange was started following two units of red cell transfusion on the day before exchange. The total amount of plasma which was removed in each procedure is given in Table 1.

After 24 h of third TPE, his serum IgM level came down to 3.13 g/dl and the patient became asymptomatic. There were no adverse reactions observed during the procedures. Till date this patient is under regular follow-up and there is no further relapse.

Discussion

The term 'hyperviscosity syndrome' refers to the clinical sequelae of mucous membrane bleeding, retinopathy and neurological impairment. Specific signs and symptoms

Table 1 Procedural details of TPE

Serial no.	Pre-exchange hematocrit (%)	Total plasma volume replaced (ml)	Replacement fluid
1	37.10	2139	^a 5 % albumin: 850 ml + FFP: 900 ml + ACD: 220 ml
2	36.80	2040	^a 5 % albumin: 800 ml + FFP: 750 ml + ACD: 187 ml
3	35.30	2087	^a 5 % albumin: 900 ml + FFP: 600 ml + ACD: 260 ml

FFP fresh frozen plasma, ACD acid citrate dextrose

^a Albumin is reconstituted with normal saline

include headache, dizziness, vertigo, visual impairment, coma, and seizures. Other manifestations include coagulation abnormalities, thrombocytopenia, anemia and peripheral polyneuropathy [12]. This syndrome occurs most typically in Waldenstrom's macroglobulinemia when the monoclonal IgM concentration exceeds 5 g/dl or when serum viscosity is greater than 4.0 centipoises (cp) [13]. Serum viscosity is proportional to the IgM concentration up to 3 g/dl and then increases sharply at higher levels. TPE does not alter the course of primary disease, it is used in conjunction with chemotherapy to decrease symptoms of hyperviscosity. TPE is also recommended in those patients with IgM more than 5 g/dl at the time of initiation of rituximab based therapy [14]. The frequency and duration of TPE should be tailored to the needs of the individual patient [15]. In hyperviscosity due to macroglobulinemia, one or two TPE procedures may be sufficient to return the plasma viscosity to near normal [15]. The relationship between blood viscosity and abnormal immunoglobulin concentration is exponential, such that removal of relatively small amount of immunoglobulin by TPE will result in a large reduction in serum viscosity [16]. In this case the patient was stratified in a high risk group according to International Prognostic Scoring System for WM depending on patient's age, symptomatic anemia and high IgM level at presentation [17]. The initial two plasma exchanges were performed on alternate day to reduce the symptomatic hyperviscosity and to prepare the patient for rituximab based therapy. But surprisingly the patient had a sharp rise in IgM level due to rituximab therapy even when the IgM level came down to less than 5 g/dl and developed symptoms of hyperviscosity due to the IgM flare. In many WM patients, a transient increase of serum IgM (IgM flare) may be noted immediately after initiation of rituximab treatment [11, 18]. The IgM flare may be related to the release of IL-6 by bystander immune response due to binding of rituximab to FcγRIIA receptors [19]. Because of the possibility that serum IgM and viscosity levels may abruptly rise, rituximab monotherapy usually not being used as sole therapy for the treatment of patients at risk for hyperviscosity symptoms [20]. But atypically in this case IgM flare was seen even after administration of bortezomib with rituximab. However, the patient responded successfully on

third plasma exchange relieving his symptoms and lowering the serum IgM level.

Therefore we concluded that careful monitoring of viscosity and IgM levels are not only necessary during treatment with rituximab monotherapy but also important for the combined chemotherapy of rituximab with bortezomib and therapeutic plasma exchange should be promptly initiated to control the treatment related hyperviscosity syndrome.

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