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Case Report

A case of acquired dysfibrinogenemia in multiple myeloma treated with therapeutic plasma exchange

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ABSTRACT

A 70 year old Caucasian woman with IgG lamda multiple myeloma presented with uncontrollable bleeding from a bone marrow biopsy site which started days after the procedure. The patient was hyperviscous, and coagulation tests showed elevated activated partial thromboplastin time (aPTT) which was not corrected with a mixing study, elevated thrombin time and reptilase time, and possible inhibitors to Factors VIII and IX. Therapeutic plasma exchange was performed using plasma with corrections of plasma viscosity (1.6 to 1.1 centipoise) and aPTT (50 to 42.1 s) observed. The bleeding was controlled, and purified IgG demonstrated dysfibrinogenemic effects of the patient's paraprotein.

1. Introduction

Multiple myeloma is a malignant disorder of plasma cells which typically results in production of high levels of monoclonal immunoglobulins. About 15% of patients with IgG multiple myeloma and more than 30% of patients with IgA and IgM myeloma may have a bleeding diathesis [1,2]. Various etiologies for the bleeding have been described including qualitative platelet dysfunction [3], acquired von Willebrand disease [4], Factor X deficiency due to absorption to amyloid [5], impaired fibrin polymerization [6,7], systemic fibrinolysis [8], circulating heparin-like anticoagulants [9], Factor VIII inhibitor [10], and thrombin inhibitor [11]. This report describes a patient with uncontrollable bleeding from her bone marrow biopsy site which started days after the procedure. It was successfully treated with therapeutic plasma exchange (TPE).

2. Case report

A 70-year-old Caucasian female with multiple myeloma with hyperviscosity and uncontrollable bleeding from a bone marrow biopsy site, which started 16 days after the procedure, was referred to the apheresis service for TPE. She had been diagnosed with IgG lamda multiple myeloma 7 years earlier and had undergone treatments which included thalidomide, dexamethasone, velcade, and autologous stem cell transplant. One year earlier, she also had a series of radiation treatments for a myelomatous lesion in T6 resulting in severe back pain. The patient bled from the biopsy site continuously for 9 days despite fresh frozen plasma (FFP) and platelet transfusions. She was started on Pomalidomide 13 days after her marrow biopsy, and 3 days later began to bleed from the biopsy site. Her clinical laboratory test results are summarized in Table 1. They were notable for elevated plasma viscosity of 1.6 centipoise [reference range (RR): 1.1–1.5 centipoise], myeloma paraprotein level of 5.0 g/dL, decreased albumin (2.7 g/dL; RR: 3.5–5 g/dL], and prolonged prothrombin time (17.2 s; RR:12.5–14.7 s), activated partial thromboplastin time (aPTT; 52.9 s; RR: 23–36.9 s), thrombin time (24.5 s;

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Table 1
Clinical laboratory testing results at the time of apheresis consult.

Test	Result	Reference range	Units
WBC	4.00	3–12	K/μL
Hemoglobin	**10.2**	11.5–16	g/dL
Hematocrit	**31.5**	34–47	%
Platelet	**60**	150–500	K/μL
Na	137	135–145	mequiv./L
K	3.6	3.5–5.1	mequiv./L
Cl	101	98–107	mequiv./L
CO2	30	22–32	mequiv./L
BUN	**34**	6–20	mg/dL
Creatinine	0.8	0.4–1	mg/dL
Bilirubin, Total	0.8	0.2–1.2	mg/dL
LD	114	100–248	IU/L
AST(GOT)	**12**	15–41	IU/L
ALT(GPT)	28	5–45	IU/L
GGT	36	7–50	IU/L
Alk Phos	37	32–91	IU/L
Ca	10.2	8.6–10.2	mg/dL
PO4	3.0	2.5–4.5	mg/dL
Mg	2.5	1.6–2.6	mg/dL
CRP	<5.00	0–10	mg/L
Uric acid	4.7	2.3–6.6	mg/dL
Albumin	**2.7**	3.5–5	g/dL
IgG, IFCC	**6600**	714–1394	mg/dL
Gamma region	**5.4**	0.7–1.6	g/dL
M-component	5.0		g/dL
Prothrombin	**17.2**	12–14.7	s
APTT	**52.9**	23–36.9	s
1:1 Mix APTT	**43.4**	23–36.9	s
Fibrinogen	198	197–447	mg/dL
D-Dimer, quant.	**0.84**	0–0.5	μg/mL FEU
Thrombin time	**24.5**	15.3–19.6	s
Reptilase time	**83.2**	13.9–20.5	s
Heparin neutralization	**51.4**	28.8–37.6	s
Plasma viscosity	**1.6**	1.1–1.5	Centipoise

Values outside of the reference ranges are shown in bold.

RR: 15.3–19.6 s), and reptilase time (83.2 s; RR: 13.9–20.5 s). Fibrinogen activity was low, but within the RR (198 mg/dL; RR: 197–447 mg/dL). APTT was similar following heparin neutralization (51.4 s; RR: 28.8–37.6), excluding the presence of heparin. The failure of aPTT to correct upon mixing (43.4 s), and increased Factors VIII and IX activities upon serum dilution (Fig. 1) suggested the presence of an inhibitor.

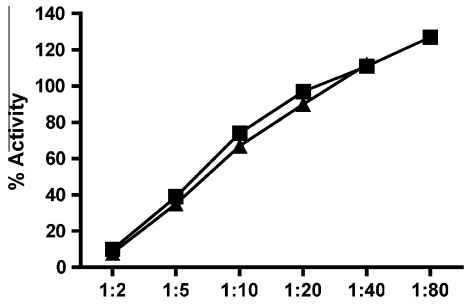

Fig. 1. Factors VIII and IX assay results of the patient's plasma showing increased activities with higher serum dilutions consistent with the presence of an inhibitor. (■) indicates Factor VIII activity levels while (▲) indicates Factor IX activity levels.

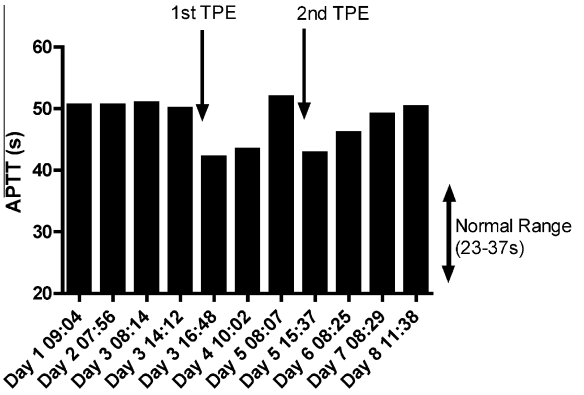

Fig. 2. APTT values of the patient around the time two TPE procedures were performed. Notable decrease in APTT values were observed after each of the two procedures performed.

As the patient was found to be hyperviscous, TPE was performed using FFP as replacement after a central line placement. The plasma viscosity decreased from 1.6 to 1.1 centipoise. APTT which was 50 s prior to the procedure, decreased to 42.1 s after the procedure (Fig. 2). A second TPE was performed 2 days later with similar corrections in aPTT (51.9–42.8 s) and plasma viscosity (1.4–1.1 centipoise). The bleeding which was barely contained with a pressure dressing prior to initiating TPE, never recurred.

IgGs were isolated from the patient plasma collected during the first TPE procedure, and from healthy control plasma (IRB approval and informed consent obtained) using Protein G agarose chromatography (Millipore Corporation, Billerica, MA). Purified IgGs (175 μl each) were combined with 1.3 ml of normal pooled plasma (NPP) (Precision BioLogic, Nova Scotia, Canada) and 262 μl of sodium citrate. The final concentrations of purified IgGs were 4.7 g/dL in the "IgG Patient" sample, 3.4 g/dL in the "Healthy IgG-High" sample, and 1.7 g/dL in the "Healthy IgG-Low" sample (Table 2). "No IgG Control" was made by adding Owren-Koller Buffer (Diagnostica Stago, Parisppany, NJ) to NPP and sodium citrate. Compared to "Healthy IgG-High", "Healthy IgG-Low", and "No IgG Control", the "Patient IgG" showed elevated aPTT, thrombin time, and reptilase time. While the aPTT corrected with mixing, the thrombin time showed near correction and reptilase time did not correct, a pattern consistent with dysfibrinogenemia or the presence of fibrin degradation products. However, D-dimers were not detected (data not shown). Inhibitory activities against Factors VIII and IX were observed (Fig. 3) but were not as prominent as those observed *in vivo* (Fig. 1). Therefore, acquired dysfibrinogenemia appeared to be the main effect of the patient's myeloma paraprotein.

3. Discussion

This manuscript reports the case of a patient with IgG lambda multiple myeloma who presented with prolonged bleeding from a bone marrow biopsy site which started