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다발성 골수종 환자에서 발생한 혈소판 기능 장애

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Platelet Dysfunction in a Patient with Multiple Myeloma: A Case Report with a Literature Review

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Multiple myeloma is a monoclonal plasma cell proliferation disorder with various symptoms and signs caused by paraproteinemias. Among these signs, a bleeding tendency is one of the major fatal causes. However, significant severe bleeding is rare in most cases. In this study, we report a case of multiple myeloma in a patient who had a severe recurrent bleeding tendency due to platelet dysfunction caused by paraproteins. After being treated with therapeutic plasma exchange and chemotherapy, the patient's monoclonal protein level decreased and the bleeding stopped. (Korean J Med 2012;83:823-827)

Keywords: Multiple myeloma; Paraproteinemias; Hemostatic disorders; Platelet function tests; Plasmapheresis

INTRODUCTION

Multiple myeloma (MM) is a malignant plasma cell disorder that accounts for approximately 10% of all hematological malignancies. Excess proliferation of monoclonal immunoglobulin can manifest as multi-organ dysfunction and various other symptoms by itself or as host responses. Symptoms of MM may include bone pain, fatigue, easy bruisability, bleeding tendency, and recurrent infections. Anemia and a bleeding tendency are the major hematological manifestations. Anemia is one of the most common clinical features of MM and presents initially in 40-73% of patients [1,2], but a bleeding tendency occurs in < 15% of patients [1]. Most MM cases with a bleeding tendency have been documented as minor bleeding. For example, one study of 43 patients with monoclonal gammopathy reported that a laboratory hemostasis defect was found in 26 patients (60%); however, bleeding symptoms were manifested in only five

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cases [3]. Although a bleeding tendency is silent in most MM cases, severe bleeding could occur as a result of platelet dysfunction caused by paraproteinemia. In the present report, we noted a severe recurrent bleeding episode in the lower extremity of a patient with MM that was is caused by platelet dysfunction with paraproteinemia.

CASE REPORT

A 69-year-old man had been diagnosed with MM (IgG lambda, M-protein 3.3 g/dL; plasmablastic type) 1 month previously at a provincial hospital and had been referred to Asan Medical Center (AMC), Seoul, Korea, a tertiary care hospital. The patient had started MM treatment with thalidomide and dexamethasone at the AMC outpatient clinic. He visited the emergency room 1 week after his first chemotherapy due to severe painful swelling of the left calf. The painful mass was red and edematous and was warm and tender to the touch. The patient had no history of trauma to this area. The dorsalis pedis artery pulse was intact. The laboratory evaluation revealed white blood cell count, 6,300/mm^3; hemoglobin, 8.2 g/dL; platelet count, 141,000/mm^3; and serum creatinine, 0.9 mg/dL. The coagulation profile showed a prothrombin time (PT) of 1.23 international normalized ratio (INR) (normal INR, 0.8-1.3), activated prothrombin time (aPTT) of 33.5 seconds (normal range, 25-35 seconds), and fibrinogen level of 349 mg/dL (normal range, 200-400 mg/dL). To evaluate the swelling, magnetic resonance imaging (MRI) had been performed in the emergency room, and the MRI findings strongly suggested the possibility of hematoma (Fig. 1A). The patient had experienced three hematoma evacuations as well as a fasciotomy caused by compartment syndrome. Embolization was subsequently performed using gel-foam material, and the bleeding improved (Fig. 1B). Although the bleeding improved following embolization, oozing of the bleeding site persisted.

A biopsy specimen showed chronic inflammation. In addition to the above laboratory results, the von Willebrand factor antigen (vWF:Ag) was 113% (normal range, 70-140%) and the ristocetin cofactor (vWF:RCo) was 183% (normal range, 60-140%). The thrombin time was 18.4 seconds (upper limit, 22 seconds), and coagulation factors were entirely normal.

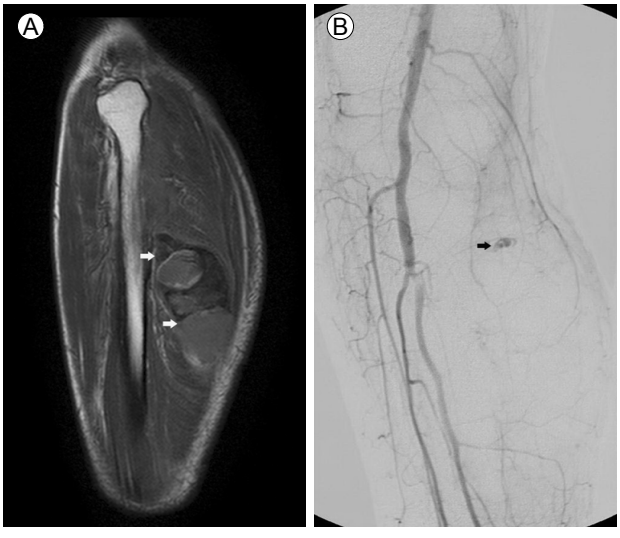

Figure 1. Magnetic resonance imaging (MRI) and angiography findings of the hematoma. (A) A large, well encapsulated and multi-septate cystic lesion showed high signal intensity in the left calf on T1-weighted MRI (white arrow). (B) Active contrast extravasation in a muscular branch of the right peroneo-posterior tibial trunk (black arrow).

Table 1. Coagulation studies and factor assays

Tests	Results
Coagulation studies	
PT	1.23 INR (0.8-1.3 INR)
aPTT	33.5 seconds (25.0-35.0 seconds)
TT	18.4 seconds (upper limit, 22 seconds)
vWF:Ag	113% (70-140%)
vWF:RCo	183% (60-140%)
Coagulation factor assays	
Factor II	90% (60-140%)
Factor V	62% (60-140%)
Factor VII	80% (60-140%)
Factor VIII	137% (60-140%)
Factor IX	246% (60-140%)
Factor X	85% (60-140%)
Factor XI	96% (60-140%)
Factor XII	73% (45-90%)

PT, prothrombin time; aPTT, activated prothrombin time; TT, thrombin time; vWF, von Willebrand factor.

Table 2. M-peak and the platelet aggregation test

	Before admission	Pre TPE	Post TPE	After chemotherapy
M-peak[a]	3.3 g/dL			1.7 g/dL
PFA-100 closure time				
Collagen/epinephrine (95% CI: 82-182 sec)		> 300 sec	217 sec	124 sec
Collagen/ADP (95% CI: 62-109 sec)		219 sec	258 sec	173 sec
Platelet aggregation test				
ADP (60-90%)		65.9%	62.3%	62.3%
Collagen (60-90%)		15.9%	78.2%	71.8%
Epinephrine (60-90%)		46.4%	35.5%	83.2%
Ristocetin (60-90%)		39.1%	69.1%	72.3%

TPE, Therapeutic plasma exchange; CI, confidence interval.
[a]The amount of monoclonal protein.

Summaries of the laboratory findings at the time of the initial study are presented in Table 1. We performed platelet aggregation tests with a platelet function analyzer (PFA) (PFA-100, Dade-Behring, Darmstadt, Germany) and classical platelet aggregometry. Collagen/epinephrine closure time on the PFA-100 test was prolonged to > 300 seconds (95% confidence interval [CI], 82-182 seconds) and the collagen/ADP closure time was 219 seconds (95% CI, 62-109 seconds), indicating a platelet defect. Collagen, epinephrine, and ristocetin were 65.9%, 15.9%, 46.4%, and 39.1%, respectively, on the classical platelet aggregometry test with ADP (normal range, 60-95%). Thus, these results indicated decreased platelet aggregation to collagen, epinephrine, and ristocetin.

Therapeutic plasma exchange was performed daily for 3 days to remove the monoclonal protein, and the platelet aggregation tests were repeated. The collagen/epinephrine closure time was 271 seconds, and the collagen/ADP closure time was 258 seconds on the PFA-100 test. ADP was 62.3%, collagen was 78.2%, epinephrine was 35.5%, and ristocetin was 69.1%. on the classical platelet aggregometry test. Then, we started the first cycle of the velcade with dexamethasone chemotherapy. After the first chemotherapy cycle, the platelet aggregation test improved to near normal, and the quantity of monoclonal protein decreased from 3.3 g/dL to 1.7 g/dL (Table 2). No further bleeding episodes have been observed.

DISCUSSION

No history of antiplatelet or anticoagulant agents medication use was observed in our patient, and there was no renal insufficiency that could cause suppression of platelet function. Thus, we searched for the cause of the bleeding diathesis related to MM. To date, several causes for a bleeding tendency have been reported in patients with MM. The bleeding mechanisms include thrombocytopenia, monoclonal thrombin inhibitor, circulating heparin-like anticoagulant, inhibition of fibrin monomers, factor X deficiency, acquired von Willebrand syndrome, paraprotein-induced qualitative platelet dysfunction, and local tissue fragility associated with amyloidosis and vascular endothelium damage [4].

We first assessed the localized tissue problem, e.g., amyloidosis or vascular abnormality, as the localized bleeding cause; however, the biopsy showed only evidence of chronic inflammation. Therefore, we searched for a systemic cause for the bleeding tendency. Bleeding tendencies associated with monoclonal thrombin inhibitor, circulating heparin-like anticoagulant, and inhibition of fibrin monomers have been reported [5-7]. However, in our case, the patient had normal thrombin time, PT time, and aPTT. Therefore, these causes did fit our case. Factor X deficiency has also been described as a cause of bleeding diathesis in patients with dysproteinemic

disorders [8]. However, our patient showed a normal range of values on the factor assays. Thrombocytopenia may be another cause for bleeding. In our case, the initial laboratory evaluation indicated a platelet count of 141,000/mm^3. Slightly decreased platelet counts were maintained throughout the patient's hospitalization; however, the degree was insignificant compared to the bleeding severity. Furthermore, one study reported that platelet count does not correlate with the occurrence of hemorrhage and is rarely low enough to affect hemostasis in patients with MM [9]. Acquired von Willebrand's syndrome (aVWS) is frequently associated with lymphoproliferative disorders and may be one of the factors that could result in bleeding diathesis in patients with MM [10]. Therefore, we checked the vWF:Ag, the vWF:RCo, and the factor VII:C (FVIII:C) level, As a result, vWF:Ag was normal, FVIII:C was normal, and vWF:RCo was elevated. Usually, aVWS show a low/normal vWF:Ag and a low/normal FVIII:C in contrast to a more marked decrease in vWF:RCo [10]. These results were not correlated with aVWS except type 2B aVWS. We also performed a von Willebrand multimer analysis due to the type 2B aVWS and the result showed a normal pattern. Therefore, we could rule out aVWS as the bleeding cause.

Platelet dysfunction has been observed frequently and may be the most consistent abnormality associated with a bleeding tendency in patients with dysproteinemias [3,9,11]. Herbert et al. studied 62 patients with high concentrations of certain paraproteins to explain the association between the paraproteinemia and abnormal bleeding [9]. They reported that bleeding was more often a problem in macroglobulinemia (36%) and occurred less often in IgG myeloma (13%) than in IgA myeloma (33%). In all cases, the kappa light chain was more often associated with a bleeding tendency, suggesting that it could be molecular size rather than the structure that is important to bleeding. We performed platelet aggregation tests using the PFA-100 and classical platelet aggregometry. The PFA closure times increased and platelet aggregation to collagen, epinephrine, and ristocetin decreased on classical platelet aggregometry tests [12]. These results suggested that the abnormality in platelet function associated with the paraproteinemia may be the cause of the bleeding in our patient.

Therapeutic plasmapheresis has been used for treating paraproteinemias to remove harmful paraproteins [13]. In our patient, 3,400 mL of plasma was exchanged daily for 3 days. After plasmapheresis, the results of the platelet function tests improved and the oozing at the bleeding site stopped. As the bleeding stopped after removing the paraproteins, we concluded that the cause of the platelet dysfunction was the paraproteinemia. Many paraproteins are removed after plasmapheresis; however, follow-up chemotherapy to inhibit further production of paraproteins is still necessary. Although therapeutic plasmapheresis produces better results when there is acute bleeding, chemotherapy may eventually correct abnormal hemostasis. As our patient had been treated 1 week previously with thalidomide and dexamethasone before the bleeding developed, another second-line chemotherapy using velcade with dexamethasone was attempted. Finally, the M-peak decreased from 3.3 g/dL to 1.7 g/dL after chemotherapy, and the repeated platelet aggregation test showed nearly normal results. To date, no further bleeding has occurred.

We treated a patient with MM who suffered from a recurrent severe bleeding tendency and hematoma in a lower extremity. Our case supports the previously reported cases that if patients have a severe bleeding problem and a plasma cell disorder such as MM, physicians must consider the possibility of platelet dysfunction and investigate with the platelet aggregation test. Therapeutic plasma exchange may be useful for removing previously existing paraproteins. Additional chemotherapy contributed to arrest the bleeding by inhibiting paraprotein production. However, why a systemic problem such as platelet dysfunction resulted in localized bleeding in our patient remains to be explained by further investigation.

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