Bleeding Diathesis Secondary to a Heparin-Like Anticoagulant in a Patient with Multiple Myeloma—A Case Report and Review of Literature

Nihar Desai[1] Seema Biswas[1] Dinesh Chandra[1] Ruchi Gupta[1] Anshul Gupta[1] Rajesh Kashyap[1]

[1] Department of Hematology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Ind J Med Paediatr Oncol 2024;45:87–91.

Address for correspondence Dinesh Chandra, DM, Department of Hematology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, 226014, Uttar Pradesh, India (e-mail: dinesh3224@gmail.com).

Abstract

Multiple myeloma (MM) is a clonal plasma cell disorder that commonly presents with anemia, renal failure, hypercalcemia, and lytic bone lesions. MM is also frequently associated with thrombotic complications; however, it may rarely present with bleeding diathesis. We report a case of a 42-year-old gentleman with relapsed immunoglobulin G lambda MM who presented with epistaxis, gingival bleeding, and oozing at the venepuncture site. Routine tests of coagulation revealed a prolonged prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time. The PT and aPTT failed to correct with pooled normal plasma and the patient was thus diagnosed to have an acquired heparin-like anticoagulant (HLAC). The source of this HLAC has long been debated, but recent data have demonstrated that this HLAC may be the paraproteins produced by the malignant plasma cells. The patient was treated with intravenous protamine sulfate, repeated cycles of plasma exchange, and a daratumumab-based quadruplet regimen but eventually succumbed to an intracranial hemorrhage. HLAC is a rare but potentially fatal complication of MM that must be considered when patients with MM present with bleeding diathesis.

Keywords
- bleeding
- multiple myeloma
- daratumumab
- heparin

Introduction

Multiple myeloma (MM) is a clonal plasma cell disorder that commonly presents with anemia, renal failure, hypercalcemia, and lytic bone lesions. MM also affects the hemostatic system and contributes to thrombosis and bleeding. Hemorrhagic manifestations usually have a multifactorial etiology with thrombocytopenia, dysfibrinogenemia, platelet dysfunction, and acquired coagulation factor deficiencies being commonly reported.[1] Rarely, paraproteins with heparin-like anticoagulant (HLAC) activity can also cause bleeding. HLAC has also been rarely identified in patients with nonhematological malignancies like metastatic bladder, breast carcinoma and in patients with acquired immunodeficiency syndrome.[2–4]

We report a case of a middle-aged man with relapsed MM who presented with epistaxis and eventually developed a fatal right parietal lobe hemorrhage. The challenges in establishing the diagnosis and management of these rare HLAC are discussed along with a brief review of the literature.

Case Report

A 42-year-old gentleman was diagnosed with MM in January 2019 when he presented with anemia, low back pain, and hypercalcemia. Investigations revealed immunoglobulin G

article published online
September 18, 2023

DOI https://doi.org/10.1055/s-0043-1769789.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

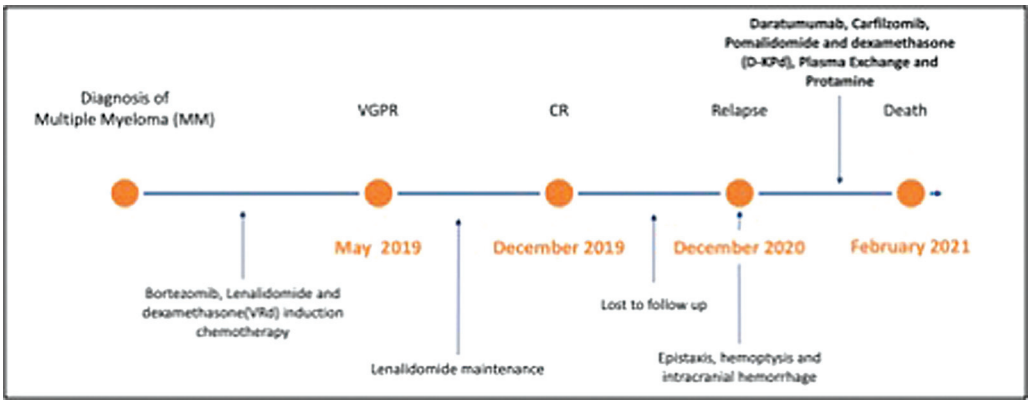

Fig. 1 Course of the disease. Complete response (CR); Very Good Partial Response (VGPR).

(IgG) lambda monoclonal protein at a concentration of 62 g/L and the bone marrow biopsy showed 80% clonal plasma cells. He was risk stratified as Revised International Staging System (R-ISS) stage II and received eight cycles of triplet induction therapy with bortezomib, lenalidomide, and dexamethasone. He attained a very good partial response but deferred autologous stem cell transplantation. Thereafter, he remained on lenalidomide maintenance for 16 months. The course of disease has been shown in ►**Fig. 1**. In his present visit, the patient complained of epistaxis, gingival bleed, and oozing at the venepuncture site.

Laboratory investigations at this time, approximately 2 years from the time of initial diagnosis, were suggestive of disease relapse with IgG lambda monoclonal band of 35 g/L and serum free light chain kappa, 1.07 mg/L; lambda, 3310mg/L; the kappa/lambda ratio, 0.0003. The platelet count was normal (183×10^9/L), but the results of his coagulation tests were deranged (►**Table 1**). The addition of an equal volume of normal plasma did not correct the elevated activated partial thromboplastin time (aPTT) and thrombin time (TT) indicating the presence of an inhibitor. Plasma levels of factor VIII, IX, and X were normal as was the fibrinogen level (Clauss assay) and D-dimer, ruling out disseminated intravascular coagulation. The addition of protamine sulfate (concentration of 100 µg/mL) to the patient's plasma in a 4:1 ratio normalized the TT. This indicated a possibility of a heparin like mechanism contributing to the derangement. A detailed review of the patient's drug chart did not identify the use of exogenous heparin. Considering this background, it was thought that an endogenous heparin activity attributable to the paraprotein was the causative factor.

Local hemostatic measures and infusion of fresh frozen plasma (15 mL/kg) did not arrest the bleeding. He was treated with a continuous infusion of protamine sulfate (5mg/hour) that led to a slight improvement in his TT in vitro (75 seconds) but did not stop his bleeding manifestations. Given the lack of evidence available for the ideal management of this rare complication, we considered managing the underlying disease aggressively with a quadruplet regimen consisting of daratumumab, carfilzomib, pomalidomide, and dexamethasone. This led to a significant reduction in his bleeding manifestations and further treatment was administered on an outpatient basis.

Table 1 Coagulation studies at the time of onset of bleeding

Test	Result	Normal value
Hemoglobin (g/L)	76	120–140
Platelet count ($x10^9$/L)	183	150–400
Prothrombin time (s)	24.6	10.8–13.6
Activated partial thromboplastin time (s)	65.8	28.6–32.6
Thrombin time (s)	154	16–21
Fibrinogen (g/L)	5.92	2–4
Mixing studies with pooled normal plasma	Not corrected	–
Factor X assay	72%	50–150%
Factor VIII assay	66%	50–150%
D-dimer	Negative	Negative
Dilute Russel viper venom test (dRVVT)	Negative	<1.20
Thrombin time with 100 µg/mL protamine sulfate mixed in a 1:4 ratio	16.6	16–21

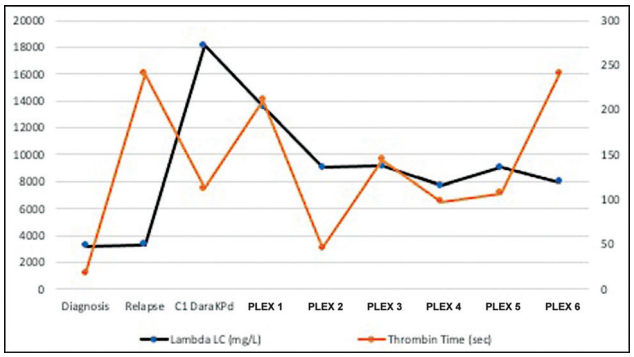

Fig. 2 Change in light chain burden and thrombin time with treatment. DaraKPD, daratumumab-carfilzomib, pomalidomide, dexamethasone; PLEX, plasma exchange (plasmapheresis).

However, he returned to us 2 weeks later with complaints of epistaxis, gingival bleed, headache, and vomiting, and a right parietal hematoma was seen on a noncontrast computed tomography of the brain. His coagulation parameters were deranged again and there was a significant increase in his lambda light chain (18,600mg/L; ►**Fig. 2**). He underwent six cycles of plasma exchange as a means to reduce his light chain burden but his clinical condition continued to worsen and he developed status epilepticus for which he was intubated. Despite continuing supportive care his hemorrhagic manifestations worsened and he could not be salvaged.

Discussion

Contrary to the more common predisposition to thrombotic complications, patients with MM have been reported to have clinically significant bleeding diathesis ranging from 13 to 36%.[5] The underlying etiology is not identified but thrombocytopenia, platelet function defects, acquired factor VIII and X deficiency, and inhibition of fibrin polymerization are some of the mechanisms proposed.[6,7] A rarely reported cause of bleeding is the presence of a circulating HLAC with less than 30 cases being reported to date (►**Table 2**).

HLAC is usually suspected when patients with monoclonal gammopathies present with hemorrhagic manifestations and an elevated prothrombin time (PT), aPTT, and TT. The aPTT remains prolonged despite mixing studies with normal plasma suggesting the presence of an inhibitor. The correction of TT on the addition of protamine sulfate further supports the diagnosis.

The mechanism by which HLAC causes hemorrhagic manifestations is unclear. It has been hypothesized that the negatively charged, sialic acid-bearing monoclonal immunoglobins bind the heparin-binding domain of antithrombin and cause a similar activation to that caused by exogenous heparin.[8] However, Khoory et al proposed that the coagulopathy was not due to a myeloma protein, but a circulating proteoglycan functioning as a cofactor for antithrombin III.[9] The source of this acquired anticoagulant is also debated with neoplastic plasma cells, their paraprotein product, damaged endothelial cells, and soluble CD138 (syndecan) being implicated by various authors.[10] Patients with primary amyloidosis also frequently present with clinically significant bleeding and a prolonged TT, suggesting that the HLAC may not always be derived from the myeloma protein.[11]

Of the reported cases, most patients presented with bleeding manifestations at the time of their initial diagnosis. However, our patient had no coagulation abnormalities at the time of diagnosis and developed fatal hemorrhage at the time of disease relapse. Patients most frequently presented with mucocutaneous bleeding, deep-seated hematomas, and bleeding from surgical/biopsy sites.[12] The severity of bleeding does not correlate with the disease burden and severe bleeding has been reported in patients with monoclonal gammopathy of underdetermined significance and smoldering multiple myeloma as well.[12] Earlier studies did report a high frequency of HLAC in patients with high disease burden like plasma cell leukemia but most contemporary reports show no such association. The impact of HLAC on the prognosis is also not known. Most of the studies have reported deaths due to bleeding and sepsis, rather than the primary disease.[13]

There is a paucity of data to guide the management of this rare complication and the treatment is usually decided by the degree of bleeding. Given the mechanism of action of this inhibitor, protamine sulfate has been used by many authors with variable success, but the optimal dose and duration of protamine therapy have not been determined.[14,15] Studies have also demonstrated an improvement in the coagulation parameters with reduction in the tumor burden and successful treatment with plasma exchange has been reported by Goddard et al.[16,17] To the best of our knowledge, this is the first report on the use of novel agents like monoclonal antibodies for these patients and also the first report from India. Our patient was treated with daratumumab, carfilzomib, pomalidomide, and dexamethasone as a means of rapidly reducing his plasma cell burden. He also underwent plasma exchange with minimal improvement in his laboratory parameters but without any clinical benefit. However, our approach was limited as experimental studies to isolate and characterize the HLAC activity of the paraprotein were not carried out. There is a paucity of literature regarding its mechanism, and treatment is largely supportive. Future research is warranted to better understand the mechanism, source, and optimal management of patients with this dreaded complication.

Conclusion

HLAC is an uncommon cause of bleeding in patients with plasma cell disorders that should be considered in those who present with bleeding diathesis and a prolonged TT. It may manifest at the time of initial presentation or later in the disease course and its severity may not correlate with the disease burden.

Table 2 Summary of coagulation abnormalities, treatment, and outcome of patients with heparin-like anticoagulant—literature review

	Author	Age	Gender	Diagnosis	Subtype	PT (s)	aPTT (s)	TT (s)	Fibrinogen (mg/dL)	At the time of diagnosis	Treatment	Outcome
1	Shen et al[13]	48	M	MM	IgD lambda	14	118	28.5		Yes	VCD	Alive
2	Torjemane et al[10]	55	M	MM	IgG lambda	14	63	65	267	No	VAD + protamine	Alive
3	Khoory et al[9]	68	F	MM	IgA kappa	12	58	>600	250		L phenylalanine mustard + corticosteroids	–
4	Chapman et al[6]	54	M	MM	IgG kappa	13.5	59	38	300	No	VMP	–
5	Kaufman et al[14]	55	M	PCL	–	14	>150	>120	345	Yes	FFP+ protamine + chemotherapy	Dead
7	Martínez-Martínez et al[18]	73	F	MM	IgG	–	75–97 at various time points	>180	–	Yes	Recombinant VIIa + chemotherapy	No further bleeds
8	Tefferi et al[12]	68	F	MM	IgA kappa	21	48	>600	138	No	Cryoprecipitate+ plasmapheresis + protamine	Dead (sepsis)
9	Tefferi et al[12]	47	M	MM	IgG lambda	25	44	>600	432		None	Dead (renal failure)
10	Tefferi et al[12]	78	F	MM	Kappa LC	28	48	>600	883			Death (bleeding)
9	Shen et al[13]	47	M	MM	IgG lambda	25	44	>600	432	Yes	Corticosteroids	Dead
10	Willner and Chisti[19]	62	F	MM	IgG kappa	12	44.3	32.3	228	No	Protamine	No further bleeds
11	Goddard et al[17]	57	M	MM	–	16		180		No	Protamine+ PLEX+ chemo	Dead

Abbreviations: aPTT, activated partial thromboplastin time; FFP, fresh frozen plasma; IgG, immunoglobulin G; MM, multiple myeloma; PCL, plasma cell leukemia; PLEX, plasma exchange; PT, prothrombin time; TT, thrombin time; VAD, vincristine, adriamycin, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VMP, bortezomib, melphalan, prednisolone.

Declaration of Patient Consent
Yes.

Funding
None.

Conflict of Interest
None.

References

1 Saif MW, Allegra CJ, Greenberg B. Bleeding diathesis in multiple myeloma. J Hematother Stem Cell Res 2001;10(05):657–660
2 Tefferi A, Owen BA, Nichols WL, Witzig TE, Owen WG. Isolation of a heparin-like anticoagulant from the plasma of a patient with metastatic bladder carcinoma. Blood 1989;74(01):252–254
3 Rodgers GM, Corash L. Acquired heparinlike anticoagulant in a patient with metastatic breast carcinoma. West J Med 1985;143 (05):672–675
4 de Prost D, Katlama C, Pialoux G, Karsenty-Mathonnet F, Wolff M. Heparin-like anticoagulant associated with AIDS. Thromb Haemost 1987;57(02):239–239
5 Perkins HA, MacKenzie MR, Fudenberg HH. Hemostatic defects in dysproteinemias. Blood 1970;35(05):695–707
6 Chapman GS, George CB, Danley DL. Heparin-like anticoagulant associated with plasma cell myeloma. Am J Clin Pathol 1985;83 (06):764–766
7 Rahman S, Veeraballi S, Chan KH, Shaaban HS. Bleeding diathesis in multiple myeloma: a rare presentation of a dreadful emergency with management nightmare. Cureus 2021;13(03):e13990
8 Saadalla A, Seheult J, Ladwig P, et al. Sialic acid-bearing paraproteins are implicated in heparin-like coagulopathy in patients with myeloma. Blood 2020;136(17):1988–1992
9 Khoory MS, Nesheim ME, Bowie EJ, Mann KG. Circulating heparan sulfate proteoglycan anticoagulant from a patient with a plasma cell disorder. J Clin Invest 1980;65(03):666–674
10 Torjemane L, Guermazi S, Ladeb S, et al. Heparin-like anticoagulant associated with multiple myeloma and neutralized with protamine sulfate. Blood Coagul Fibrinolysis 2007;18(03): 279–281
11 Mumford AD, O'Donnell J, Gillmore JD, Manning RA, Hawkins PN, Laffan M. Bleeding symptoms and coagulation abnormalities in 337 patients with AL-amyloidosis. Br J Haematol 2000;110(02): 454–460
12 Tefferi A, Nichols WL, Bowie EJ. Circulating heparin-like anticoagulants: report of five consecutive cases and a review. Am J Med 1990;88(02):184–188
13 Shen H, Wu C, Chen L, Zhang R. Acquired heparin-like anticoagulation process in a patient with multiple myeloma: a case report and literature review. Transl Cancer Res 2020;9(11): 7366–7371https://tcr.amegroups.com/article/view/45909 cited 2022Mar27 [Internet]
14 Kaufman PA, Gockerman JP, Greenberg CS. Production of a novel anticoagulant by neoplastic plasma cells: report of a case and review of the literature. Am J Med 1989;86(05):612–616
15 Palmer RN, Rick ME, Rick PD, Zeller JA, Gralnick HR. Circulating heparan sulfate anticoagulant in a patient with a fatal bleeding disorder. N Engl J Med 1984;310(26):1696–1699
16 Llamas P, Outeiriño J, Espinoza J, Santos AB, Román A, Tomás JF. Report of three cases of circulating heparin-like anticoagulants. Am J Hematol 2001;67(04):256–258
17 Goddard IR, Stewart WK, Hodson BA, Dawes J. Plasma exchange as a treatment for endogenous glycosaminoglycan anticoagulant induced haemorrhage in a patient with myeloma kidney. Nephron J 1990;56(01):94–96
18 Martínez-Martínez I, González-Porras JR, Cebeira MJ, et al. Identification of a new potential mechanism responsible for severe bleeding in myeloma: immunoglobulins bind the heparin binding domain of antithrombin activating this endogenous anticoagulant. Haematologica 2016;101(10):e423–e426
19 Willner CA, Chisti MM. Treatment of bleeding diathesis associated with a heparin-like anticoagulant in plasma cell neoplasia using protamine. Case Rep Hematol 2018;2018:4342301

