Received: 25 September 2023 | Revised: 6 December 2023 | Accepted: 15 December 2023

DOI: 10.1002/ccr3.8361

CASE REPORT

Clinical Case Reports Open Access WILEY

Acquired von Willebrand syndrome in a patient with monoclonal gammopathy of unknown significance: A case report

Garima Gupta | **Janeesh Sekkath Veedu** | **Zena Chahine** | **Chaitanya Iragavarapu**

Division of Hematology and Oncology, University of Kentucky College of Medicine, Lexington, Kentucky, USA

Correspondence
Garima Gupta, Department of Hematology/Oncology, University of Kentucky, Markey Cancer Center CC402, 800 Rose Street, Lexington, KY 40536, USA.
Email: garima.gupta83@gmail.com

Abstract

Monoclonal gammopathy of uncertain significance associated acquired von Willebrand syndrome is a serious bleeding condition driven by immunological clearance of von Willebrand factor and has limited treatment options. We present a patient who achieved durable remission through eradication of the monoclonal paraprotein with clonal directed therapy with bortezomib.

KEYWORDS

acquired von Willebrand disease, bortezomib, IVIG, MGUS, MGUS-associated acquired von Willebrand syndrome, rituximab

1 | BACKGROUND

Acquired von Willebrand syndrome (AvWS) is a rare life-threatening bleeding disorder associated with hematological malignancies, autoimmune diseases, cardiovascular conditions among other causes.[1,2] Multiple cases of patients with monoclonal gammopathy of unknown significance (MGUS) and AvWS have been reported, with IgG being the most common sub-type.[3–5] While patients present at a later age and have no personal or family history of a bleeding diathesis, their laboratory abnormalities are similar to what is found in the congenital form of von Willebrand disease (vWD). Proposed underlying mechanisms of increased elimination of circulating von Willebrand factor (vWF) include autoantibodies that bind directly to vWF or antibodies that form complexes with factor VIII-vWF, both resulting in rapid immunological clearance.[6,7]

Management of MGUS-associated AvWS involves both short- and long-term bleeding control. Short-term treatment options typically include 1-deamino-8-d-arginine vasopressin (DDAVP), factor replacement therapy, plasmapheresis, immunosuppressants such as steroids and intravenous immunoglobulin (IVIG).[8,9] In a systematic review, IVIG was noted to have the highest clinical success rate of 85% compared to DDVAP and factor replacement.[3] While IVIG results in the most sustained response among these options, repeat doses are often required and relapses are frequent, which makes treatment challenging.[5,8] In order to achieve lasting results, therapies targeting suppression of the immunological process through elimination of the monoclonal plasma cell population driving it would appear reasonable. This could explain why rituximab has been found to be ineffective, as it does not target the plasma cell clone.[10–12] There are scarce data on use of other plasma cell-depleting agents, such as lenalidomide and bortezomib, in refractory cases.[3,12–16] Herein, we report a case of MGUS-associated AvWS successfully treated with bortezomib after short-term response to factor replacement in combination with IVIG and intolerance to rituximab. To our knowledge, there have only been two other cases described in the literature where bortezomib resulted in long-term remission of MGUS-associated AvWS, both in patients with IgG kappa MGUS.[12,15]

2 | CASE PRESENTATION

A 74-year-old female undergoing preoperative workup prior to an elective knee replacement surgery for significant osteoarthritis was found to an elevated activated partial thromboplastin time (aPTT) of 43 (normal range 26–34 s) in May 2018. She was not on anticoagulation or antiplatelet medications and denied a personal and family history of bleeding disorders. She had undergone multiple surgeries in the past with no bleeding complications. On further evaluation, laboratory testing was significant for an elevated aPTT of 47, which corrected on mixing study and low factor VIII activity of 4% (normal range 56%–191%), von Willebrand antigen (vWF:Ag) of 7% (normal range 50%–160%), and vWF ristocetin cofactor activity (vWF:RCo) of <10% (normal range 51%–121%). vWF multimers study revealed high molecular weight (MW) 9%, intermediate MW 12%, and low MW 80% multimers. While Types 2A and 2B vWD were considered, patient's laboratory defects were more severe than the pattern typically seen in those patients where the vWF:RCo is decreased out of proportion to vWF:Ag, the factor VIII activity may be normal or reduced and the high MW multimers are decreased on multimer electrophoresis. Therefore, given the absence of personal and family history of bleeding and these laboratory findings, a question of AvWS with no clear etiology was raised. She received vWF/FVIII complex prior to surgery twice with no improvement in vWF:Ag and factor VIII activity. vWF Ristocetin cofactor 1:1 mix was within normal limits ruling out presence of an inhibitor. She then received vWF/FVIII complex along with IVIG and successfully underwent a left knee replacement in August of 2018 and a right knee replacement in 2019 without any significant bleeding. Unfortunately, 2 years later, in 2021, our patient developed acute upper gastrointestinal (GI) bleed for which she received vWF/FVIII complex and IVIG with correction of coagulopathy for a brief period. For long-term management, she started on rituximab but developed a severe infusion reaction. The patient was not re-challenged with rituximab.

She then had recurrence of upper GI bleeding and got admitted to our hospital. She was stabilized with IVIG and vWF/FVIII complex. Patient underwent esophagogastroduodenoscopy (EGD) and colonoscopy, and no sources of an active bleed could be identified. Therefore, there was concern for intermittent bleeding from arteriovenous malformations (AVMs), however capsule endoscopy and push enteroscopy were negative as well. Incidentally on further review of prior testing from 2018, we noted that the patient had a circulating IgG kappa monoclonal paraprotein of 0.6 g/dL. Repeat serum electrophoresis and immunofixation were performed and confirmed a mild increase in the IgG kappa monoclonal paraprotein concentration to 0.9 g/dL. On further evaluation, she did not meet criteria for smoldering or active myeloma. Our working diagnosis at this time changed to MGUS-associated AvWS due to low levels of vWF:Ag, vWF:RCo, factor VIII activity, and increased small multimers along with the presence of a monoclonal protein. To eradicate this plasma cell clone, we began treatment with bortezomib 1.3 mg/m^2 and dexamethasone 40 mg (both on days 1, 8, 15, and 22). Bortezomib dose was reduced to 1 mg/m^2 starting Cycle 3 due to peripheral neuropathy. She completed three cycles of bortezomib with no further episodes of bleeding. In January 2022, the monoclonal paraprotein became undetectable and there was normalization of vWF:Ag, vWF:RCo and factor VIII activity. She was then actively followed with no recurrence of bleeding and maintained eradication of monoclonal paraprotein and resolution of AvWS with her last bortezomib dose being more than 18 months ago.

3 | DISCUSSION AND CONCLUSIONS

As previously stated, the pathophysiology of MGUS-associated AvWS likely involves accelerated immunologic clearance of circulating vWF. This explains why, in our patient, an autoantibody or a nonspecific antibody were not identified in vitro but suggested in vivo when she failed to respond to factor replacement. Antibodies bind either to the functional or non-functional domain of vWF, form immune complexes and are rapidly cleared by the reticuloendothelial system. Among antibodies, inhibitors have been reported to recognize the binding sites to glycoprotein (GP) Ib, collagen, and megakaryocyte- and platelet-specific integrin GP IIb-IIIa or CD41/CD61 ($\alpha_{IIb}\beta_3$).[17] An underlying immunological mechanism also clarifies why DDAVP, and factor replacement are not as effective as IVIG. As seen in our patient, factor replacement alone was ineffective but IVIG in combination with vWF/FVIII complex led to improvement in laboratory markers as well as bleeding control. Studies have demonstrated there may be selective binding of the monoclonal antibody to large vWF multimers, resulting in their clearance, a pattern similar to type 2A vWD,[3,6,18] which was also noted in our patient when multimeric analysis was performed.

To date, there are no standard guidelines on long-term management of MGUS-associated AvWS. As depicted in our case, IVIG and factor replacement only resulted in short-term control of bleeding and improvement in laboratory markers. This is because the culpable paraprotein remains viable as soon as the immunosuppressive effects of IVIG wear off. The longest response to IVIG has been reported to be 54 days.[19]

In our patient, targeting the plasma cell clone via proteasome inhibitor, bortezomib was effective and resulted in long-lasting control of MGUS-associated AvWS. In a previous publication, bortezomib was given at the same dose of 1.3 mg/m^2 as in our patient but on a different schedule of a 21 day cycle with treatment on days 1, 4, 8, and 11. While normalization of vWF-propeptide (vWFpp) and eradication of the paraprotein was achieved after three cycles of Bortezomib, treatment was continued for a total of six cycles.[12] In another report, bortezomib was given weekly at a higher dose of 1.5 mg/m^2 for a total of five cycles with a dose reduction to 1.3 mg/m^2 starting with cycle 3.[15] While due to differences in dosing schedules, direct comparisons cannot be made, our report does demonstrate that bortezomib is effective at a dose of 1.3 mg/m^2 and one can consider discontinuing treatment after there is evidence of normalization of vWF and factor VIII activity on laboratory testing, complete removal of the monoclonal paraprotein and no recurrence of bleeding.

Interestingly, in another report of a patient with IgG kappa MGUS-associated AvWS, bortezomib was ineffective at a dose of 1.3 mg/m^2 given biweekly in cycles of 2 weeks on and 1 week off and was instead successfully treated with lenalidomide.[13] There is also evidence that suggests lenalidomide has anti-angiogenic activity and was effective in controlling intractable GI bleeding in a patient who had persistent bleeding despite eradication of the paraprotein with rituximab.[16]

Our case demonstrates that clonal-directed therapy with three cycles of bortezomib resulted in eradication of the paraprotein and a durable remission of MGUS-associated AvWS. Alternatively, treatment with lenalidomide can also be considered depending on baseline clinical status of the patient such as presence of neuropathy. Combination treatments typically used in myeloma management are most likely too aggressive and there is no evidence to favor them over monotherapy with bortezomib.

AUTHOR CONTRIBUTIONS

Garima Gupta: Conceptualization; project administration; writing – original draft; writing – review and editing. **Janeesh Sekkath Veedu:** Writing – review and editing. **Zena Chahine:** Writing – review and editing. **Chaitanya Iragavarapu:** Supervision; writing – review and editing.

ACKNOWLEDGMENTS

The authors thank the patient and her family for their participation.

FUNDING INFORMATION

Not applicable.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

This study qualified for ethics approval exemption, and the index patient gave informed consent.

CONSENT

Written informed consent was obtained from the patient to publish this report per the journal's patient consent policy.

DECLARATIONS

A pre-print of this manuscript is available on Research Square at: https://doi.org/10.21203/rs.3.rs-3220729/v1.

ORCID

Garima Gupta https://orcid.org/0000-0002-8730-006X

REFERENCES

1. Horiuchi H, Doman T, Kokame K, Saiki Y, Matsumoto M. Acquired von Willebrand syndrome associated with cardiovascular diseases. *J Atheroscler Thromb*. 2019;26(4):303-314. doi:10.5551/jat.RV17031
2. Michiels JJ, Budde U, van der Planken M, van Vliet HH, Schroyens W, Berneman Z. Acquired von Willebrand syndromes: clinical features, aetiology, pathophysiology, classification and management. *Best Pract Res Clin Haematol*. 2001;14(2):401-436. doi:10.1053/beha.2001.0141
3. Abou-Ismail MY, Rodgers GM, Bray PF, Lim MY. Acquired von Willebrand syndrome in monoclonal gammopathy-a scoping review on hemostatic management. *Res Pract Thromb Haemost*. 2021;5(2):356-365. doi:10.1002/rth2.12481
4. Jeryczynski G, Agis H, Eichinger-Hasenauer S, Krauth MT. Successful treatment of acquired von Willebrand syndrome associated with monoclonal gammopathy: breaking a dangerous bond. *Wien Klin Wochenschr*. 2022;134(11–12):478-482. doi:10.1007/s00508-022-02012-3
5. Voisin S, Hamidou M, Lefrancois A, Sigaud M, Mahe B, Trossaert M. Acquired von Willebrand syndrome associated with monoclonal gammopathy: a single-center study of 36 patients. *Medicine (Baltimore)*. 2011;90(6):404-411. doi:10.1097/MD.0b013e3182397166
6. Gan TE, Sawers RJ, Koutts J. Pathogenesis of antibody-induced acquired von Willebrand syndrome. *Am J Hematol*. 1980;9(4):363-371. doi:10.1002/ajh.2830090403
7. Mannucci P, Lombardi R, Bader R, et al. Studies of the pathophysiology of acquired von Willebrand's disease in seven patients with lymphoproliferative disorders or benign monoclonal gammopathies. *Blood*. 1984;64(3):614-621. doi:10.1182/blood.V64.3.614.614

8. Federici AB, Stabile F, Castaman G, Canciani MT, Mannucci PM. Treatment of acquired von Willebrand syndrome in patients with monoclonal gammopathy of uncertain significance: comparison of three different therapeutic approaches. *Blood*. 1998;92(8):2707-2711.
9. Tiede A, Rand JH, Budde U, Ganser A, Federici AB. How I treat the acquired von Willebrand syndrome. *Blood*. 2011;117(25):6777-6785. doi:10.1182/blood-2010-11-297580
10. Grimaldi D, Bartolucci P, Gouault-Heilmann M, Martin-Toutain I, Khellaf M, Godeau B. Rituximab failure in a patient with monoclonal gammopathy of undetermined significance (MGUS)-associated acquired von Willebrand syndrome. *Thromb Haemost*. 2008;99(4):782-783. doi:10.1160/TH07-07-0456
11. Mazoyer E, Fain O, Dhote R, Laurian Y. Is rituximab effective in acquired von Willebrand syndrome? *Br J Haematol*. 2009;144(6):967-968. doi:10.1111/j.1365-2141.2008.07538.x
12. Ojeda-Uribe M, Caron C, Itzhar-Baikian N, Debliquis A. Bortezomib effectiveness in one patient with acquired von Willebrand syndrome associated to monoclonal gammopathy of undetermined significance. *Am J Hematol*. 2010;85(5):396. doi:10.1002/ajh.21692
13. Green A, Shen Y-MP, Nelson AT, et al. Successful use of lenalidomide to treat refractory acquired von Willebrand disease associated with monoclonal gammopathy. *Ann Hematol*. 2022;101(12):2627-2631. doi:10.1007/s00277-022-04991-9
14. Lavin M, Brophy TM, Rawley O, et al. Lenalidomide as a novel treatment for refractory acquired von Willebrand syndrome associated with monoclonal gammopathy. *J Thromb Haemost*. 2016;14(6):1200-1205. doi:10.1111/jth.13317
15. Saldanha A, Veiga ME, Okazaki E, et al. Acquired von Willebrand syndrome secondary to monoclonal gammopathy of undetermined significance: long-term remission after treatment with bortezomib. *J Thromb Thrombolysis*. 2023;55(4):770-774. doi:10.1007/s11239-023-02799-6
16. Thomas W, Warner E, Cameron E, Symington E. Successful treatment of acquired von Willebrand disease with lenalidomide leading to dramatic resolution of intractable gastrointestinal bleeding: a case report. *Haemophilia*. 2018;24(3):e140-e142. doi:10.1111/hae.13464
17. Mohri H. Acquired von Willebrand syndrome: its pathophysiology, laboratory features and management. *J Thromb Thrombolysis*. 2003;15(3):141-149. doi:10.1023/B:THRO.0000011369.70824.e6
18. van Genderen PJ, Terpstra W, Michiels JJ, Kapteijn L, van Vliet HH. High-dose intravenous immunoglobulin delays clearance of von Willebrand factor in acquired von Willebrand disease. *Thromb Haemost*. 1995;73(5):891-892.
19. Désage S, Le Quellec S, Karlin L, Lienhart A, Meunier S, Rugeri L. A prolonged treatment response in acquired von Willebrand syndrome. *Hamostaseologie*. 2019;39(4):409-412. doi:10.1055/s-0039-1696960

How to cite this article: Gupta G, Veedu JS, Chahine Z, Iragavarapu C. Acquired von Willebrand syndrome in a patient with monoclonal gammopathy of unknown significance: A case report. *Clin Case Rep*. 2024;12:e8361. doi:10.1002/ccr3.8361