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CASE REPORT

Intravenous Immunoglobulin offers temporary improvement in acquired von Willebrand syndrome due to monoclonal gammopathy: A case report

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Abstract

Acquired von Willebrand syndrome (AVWS) is a bleeding disorder in which an underlying condition induces a quantitative or qualitative deficiency in the von Willebrand factor. This case demonstrates the rare diagnosis of AVWS due to an Immunoglobulin G monoclonal gammopathy in an elderly woman who presented with significant gastrointestinal bleeding. Originally thought to be type 1 von Willebrand disease, this case provides a cautious example to clinicians that without a detailed history or an understanding of the associated laboratory work-up, AVWS may be missed with potentially fatal consequences. Fortunately, AVWS was recognized and treated with intravenous immunoglobulin with a resolution of bleeding.

KEYWORDS
bleeding disorders, clinical hematology, coagulation, immunoglobulin, MGUS, platelet aggregation

1 | INTRODUCTION

Acquired von Willebrand syndrome (AVWS) is a distinct bleeding disorder that represents 1%–5% of all cases of von Willebrand disease (VWD) [1]. Frequently associated with an underlying autoimmune, lymphoproliferative, or myeloproliferative disorder [2], differentiating AVWS from VWD can prove difficult due to the clinical and laboratory similarities that may exist during the initial evaluation [3]. Although fatalities from bleeding due to AVWS have seldom been reported [4], instituting appropriate therapy [5–7] to control bleeding is paramount in mitigating the risk of adverse events. The case herein highlights the work-up and management of a patient originally believed to have VWD but was later diagnosed with AVWS.

1.1 | Clinical case

A 69-year-old woman with morbid obesity presented for further evaluation of presumed VWD. A few months prior, she was hospitalized for weakness and melena, with a work-up notable for acute anemia. Endoscopy revealed an oozing angiodysplasia in the upper gastrointestinal tract that was ligated. She required readmission three subsequent times for recurrent, severe gastrointestinal bleeding necessitating multiple red blood cell transfusions.

She then presented to an outpatient hematologist and was noted to have a prolonged activated partial thromboplastin time (aPTT) of 75 s (27–38 s; Table 1, Column A), a prothrombin time of 11.1 s (9.8–12.8 s), factor VIII (FVIII:C) of 16% (55%–180%), von Willebrand factor antigen (VWF:Ag) of 13% (50%–220%), and GP1bM activity (VWF:GP1bM) of 10% (52%–180%) raising concern for type 1 VWD (Table 1, Column A). Factors IX, XI, and XII were normal. A repeat endoscopy was planned in addition to a DDAVP challenge, however she was first referred to us.

Upon inquiry, she denied any major bleeding during childhood or a family history of bleeding diathesis. Her menstrual cycles were normal and prior surgeries, including cholecystectomy and a hernia repair in 2004, were uneventful. She developed post-menopausal bleeding in 2017 and underwent dilation and curettage with a normal endometrial

TABLE 1 Relevant laboratory studies obtained during the initial stages of diagnosis and following treatment. Column A represents the initial labs drawn by an outside hematologist, column B represents repeat labs drawn once seen for a second opinion, and column C represents labs drawn two weeks following treatment with intravenous immunoglobulin (IVIG).

Lab	A. Initial labs	B. Repeat labs	C. Labs following IVIG	Reference range
aPTT	75 s	76 s * *Normalized with mixing study.	Not obtained	27–38 s
FVIII:C	16%	14%	236%	55%–180%
VWF:Ag	13%	19%	229%	50%–220%
vWF:GP1bM	10%	4%	160%	52%–180%
HMW Multimer study	Not obtained	Absent	Present	Present
VWF:Ag pro-peptide	Not obtained	215%	Not obtained	65%–183%

biopsy. Since then, two dental extractions and carpal tunnel surgery in 2021 were complicated by post-procedure bleeding. Additionally, she endorsed ecchymoses following immunizations and intractable nosebleeds over the past year.

Additional work-up by us showed correction of a prolonged aPTT with a mixing study. Repeated workup for VWD showed persistently low VWF:Ag, FVIII:C, and VWF:GP1bM (Table 1, Column B), and multimer analysis detected the absence of high molecular weight multimers (HMWM; Figure 1). Given the absence of childhood bleeding and the presentation of significant bleeding later in life, AVWS was suspected. VWF:Ag pro-peptide was reported at 215% (65-183%). As part of a broad workup, she was found to have a free lambda light chain of 5.70 mg/dL (0.57–2.63 mg/dL), free kappa light chain of 2.85 mg/dL (0.33–1.94 mg/dL), and M-protein of 0.2 g/dL (0 g/dL), which was determined to be monoclonal Immunoglobulin G (IgG) lambda in the gamma region via serum immunofixation. Total IgG, IgA, and IgM were within their respective reference ranges.

Due to concern for an AVWS secondary due to an underlying IgG monoclonal gammopathy, we treated her with intravenous immunoglobulin (IVIG) at a dose of 1 g/kg over two consecutive days. Repeat VWD testing revealed an improvement in VWF:Ag, FVIII:C, VWF:GP1bM, and normalization of HMWM (Table 1, Column C and Figure 1). She had no further bleeding, and IVIG was continued every 4 weeks.

2 | DISCUSSION

AVWS is characterized by functional or structural deficiencies in the von Willebrand factor (VWF) that are secondary to an underlying condition [5]. Etiologies include a variety of autoimmune disorders, cardiovascular disorders such as aortic stenosis, myeloproliferative or lymphoproliferative disorders such as essential thrombocythemia and monoclonal gammopathy, respectively [7]. The pathogenesis of AVWS depends on the underlying cause, with potential mechanisms including proteolytic cleavage of VWF in areas of high shearing forces as seen in aortic stenosis [8], or the development of autoantibodies against VWF that either inactivate it or form immune complexes that are cleared, as seen in cases associated with lymphoproliferative and autoimmune disorders [9].

Often, it is not possible to distinguish AVWS from VWD from laboratory work-up alone, thus a negative family history of any bleeding disorders or a new presentation of bleeding diathesis should prompt clinicians to suspect an acquired syndrome [7]. Both disorders can present with an isolated prolonged aPTT in addition to decreased VWF:Ag and FVIII:C levels. Analysis of VWF:Ag levels in conjunction with VWF:GP1bM can help to distinguish between the various types of VWD, with a decreased ratio of VWF:GP1bM to VWF:Ag level supportive of a functional defect seen in the type 2 VWD subtypes [10, 11]. HMWM, which facilitates contact between vWF and both collagen and platelet receptors, further helps characterize type 2 VWD [12], as HMWM is absent in type 2A or 2B, but present in 2 M and 2N. Increased VWF:Ag pro-peptide, which is involved in the intracellular processing and multimerization of vWF, is suggestive of increased plasma vWF destruction or clearance rather than an intrinsic deficiency of vWF production, and may be seen in type 2N [7, 11–13].

Our patient's repeat labs showed VWF:GP1bM to VWF:Ag ratio of 0.21 as well as absent HMWM, more suggestive of type 2 VWD. However, the lack of prior menorrhagia or surgical bleeding with a late onset of epistaxis, gastrointestinal hemorrhage, and post-operative bleeding favored an acquired etiology. Additionally, the ratio of VWF:Ag propeptide to VWF:Ag is elevated, indicative of increased clearance of VWF rather than a quantitative VWF deficit, further supporting a diagnosis of AVWS [14]. Her complete blood count showed no evidence to suggest a lymphoproliferative disorder, thyroid stimulating hormone was within normal range, and an echocardiogram showed no evidence of valvular disease, all of which eliminated potential causes. Further work-up, however, revealed an underlying monoclonal gammopathy of undetermined significance as the suspected etiology. A bone marrow biopsy is planned to definitively determine whether the patient has MGUS or a more advanced plasma cell dyscrasia such as smoldering myeloma, however, her relatively low M-protein of 0.2 g/dL and the absence of end-organ damage make this less likely.

The mechanism of AVWS due to MGUS and other plasma cell dyscrasias is complex and may vary between patients. Dicke et al. (2016) report that accelerated immunologic clearance led to AVWS

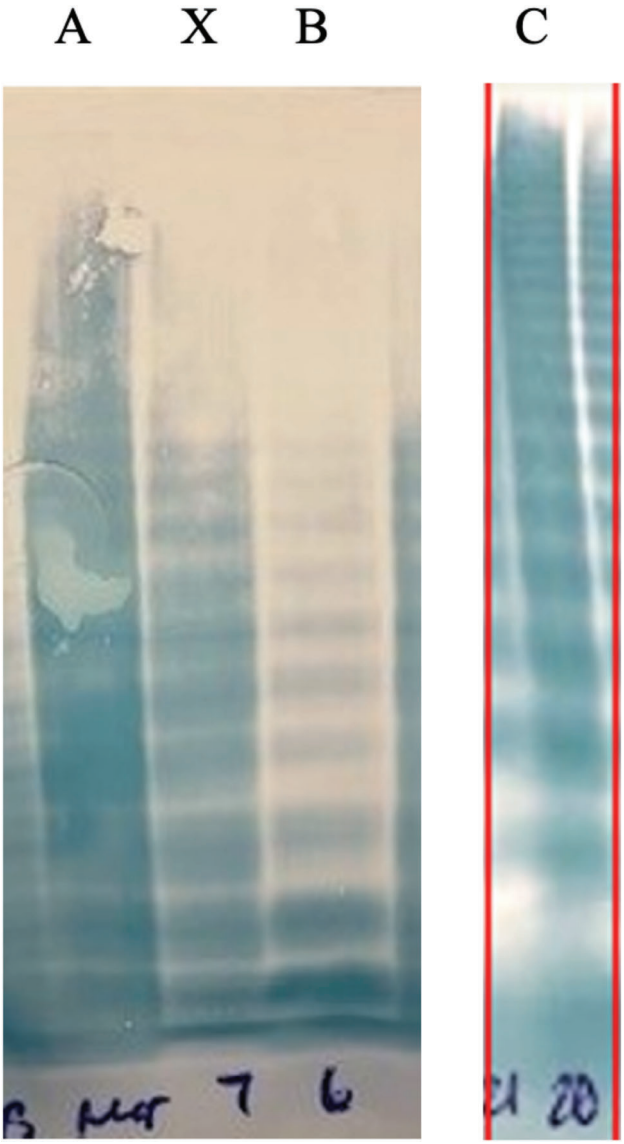

FIGURE 1 Von Willebrand multimer analysis via gel electrophoresis. Column A represents a normal sample with present multimers, with Column B representing the patient's absent multimers. Column C represents restoration of the patient's multimers following treatment with intravenous immunoglobulin (IVIG). Note Column X represents a separate patient's sample.

in one IgG MGUS patient, which responded to the administration of IVIG [15]. However, a second IgG MGUS patient had a less optimal response to IVIG, suggestive of an alternative mechanism. Additional mechanisms include plasmin-mediated degradation of VWF causing AVWS and paraprotein-induced interference between platelet GP1b and VWF or VWF and collagen [15, 16].

Treatment of AVWS is dependent on the cause. For example, steroids or cyclophosphamide may be indicated in AVWS caused by rheumatologic entities such as systemic lupus erythematosus, whereas chemotherapy may be used in cases associated with lymphoproliferative or myeloproliferative disorders [7]. In this case, the patient's symptoms improved and her testing normalized following the administration of IVIG, which can prevent the increased clearance of VWF in the liver associated with this subtype of AVWS [17]. IVIG characteristically induces a response that lasts only two to three weeks [18], necessitating repeated infusions or alternative agents. In this case, FVIII:C approximately two weeks after IVIG treatment was 236% (Table 1 and column C), whereas it declined to pre-treatment levels approximately one month after IVIG treatment, consistent with the literature.

Alternatives to IVIG that produce durable responses include cyclophosphamide and dexamethasone or bortezomib, the latter of which has been shown to induce a response lasting at least two years in a case of refractory to both cyclophosphamide and dexamethasone [19]. Additionally, the combination of lenalidomide and dexamethasone has been shown to induce a response lasting at least two years in a case that was refractory to both bortezomib followed by rituximab [20]. In other cases, daratumumab has been used as part of a multi-drug regimen that has been shown to be able to elicit a more durable response [21]. With these treatment options, response to therapy may take weeks to months since these therapies target the clonal cell population and thus decrease the production of the monoclonal protein. Multiple reports indicate that the response rate of patients with AVWS induced by MGUS to IVIG is high albeit with limited study sizes, with one report showing six out of six patients with AVWS secondary to IgG MGUS exhibiting a measurable response [22], and another with two out two patients exhibiting a response [23]. It is important to note that in general, response to IVIG is noted mainly in IgG MGUS [23]. Therefore, IVIG may reasonably be considered a first-line therapeutic in patients with AVWS secondary to IgG MGUS given its high success rate and milder side effect profile when compared with other cytotoxic agents. However, in patients who necessitate a more sustained response, alternative therapies can be considered simultaneously so that bleeding may be controlled with IVIG before the alternative targeted therapies begin to take effect.

In the setting of gastrointestinal hemorrhage, which may occur due to the known association of VWD and AVWS with arteriovenous malformations [24], it is imperative to understand the best method to restore hemostasis. IVIG has been shown to be the preferred agent in acute bleeding or preoperative management, whereas DDAVP or factor replacement therapy should only be considered to help control minor bleeds or in cases of drug shortage [25]. Given the short duration of benefits with IVIG, it is best to plan procedures and confirm response to IVIG in advance of the procedure. Further, it would be prudent to maintain the patient on IVIG infusion every 3–4 weeks post-procedure to maintain hemostasis. In this case, the patient was planned for a repeat endoscopy without IVIG pre-treatment, which could have led to uncontrolled bleeding.

3 | CONCLUSION

The ability to differentiate AVWS from VWD may be challenging, nonetheless, it is critically important to be able to distinguish these diseases. A detailed history in addition to an understanding of the

various laboratory studies used to establish VWD can aid the practicing hematologist in accurate diagnosis.

AUTHOR CONTRIBUTIONS

Kevin Zablonski wrote the manuscript, which was revised by Aarthi Rajkumar and Lalitha Nayak. The patient's medical management was directed by attending physician Lalitha Nayak. All authors interviewed the patient.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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Verbal consent was obtained for publishing.

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