Successful use of lenalidomide to treat refractory acquired von Willebrand disease associated with monoclonal gammopathy

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Abstract

Acquired von Willebrand syndrome (AVWS) is a rare hematologic disorder characterized by quantitative or qualitative defects of von Willebrand factor (vWF), a protein crucial for normal hemostasis. AVWS has been described in association with several pathologic entities with varied mechanisms. Among these, lymphoproliferative disorders are the most common, with monoclonal gammopathy of undetermined significance (MGUS) being the most frequently reported. AVWS in this setting is commonly associated with the development of bleeding that is clinically challenging to manage due to accelerated clearance of vWF, limiting the utility of many conventional treatment modalities such as DDAVP or vWF/FVIII. We report a case of a 43-year-old male who was sent to our institution for new-onset easy bruising and laboratories concerning for von Willebrand disease (vWD). Further diagnostic workup revealed evidence of an IgG monoclonal gammopathy and findings suggestive of vWF inhibition. Ultimately, he was found to have monoclonal gammopathy of clinical significance (MGCS)-associated AVWS refractory to conventional treatment but responsive to lenalidomide and dexamethasone. This case suggests that lenalidomide may be suitable for patients with AVWS secondary to MGCS.

Keywords Acquired von Willebrand syndrome · Dexamethasone · Lenalidomide · Monoclonal gammopathy of undetermined significance · Monoclonal gammopathy of clinical significance

Introduction

vWD is the most common congenital bleeding disorder, with a prevalence approaching 1% of the population [1]. It is characterized by defects in the quantity or quality of vWF, a protein essential for hemostasis [2]. Congenital forms of vWD predominate, with AVWS only accounting for an estimated 5% of all diagnoses [3]. AVWS has been associated with several pathologic entities with varied mechanisms.

Monoclonal gammopathy is characterized by monoclonal immunoglobulin in serum or urine produced by an abnormal population of clonal B cells. These monoclonal B cells may remain quiescent without associated clinical complications (i.e., MGUS). Alternatively, this B-cell population may expand, leading to end-organ damage, dysfunction, and clinical manifestation (lymphoproliferative disorders, most notably Waldenstrom macroglobulinemia or multiple myeloma). An alternative clinical presentation, MGCS, is increasingly recognized, in which a broad spectrum of end-organ damage and clinical complications may occur despite the absence of clonal expansion [4].

In monoclonal gammopathies such as MGCS, or multiple myeloma, AVWS arises from accelerated clearance of vWF. This accelerated clearance of vWF poses a significant challenge in medical management as the efficacy of therapies aimed at repleting vWF concentrations, such as vWF/FVIII or DDAVP, is often transient and ineffective [5]. Consequently, alternative therapeutic modalities are needed, particularly when attempting to obtain durable remission of AVWS. Herein, we report a case of AVWS successfully treated with lenalidomide. This is only the seventh case describing the use of lenalidomide in MGCS-associated AVWS [6–9].
Case report

A 43-year-old male with no significant past medical presented with new-onset, spontaneous bruising over several months. The patient has a history of multiple surgical challenges without bleeding complications and no prior personal or familial bleeding history. Laboratory evaluation at the outside facility demonstrated decreased vWF Antigen (vWF:Ag) and vWF activity (vWF:RCo) of 24% and 10%, respectively. vWF multimer analysis showed a normal multimer distribution. These findings prompted a referral to our hematologic clinic for evaluation. Laboratory evaluation revealed a von Willebrand pro-peptide (vWF:pp) level of 76 IU/dL (RR 62-183 IU/dL); vWFpp/Ag ratio of 3.2; vWF:Ag < 20% and vWF:RCo of 27%. Repeat vWF multimer analysis demonstrated a low, intermediate, and high molecular weight distribution of 44%, 44%, and 12%, respectively, consistent with a type 2A pattern of VWD. An echocardiogram excluded valve disease. Relative to the baseline vWF:RCo < 20%, immediate and incubated 1:1 mixing studies showed only moderate correction (36% and 35%, respectively), suggesting the presence of an inhibitor. Serum protein electrophoresis showed an IgG kappa monoclonal paraprotein of 0.61 g/dL, consistent with a monoclonal gammopathy. Immunofixation electrophoresis demonstrated an IgG component in the beta fraction, a common finding in the presence of immune complexes. IgA, IgG, and IgM levels were 69 mg/dL, 883 mg/dL, and < 25 mg/dL, respectively. Kappa and lambda serum-free light chains were 12.5 mg/L and 7.7 mg/L, respectively, with a kappa to lambda ratio of 1.6. Bone marrow biopsy and flow cytometry revealed a minute population (< 1% cellularity) of monoclonal plasma cells, consistent with a diagnosis of IgG MGCS. Cytogenetic analysis revealed a normal male karyotype without clonal immunoglobulin gene rearrangement.

Following his initial hematologic workup and subsequent diagnosis, he did not experience any additional episodes of spontaneous bleeding nor required any hemostatic intervention. Repeat multimer analysis 3 years later revealed low, intermediate, and high molecular weight multimer distribution of 54%, 41%, and 5%, respectively. At this time, vWFpp was 109 IU/dL, and vWF:Ag and vWF:RCo were both 32% (vWFpp/Ag ratio of 3.4). He underwent several interventions, including a bursal hip injection, an esophagogastroduodenoscopy, and multiple rhizotomies without significant bleeding complications with prophylactic supplementation of FVIII/vWF complex (25–30 u/kg, Humate P, CSL Behring, King of Prussia, PA).

However, subsequently, despite receiving a prophylactic dose of FVIII/vWF complex (30 u/kg) before hip abductor tendon repair and post-surgical dosing (30 u/kg every 12 h), he developed post-operative bleeding with a marked hemoglobin decrease from 16.6 to 9.6 g/dL and required admission to the hospital for observation. Following admission, serial vWF:RCo assessments revealed baseline, 1-h post-infusion, and 4-h post-infusion levels of < 20%, 38%, and < 20%, respectively, suggesting either consumption or inhibition of vWF. He was treated with tranexamic acid (1300 mg, q8hrs) and FVIII/vWF complex (60 u/kg, every 8 h for 3 days) with the resolution of bleeding.

Later, he presented with recurrent, episodic gum bleeding and epistaxis over 6 months, with laboratory evaluation showing an IgG Kappa monoclonal paraprotein up to 0.70 g/dL. These findings and the continued clinical bleeding prompted the initiation of anti-plasma cell therapy with bortezomib (1.3 mg/m² biweekly in cycles of 2 weeks on and 1 week off). Following 6-cycles of bortezomib, IgG Kappa paraprotein persisted at 0.49 g/dL with low levels of vWF:Ag and vWF:RCo < 20%. Therefore, he was transitioned from bortezomib to rituximab (375 mg/m² weekly for 4 doses). This provided a mild transient increase in vWF:Ag with a peak of 41.7% at week 3 without improvement in vWF:RCo. By week 4, vWF:Ag had declined to 32.5%. Due to the lack of response after more than 4 weeks, additional therapies were considered.

Following interdisciplinary discussions, treatment with lenalidomide combined with dexamethasone was initiated based on a previous report describing the success of this approach [5]. Lenalidomide (25 mg daily, 28-day cycles, on-therapy days 1–21, off-therapy days 22–28) and dexamethasone (40 mg weekly) were initiated. At the time of initiation, vWF:Ag and vWF:RCo were both < 20%. Following 3 cycles, IgG Kappa paraprotein declined from 0.60 g/dL to < 0.30 g/dL; vWF:Ag increased to 31%; and vWF:RCo remained < 20%. Following 5 cycles, vWF:Ag and vWF:RCo had increased to 90% and 40%, and the M protein had declined to < 0.30 g/dL (Fig. 1).

After 7 cycles of lenalidomide and dexamethasone, he was admitted with respiratory distress secondary to a SARS-CoV-2 infection and required mechanical ventilation. Lenalidomide and dexamethasone were discontinued due to concerns for immunosuppression. Notably, dexamethasone was stopped before its established role in managing COVID-19. Following treatment with remdesivir, he recovered and was discharged. Neither lenalidomide nor dexamethasone was reinitiated. Laboratory evaluation demonstrated vWF:Ag and vWF:RCo levels of 241% and 249%, respectively, a finding likely explained by the extensive inflammation and acute phase response associated with severe COVID-19. This marked increase in antigen and activity levels was transient, with normalization of these values corresponding with the resolution of our patient’s acute infection. Over the nearly
3 years following discontinuation of lenalidomide and dexamethasone, M-protein remains undetectable, while vWF:Ag and vWF:RCo remain within or slightly above the reference range (127% and 157%, respectively), and the patient has had no demonstrable bleeding episodes.

Discussion

Findings from our case suggest that lenalidomide may serve as a viable treatment option in MGCS-associated AVWS. Despite treatment with FVIII/vWF concentrate, rituximab, and bortezomib, our patient demonstrated a limited response in vWF:Ag or vWF:RCo or IgG paraprotein plasma concentrations. However, after receiving lenalidomide and dexamethasone treatment, our patient exhibited a progressive normalization of vWF:Ag and vWF:RCo laboratory values. These findings were accompanied by the resolution of recurrent mucocutaneous bleeding episodes. Moreover, our patient maintained normal laboratory values without bleeding for more than 2 years despite discontinuation of lenalidomide and dexamethasone therapy.

Findings from our case are significant, as conventional therapies such as DDAVP and vWF/FIII frequently only show transient mitigation of bleeding, and correspondingly, correction of laboratory values is short-lived (< 6 h). These observations are likely due to the proposed pathologic mechanisms underlying lymphoproliferative-associated AVWS. First, studies have suggested that monoclonal antibodies produced by clonal cell populations preferentially bind to and accelerate the clearance of high molecular weight (HMW) and intermediate-vWF multimers [10]. Alternatively, studies have suggested that HMW-vWF multimers may be rapidly cleared through adsorption by neoplastic cells or platelets [11, 12]. Accordingly, therapies replacing vWF concentrations are likely to provide limited short-term benefits as repleted multimers are expected to undergo rapid clearance through antibody-dependent or antibody-independent mechanisms. These pathologic mechanisms could also explain why rituximab therapy, in most cases, including our own, has been largely ineffective, as it does not address clonal plasma cells responsible for monoclonal antibody synthesis [13].

The utilization of IVIG with the intent of eliminating or mitigating the effects of monoclonal antibodies has been one of the more commonly described adjunct therapies in lymphoproliferative-associated AVWS. The reported clinical efficacy of the use of IVIG alone for monoclonal gammopathies has been largely successful, with reported response rates of 76.5%, 100%, and 91.9% when treating major acute bleeding, acute minor bleeding, and in the perioperative setting, respectively [13]. However, given IVIG’s delayed onset of action (elevation in FVIII and vWF concentrations observed within 24–48 h), it is generally recommended that IVIG is
administered in concert with more immediate acting therapies such as DDAVP or vWF/FVIII concentrates [14]. Moreover, unlike the short-lived correction of laboratory values seen following treatment with DDAVP or vWF/FVIII concentrate, the effects of IVIG are maintained anywhere between 10 and 54 days [13, 15]. The reported evidence describing IVIG use is limited to acute bleeding episodes or perioperative optimization. The most appropriate dose and frequency of administration of IVIG to maintain long-term remission are unclear, and IV access requirements pose a logistical challenge. Lastly, while IVIG may inhibit the pathologic effects of monoclonal antibodies and modulate the function of B cell and T cells, it does not eliminate the clonal cell population responsible for monoclonal antibody production.

Therapies aimed at treating the underlying lymphoproliferative disorder may serve as a viable treatment option to maintain durable remission in patients with MGCS-associated AVWS recalcitrant to DDAVP or FVIII/vWF concentrate or in whom IVIG is not suited. The proteasome inhibitor bortezomib and immune modulators such as thalidomide and lenalidomide are widely utilized in treating multiple myeloma. In theory, bortezomib treatment would be ideal for eliminating clonal cell populations responsible for monoclonal antibody synthesis. However, in our case, similar to other reports, we observed little change in vWF antigen or activity or IgG Kappa paraprotein following 6 cycles of bortezomib therapy [13]. While lenalidomide’s mechanism of action in MGCS-associated AVWS is still uncertain, in addition to targeting clonal plasma cell populations, elevations in vWF and FVIII concentrations following treatment have been reported [16]. Additionally, the anti-angiogenic properties of lenalidomide are also likely to mitigate AVWS-associated angiodysplasia in patients with significant gastrointestinal bleeding [17–19]. Lenalidomide, as a treatment for long-term remission, may not be suitable for all patients. Given the reported risk of thromboembolism following lenalidomide treatment in patients with multiple myeloma, anticoagulants are often used [20]. Unfortunately, prophylactic anticoagulants are unlikely to be feasible in patients with MGCS-associated VWD that are already predisposed to bleeding. Consequently, lenalidomide is unlikely suited as a treatment in patients with an elevated risk of thromboembolism or a prior history of thromboembolism. In this setting, an alternative combinations of therapies including daratumumab, bortezomib, cyclophosphamide, and dexamethasone may be considered [21, 22].

Conclusion

In conclusion, our case suggests that lenalidomide may serve as a viable treatment modality to maintain long-term remission in patients with MGCS-associated AVWS, given its anti-angiogenic properties and capacity to treat underlying clonal plasma cells responsible for monoclonal antibody production. The literature describing lenalidomide utilization in MGCS-associated AVWS is limited. While early data is promising, several questions and concerns should be addressed before its widespread use, with studies evaluating its long-term efficacy and safety, including potential thromboembolic risks (especially in patients with underlying comorbidities).

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Declarations

Ethics approval This article does not contain any studies with human participants or animals.

Consent to participate Informed consent was obtained from the individual described in this manuscript.

Conflict of interest The authors declare no competing interests.

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