BMJ Case Reports

## TITLE OF CASE

**A Surprise Diagnosis of Acquired von Willebrand syndrome in a Patient Previously Thought to Have Type III Von Willebrand Disease: Evaluation and peri-procedural management**

## SUMMARY

Acquired von Willebrand syndrome (AVWS) is a rare disorder that is characterized by an acquired deficiency of von Willebrand factor. AVWS was suspected in a patient with type III von Willebrand disease (VWD) who did not respond to factor replacement therapy. Given the crucial implications for management, we describe this patient's clinical presentation, diagnosis, and peri-procedural management. To facilitate pericardiocentesis, peri-procedural management included steroids, intravenous immunoglobulin, and factor replacement therapy. In other patients with suspected immune-mediated AVWS, a similar approach may be effective. This case also highlights the importance of distinguishing AVWS from inherited VWD.

## BACKGROUND

Acquired von Willebrand syndrome (AVWS) is a non-inherited von Willebrand factor (VWF) deficiency caused by acquired changes in VWF synthesis, secretion, proteolysis, or clearance [1,2]. AVWS has been associated with lymphoproliferative, myeloproliferative, cardiovascular, neoplastic, and immunologic diseases [3]. AVWS is often challenging to diagnose: Laboratory tests to diagnose von Willebrand disease (VWD), such as VWF activity and multimer analysis, do not readily distinguish between VWD and AVWS. Depending on the underlying mechanism of AVWS, specialized tests, such as VWF inhibitor screens, vary in diagnostic sensitivity and specificity [2]. Therefore, diagnosis of AVWS often relies heavily on clinical suspicion based on late onset of bleeding, lack of family history of bleeding disorders, and presence of AVWS-associated diseases. AVWS is also challenging to treat: Clinical management guidelines for AVWS are limited due to paucity of data, and AVWS responds to therapy differently depending on the underlying etiology. In the acute setting, in particular, variable response to therapy can make management decisions challenging [3–5]. Herein, we report on the diagnosis and peri-procedural management of a patient with a diagnosis of type III VWD who was suspected to have AVWS; his diagnosis of AVWS was confirmed by his response to immunosuppressive therapy.

## CASE PRESENTATION

A man in his late 60s presented to the Emergency Department with progressive dyspnea. Physical exam was notable only for pulsus paradoxus and 4+ bilateral lower extremity edema. Vitals and relevant diagnostic studies on admission are listed in Table 1. His echocardiogram revealed a large pericardial effusion. He was also noted to have a dilated inferior vena cava with diastolic collapse of the right atrium and right ventricular outflow tract. Given the high risk for cardiac tamponade, pericardiocentesis was planned. His past medical history was notable for hypertension, angiodysplasia causing recurrent gastrointestinal (GI) bleeds, iron deficiency anemia, monoclonal gammopathy of undetermined significance (MGUS), and type III VWD.

**Table 1. Vitals and relevant diagnostic tests on admission.** Ref = reference range.

| | |
|---|---|
| Temperature | 36.9 °C |
| Heart rate | 76 /min |
| Blood pressure | 176/93 mmHg |

| | |
|---|---|
| Respiratory rate | 21 /min |
| $SpO_2$ | 94% |
| White blood cells (Ref: 3,200–9,800 /mcL) | 5,100 /mcL |
| Hemoglobin (Ref: 13.7–17.3 g/dL) | 7.7 g/dL |
| Platelets (Ref: 150,000–450,000 /mcL) | 345,000 /mcL |
| Creatinine (Ref: 0.6–1.3 mg/dL) | 1.6 mg/dL |
| Prothrombin time (Ref: 9.5–13.1 seconds) | 13.9 seconds |
| Activated partial thromboplastin time (Ref: 26.8–37.1 seconds) | 56.9 seconds |
| Electrocardiogram | Normal sinus rhythm, left axis deviation, nonspecific T wave abnormalities |

With regard to his VWD history, he was first diagnosed with type III VWD four years prior to presentation. He did not have a family history of bleeding disorders. Prior to age 60, he had no abnormal bleeding history. He also had no bleeding with prior surgeries – a sinonasal surgery and a spinal fusion. In his early 60s, however, he developed GI bleeding. GI bleeding was evaluated with endoscopy, which showed small bowel angiodysplasias. Besides GI bleeding, significant bleeding history was not reported. After three years of recurrent GI bleeds, a work-up was concerning for VWD: VWF antigen was 9% (reference range: 50–217%), VWF activity (as measured by the ristocetin cofactor assay) < 20% (reference range: 42–200%), and factor VIII activity 6% (reference range: 50–217%). VWF multimer analysis showed increased intensity of the first oligomer band, with markedly reduced intensity of the other low, moderate, and high molecular weight multimers. This pattern was most consistent with type III VWD. Given this diagnosis, he was treated two to three times weekly with plasma-derived VWF, Humate-P (CSL Behring, King of Prussia PA). Despite Humate-P, his VWF activity remained < 20%, and he continued to have GI bleeding requiring hospitalization, though less frequently. When he underwent surgery for spinal fusion and gastric bezoar removal, daily Humate-P was administered for one week peri-operatively without bleeding complications.

On presentation with the pericardial effusion, VWF antigen was < 8.5%, VWF activity < 19%, and factor VIII activity 11% (Table 2). In preparation for pericardiocentesis, he received VWF replacement, Wilate (Octapharma USA, Paramus, NJ), 30 units/kg. VWF and factor VIII levels remain unchanged. He showed no response to a variety of replacement products given sequentially: a repeat dose of Wilate, 50 units/kg; Humate-P, 40 units/kg; and recombinant VWF, Vonvendi (Baxalta US Inc., Illinois City, IL), 60 units/kg. When measured 1 to 2.5 hours after each administration, VWF activity remained < 19%. Given the lack of response to factor replacement and absent bleeding history prior to age 60, the diagnosis of inherited type III VWD was questioned. There was increased clinical suspicion for an acquired etiology.

**Table 2. VWF and factor VIII levels before and after treatment with different replacement products.** Factor replacement products were given in sequential order as listed from left to right. VWF activity was measured using the ristocetin cofactor assay. Values are expressed as %. References ranges are as follows: VWF antigen 40–190%, VWF activity 45–150%, Factor VIII level 74–212%.

| | Initial | After Wilate 30 units/kg | After Wilate 50 units/kg | After Humate-P 40 units/kg | After Vonvendi 60 units/kg |
|---|---|---|---|---|---|
| VWF antigen | <8.5 | <8.5 | 10.0 | 10.0 | 12.0 |
| VWF activity | <19.0 | <19.0 | <19.0 | <19.0 | <19.0 |
| Factor VIII level | 11 | 14 | 12 | 12 | 6 |

## INVESTIGATIONS

Given refractoriness to factor replacement, further investigations were conducted to evaluate for an inhibitor. Mixing studies were sent to evaluate his prolonged activated partial thromboplastin time (aPTT) of 56.9 seconds. His aPTT corrected to 32.4 seconds at 0 minutes (control: 32.4 seconds) and to 36.0 seconds at 60 minutes (control: 35.9 seconds). This pattern was consistent with factor deficiency and not inhibitor. Consistent with this finding, factor VIII inhibitor assay was negative. Additional

evaluation for assay interference of VWF levels showed that they remained low (< 2%) when measured using an alternative activity assay (GPIbM). A VWF inhibitor assay was performed as a mixing study using the GPIbM activity assay and resulted negative.

In the absence of factor VIII or VWF inhibitor, we hypothesized that there might be an antibody causing rapid clearance of both endogenous and exogenous VWF. His VWF propeptide antigen level was 117% with VWF antigen level 12%. These levels corresponded to an elevated VWF propeptide-to-antigen ratio of 9.75 and was consistent with accelerated VWF clearance. However, enzyme-linked immunosorbent assays (ELISA) for anti-VWF IgG and IgM antibodies were negative. Analysis of VWF multimers showed severely reduced levels of all multimers, however the full range of multimers was present.

## DIFFERENTIAL DIAGNOSIS

The elevated VWF propeptide-to-antigen ratio suggested rapid VWF clearance. The non-response to exogenous VWF further suggested that the rapid VWF clearance was not due to an intrinsic VWF abnormality. When considered together with the absent bleeding history prior to age 60, the prior diagnosis of type III VWD was not consistent. His clinical findings strongly suggested a diagnosis of AVWS.

The presence of an antibody targeting VWF was not excluded by the negative VWF inhibitor assay, which only detects antibodies that bind to functional epitopes, nor by the negative anti-VWF antibody assay, which does not detect non-IgG non-IgM antibodies or antibodies that bind VWF indirectly. Notably, he had a history of IgG-kappa MGUS: Serum IgG-kappa monoclonal protein was 0.07 grams/dL, and free kappa-to-lambda ratio was 18.54. This pattern would suggest MGUS-associated AVWS. Other possible mechanisms of increased clearance of VWF include adhesion to platelets or malignant cells [1,2]. However, these mechanisms were less plausible because his platelet counts were normal and malignancy was not detected. He also did not have evidence of underlying autoimmune disease – anti-nuclear antibody and rheumatoid factor were negative – and an echocardiogram did not show evidence of valvular disease. Finally, AVWS has also been reported secondary to increased proteolysis by plasmin and other proteases [6,7]. His VWF multimer analysis showed the full range of multimers, albeit severely reduced in quantity, ruling out increased proteolysis.

## TREATMENT

Although he remained clinically stable and did not have any active bleeding, his absent response to VWF replacement led to the pericardiocentesis being delayed. Since an antibody leading to increased VWF clearance was suspected, he was given intravenous immunoglobulin (IVIG), 1 g/kg, followed by Wilate, 60 units/kg (Figure 1 and Table 2). At 1.5 hours after Wilate administration, VWF antigen, VWF activity, and factor VIII activity increased to normal levels. However, 12 hours after Wilate administration, his levels declined. With these results demonstrating proof of principle, the decision was made to facilitate the pericardiocentesis using immunosuppression. To this end, the next day, prior to pericardiocentesis, he received dexamethasone, 40 mg, and IVIG , 1 g/kg, followed by Wilate, 60 units/kg. After Wilate administration, he went immediately for the pericardiocentesis. The procedure was successful with drainage of 1.4 liters of serosanguinous fluid.

After Wilate infusion, VWF activity increased to 84% at 30 minutes, but declined to 47% at 5 hours. Therefore, he was given another dose of Wilate, 40 units/kg, followed by a continuous infusion at 5 units/kg per hour for 24 hours. He also continued dexamethasone, 40 mg/day, for another 3 days. On this regimen, VWF activity remained 94–100% during the Wilate infusion. Then after the Wilate infusion was discontinued, VWF activity slowly declined to 34% over 34 hours.

**Table 3. VWF and factor VIII levels before and after treatment with factor replacement product in combination with IVIG and dexamethasone.** Treatments were given in sequential order as listed from left to right. VWF activity was measured using the ristocetin cofactor assay. Values are expressed as %.

| | Before treatment | Hours after dose 1 of IVIG 1 g/kg and Wilate 60 units/kg | | Hours after dose 2 of IVIG 1 g/kg and Wilate 60 units/kg, with dexamethasone 40 mg | |
|---|---|---|---|---|---|
| | | 1.5 hours | 12 hours | 0.5 hours | 5 hours |
| VWF antigen | 12.0 | 126.0 | 38.0 | 134.0 | 86.0 |
| VWF activity | <19.0 | 86.0 | <19.0 | 84.0 | 47.0 |
| Factor VIII level | 6 | 139 | 81 | 113 | 93 |

## OUTCOME AND FOLLOW-UP

He tolerated the pericardiocentesis without any periprocedural bleeding. Pericardial fluid cytology evaluation for malignancy was negative. Two days after the procedure, an echocardiogram showed re-accumulation of small to moderate pericardial fluid. However he was asymptomatic. Based on clinical assessment and imaging, cardiac tamponade was absent, and he was subsequently discharged. Discharge medications included prednisone, 90 mg/day (1 mg/kg/day), and previous regimen of Humate-P, 4000 units twice weekly. A follow-up echocardiogram two weeks after discharge was stable. Three weeks after discharge, he remained without bleeding. At that time, laboratory studies showed VWF antigen of 12%, VWF activity < 19%, and factor VIII activity of 12%.

Two months later, he had re-accumulation of his pericardial effusion. He was treated with IVIG followed by Wilate bolus and infusion, and then underwent pericardial window. He tolerated the procedure well without bleeding complications.

## DISCUSSION

In this case, based on the clinical presentation, a prior diagnosis of type III VWD was revised to AVWS. Revising the diagnosis to AVWS was critical for his appropriate management. Given his AVWS, his prior VWF replacement therapy was likely ineffective. Untreated AVWS likely explained his persistently low VWF levels and recurrent GI bleeds. On his presentation with a pericardial effusion that required drainage, his unexpected non-response to VWF replacement delayed the pericardiocentesis by several days. However, once AVWS was diagnosed, pericardiocentesis was safely performed with peri-procedural steroids, IVIG, and VWF replacement.

Since there is no single test that confirms the diagnosis, AVWS is difficult to diagnose [1,2]. In his case, AVWS was the most likely diagnosis based on a combination of clinical history, laboratory testing, and treatment response. His history of new-onset GI bleeding suggested an acquired condition. Furthermore, his elevated VWF propeptide-to-antigen ratio was strongly suggestive of increased VWF clearance [8,9]. His negative VWF inhibitor and anti-VWF antibody assays make it difficult to ascribe his AVWS to a specific mechanism. However, an AVWS diagnosis is not excluded by these tests [2]. In fact, in AVWS, VWF inhibitors are detected infrequently because antibodies that accelerate clearance of VWF by binding to non-functional epitopes are not typically captured by VWF inhibitor screens [2,3]. This problem can be theoretically circumvented by anti-VWF antibody assays; however, the sensitivity and specificity of these assays has not been fully characterized [2,10,11]. Finally, the diagnosis of AVWS leading to immune-mediated clearance of VWF is supported by his lack of response to VWF replacement alone and his response to the combination of dexamethasone, IVIG, and VWF replacement.

The management of AVWS is variable. This variability occurs, in part, because AVWS is relatively rare and there is limited data on appropriate management. It also occurs because AVWS encompasses a wide range of distinct mechanisms that can lead to low VWF levels [1–3]. In our patient, rapid VWF clearance led to suspicion for an immune-mediated mechanism. For this reason, he was treated with the combination of dexamethasone, IVIG, and continuous VWF replacement [1,12,13]. Even though VWF

inhibitor or anti-VWF antibodies were not detected, this approach was successful. Other approaches that have been used with variable success include therapeutic plasma exchange and other immunosuppression, including azathioprine, cyclophosphamide, and rituximab [1–4]. Importantly, depending on disease association, the efficacy of different management approaches seems to vary: steroids are highly effective in AVWS associated with systemic lupus erythematosus; IVIG has a high rate of efficacy in IgG MGUS; and immunosuppressive agents such as rituximab are often effective in autoimmune disease-associated AVWS but are generally ineffective in MGUS-associated AVWS, in which case plasma cell directed therapies might be more successful [1,4]. Thus, both the acute and chronic management of AVWS depend on the mechanisms underlying the VWF deficiency.

In summary, AVWS is a rare disorder comprising a variety of mechanisms that lead to a common syndrome of low VWF levels. We report a case in which a patient with a prior diagnosis of type III VWD was given the revised diagnosis of AVWS and successfully managed peri-procedurally. This case highlights the importance of a prompt AVWS diagnosis. It also illustrates how a diagnosis of AVWS can be reached through a combination of clinical history, specialized laboratory testing, and assessment of treatment response. Moreover, this case report demonstrates that, even in the absence of measurable VWF inhibitor or anti-VWF antibodies, the combination of steroids, IVIG, and factor replacement can be effective. Given the variability of response to therapy depending on etiology, it is especially important to assess response with close monitoring of VWF levels.

## LEARNING POINTS/TAKE HOME MESSAGES

- The timely diagnosis of AVWS is critical to avoid delays in treatment.
- A diagnosis of AVWS should be considered when evaluating patients who carry a diagnosis of VWD but whose bleeding history does not match the expected pattern of an inherited disorder.
- In the appropriate clinical context, lack of response to factor replacement and elevated VWF propeptide-to-antigen ratio can support a diagnosis of acquired von Willebrand syndrome due to accelerated clearance of VWF.
- Even in the absence of confirmatory laboratory tests, a patient strongly suspected of having immune-mediated AVWS can be managed in the peri-procedural setting with steroids, IVIG, and factor replacement with close monitoring of factor levels.

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## FIGURE/VIDEO CAPTIONS

**Figure 1: Response to treatment with IVIG and factor replacement.** VWF antigen level (purple line), VWF activity level (using the ristocetin cofactor assay, red line), and factor VIII activity level (blue line) over time. Markers at the top denote timing of (1) 1 gram/kg IVIG (green arrow) and 60 units/kg Wilate (dark gray arrow); (2) 1 gram/kg IVIG (green arrow) and 60 units/kg Wilate (dark gray arrow); (3) pericardiocentesis (maroon bar); and (4) 40 units/kg Wilate (vertical dark gray arrow) followed by 5 units/kg per hour of Wilate for 24 hours (horizontal dark gray arrow). Gray diamonds denote timing of four doses of 40 mg dexamethasone.

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