Pathophysiology and Management of Acquired von Willebrand Syndrome

12

Dominder Kaur and Sarah H. O'Brien

Case Presentation You are consulted on an 8-year-old male with history of Ebstein's anomaly, aberrant right subclavian artery, and initial tricuspid valve replacement complicated by venoarterial extracorporeal membranous oxygenation (VA-ECMO) postoperatively, who recently underwent Glenn procedure and right ventricular plication, followed by tricuspid valve replacement 1 week later. Recent procedure was also complicated

D. Kaur (✉)
Department of Pediatrics, Division of Pediatric Hematology/Oncology/
Stem Cell Transplant, Columbia University Irving Medical Center,
Children's Hospital of New York/New York Presbyterian Morgan
Stanley Children's Hospital, New York, NY, USA
e-mail: dk3076@cumc.columbia.edu

S. H. O'Brien
Nationwide Children's Hospital, Division of Pediatric Hematology,
Oncology and Bone Marrow Transplant, Columbus, OH, USA

Center for Innovation in Pediatric Practice, Abigail Wexner Research
Institute at Nationwide Children's Hospital, Columbus, OH, USA

Department of Pediatrics, The Ohio State University College of
Medicine, Columbus, OH, USA
e-mail: Sarah.Obrien@nationwidechildrens.org

by the need for VA-ECMO, and he had hemodynamic instability related to bleeding post chest tube closure, responsive to volume resuscitation. He was stable for the subsequent day with his hemodynamic status improving and labs stabilizing. You are now consulted because yesterday evening, he developed bleeding from chest wound, from his nares, and around chest tubes, requiring heparin to be held. Cardiology and the intensive care units are concerned about acquired von Willebrand disease, as he had similar issues when he was on ECMO the last time.

Multiple Choice Management Question

You will send off which among the following evaluations?

(a) Coagulation screen with prothrombin time (PT) and activated partial thromboplastin time (aPTT)
(b) Platelet function analysis (PFA)
(c) Von Willebrand antigen and activity levels
(d) Multimer distribution evaluation
(e) **All of the above**

> This is a patient context wherein acquired von Willebrand disease is high on the differential. The initial evaluation can begin with a complete blood count (CBC), prothrombin time (PT), activated partial thromboplastin time (aPTT), PFA, von Willebrand panel (antigen and activity levels), factor VIII level, and VW multimer evaluation. Hence, the answer is e.

Epidemiology, Clinical Presentation, and Pathophysiology

Acquired von Willebrand syndrome (AVWS), as the name suggests, occurs due to acquired defects of the von Willebrand factor – and can be qualitative or quantitative. It is a rare bleeding

disorder that can develop in susceptible populations and requires a high index of suspicion for correct diagnosis.

Due to the possibility of being underreported and underdiagnosed, its true incidence remains unclear, but estimates from 0.04% to 5% occurrence in the susceptible populations have been reported [1].

As evidenced by the case example above, AVWS often occurs in the setting of a complicated medical background. Concurrent anticoagulation therapy and quantitative or qualitative platelet issues may be present simultaneously and make initial evaluation difficult.

AVWS is common in patients with congenital cardiac diseases or postsurgical anatomical cardiac configurations. The most commonly implicated lesion is aortic stenosis. Patients who are on left or other ventricular assist devices (VAD) or extracorporeal membrane oxygenation (ECMO) additionally are at high risk of developing AVWS. Such AVWS often has a rapid onset and can occur within a week of initiating such mechanical support [2]. In children, Wilms tumor is known to be associated with AVWS. Patients on certain medications, along with those with glycogen storage diseases and autoimmune conditions like systemic lupus erythematosus (SLE) or hypothyroidism, may also present with this defect.

The underlying hemostatic defect emanates from loss of high, and sometimes intermediate, molecular weight von Willebrand multimers. With the most active areas of the protein being lost, the interactions between the von Willebrand factor (VWF) protein, subendothelium, and platelets are adversely affected. Additionally, a low circulatory factor VIII (FVIII) level may result due to reduced protection from its carrier protein. All of these issues together lead to an increased bleeding risk, which may manifest as mucocutaneous bleeding or deeper organ/tissue bleeding due to low FVIII.

There are multiple postulated mechanisms for acquired VWD. These can be broadly categorized as immune-related or otherwise. Nonimmune mechanisms can affect both production and proteolysis of the VWF. Decreased production leading to AVWS is seen in hypothyroidism and possibly in patients on valproic acid therapy [3]. Other drugs implicated in AVWS include few antimicrobials (e.g., ciprofloxacin, griseofulvin) and hydroxyethyl starch [4].

Increased proteolysis in the setting of high-shear flow rate environments, is the primary mechanism in populations with underlying cardiac pathologies and circulatory support devices, e.g., aortic stenosis, ventricular septal defects, and VADs/ECMO (Fig. 12.1). In these high-shear high-flow-rate vascular environments, the globular conformation of VWF is unfurled into a linear form, and this exposes the A2 domain. With this change, the cryptic ADAMTS13 binding sites become open and available, resulting in proteolytic loss of the high molecular weight (HMW) multimers. Heyde syndrome is the classic example of such acquired type 2 VWD in patients with aortic stenosis, which manifests with angiodysplasia and gastrointestinal bleeding [5]. Modified flow dynamic in pulmonary hypertension also leads to similar proteolysis.

The pathophysiology in myeloproliferative disorders and thrombocytotic scenarios is different – with cellular adsorption of VWF being the underlying mechanism. Increased binding of the hemostatic HMW multimers occurs onto the more numerous cells in essential thrombocythemia, reactive thrombocytosis, polycythemia vera, or some other tumor cells [6]. This results in effective removal of these complexes from circulation. Partial reduction in available VWF, due to some of it remaining platelet bound, also contributes to the acquired VWF deficiency [7].

Immune-related mechanisms include antibody-mediated clearance or inhibition of VWF. Cell-mediated or drug-induced clearance of VWF also fall in the immune category. These autoimmune mechanisms can also be seen in the lymphoproliferative diseases and malignancies and have also been implicated in SLE.

Differential Diagnosis

The differential for AVWS includes other acquired bleeding disorders and platelet dysfunction. As AVWS often occurs in complex medical situations, other etiologies for bleeding like synthetic or consumptive coagulopathies (e.g., liver failure or disseminated intravascular coagulation/DIC) and acquired conditions, like thrombotic thrombocytopenic purpura or atypical hemolytic
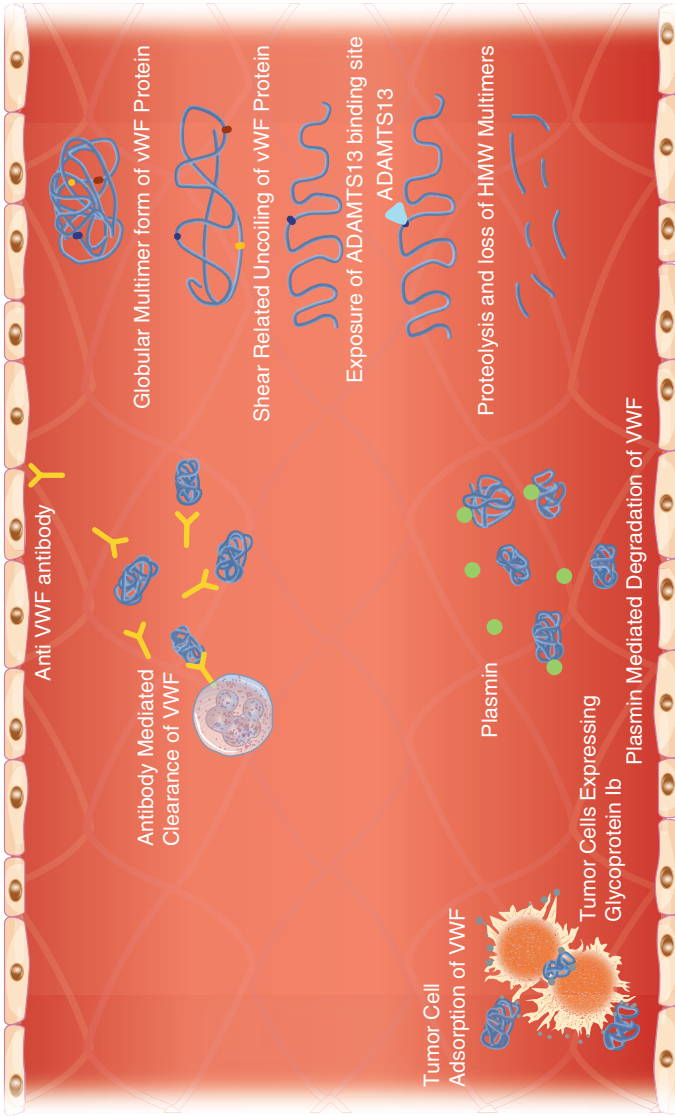
Fig. 12.1 Pathophysiology and mechanisms leading to development of acquired von Willebrand disease

uremic syndrome, should be considered. Overanticoagulation with supratherapeutic heparin or warfarin levels or platelet inhibition leading to bleeding, can also happen in the cardiac population. Acquired hemophilia may be similar in its initial evaluation as FVIII levels can be low in both these diseases but underlying mechanism and the patient presentation and history are different. It becomes important to differentiate AVWS from congenital VWD because the management approaches can vary.

Laboratory Findings

Laboratory evaluation in AVWS should start with a complete blood count, coagulation screen with prothrombin time (PT), and activated partial thromboplastin time (aPTT). These may be normal in some cases, but low platelet counts can be seen, if VWF-platelet complexes are produced as part of the underlying etiology, as these will be cleared out of the circulation. In the absence of other platelet inhibition/dysfunction, a PFA can also prove quite sensitive to AVWS. A prolonged aPTT may be seen when the FVIII level has been affected. The other evaluations are similar to those in VWD, and may identify decreased values for VWF:Ag, VWF:RCo, or FVIII. A change in the VWF multimer distribution can be very informative in showing a decrease in large molecular weight multimers but may also be normal at times. If collagen binding assay is available, it will also show similar decrease in binding. If propeptide testing is available, an increased propeptide/VWF:Ag ratio will be seen. Being a marker of VWF production, the propeptide level is normal, while the VWF antigen will be reduced in AVWS.

Multimer distribution pattern is the closest to that seen in type 2A among the VWD variants. At times, bleeding can occur with only a reduction in the VWF activity to antigen ratio, while their absolute values remain within acceptable ranges. This can be an early stage in AVWS; and on multimer evaluation, abnormal distribution may be seen, helping with the diagnosis. New onset of mucocutaneous bleeding in an at-risk patient population should stimulate consideration for AVWS. Personal history of

previously normal hemostasis and a negative family history, also prove useful in differentiating acquired from congenital VWD. Genetic testing to confirm this may not always be available in a timely manner.

In immune-mediated pathologies, like lymphoproliferative disorders, detection of VWF antibodies may aid AVWS diagnosis. Caution should be exercised while utilizing this testing for diagnosis, as a low rate of antibody detection is reported. This could be due to assay limitations, as well as due to poor detection of some of the antibodies because of them remaining bound to the VWF. Non-neutralizing antibodies are easier to detect and can be identified on enzyme-linked immunosorbent assays (ELISA) [8]. VWF survival testing after VWF infusion or DDAVP administration, may prove useful in some settings [4].

Management

The management goals in AVWS are to stop and prevent bleeding events, as well as to take steps toward reversal or remission of the disease-causing defect. An important aspect of AVWS management is taking prophylactic measures when high-risk situations are identified.

Desmopressin or DDAVP (at a dose of 0.3 µg/kg per dose, with maximum 20 µg) is useful for acute bleeding events in AVWS as for a short term; it leads to new VWF being released from endothelial cells. A DDAVP response evaluation is recommended and should be carried out whenever feasible. This can help differentiate complete and partial responders and nonresponders. DDAVP is most effective for immune-mediated AVWS, but some improvement can also be seen in cardiovascular or thrombocytosis pictures, wherein proteolysis and adsorptive mechanisms of disease are in play. Due to its ability to transiently increase VWF, DDAVP can be used as prophylaxis for minor hemostatic challenges in other patients as well, once they are identified to be responders (e.g., patient with aortic stenosis or thrombocytosis). When using DDAVP, one must remain mindful of its effects on fluid balance and possibility of hyponatremia.

Von Willebrand factor concentrates are useful in AVWS as well. They may be needed in patients wherein a sustained response cannot be obtained with DDAVP alone or when there is significant bleeding despite DDAVP and additional support is needed, before a dose can be repeated for concern of tachyphylaxis. VWF concentrates are dosed based on the ristocetin cofactor units, or on the factor FVIII units in the product. An initial dose can be 50 to 100 RCo IU/kg, and further dosing is based on the response. With both DDAVP and VWF replacement therapies, pharmacokinetic studies with post-dose levels prove helpful in guiding frequency of therapy and future doses. Such recovery levels are especially useful in the setting of neutralizing VWF antibodies.

Antifibrinolytics are a useful adjunctive therapy for AVWS, especially when DDAVP or VWF replacement is being utilized. The commonly used forms are epsilon aminocaproic acid and tranexamic acid, which are both lysine analogs that work via inhibition of plasmin activity on fibrin. They may suffice alone for minor bleeding events in areas with high fibrinolytic activity, like the mouth or the gut. They are also helpful for menstrual bleeding and small oral/dental procedures.

Use of recombinant factor VIIa (rFVIIa) is indicated in patients with anti-VWF alloantibodies and severe bleeding. The basis of its use is similar to hemophilia therapy in the setting of an inhibitor and rFVIIa works as a bypassing agent. Thus, dosing similar to that used in hemophilia, i.e., 90 µg/kg, can be utilized. The data on this are relatively limited, and there is associated thrombosis risk, that one should remain cautious of [9].

For our case, DDAVP and VWF factor concentrate can be considered as therapies. If DDAVP is successful in stopping bleeding, antifibrinolytic therapy can also be used as an adjunct, while being mindful of the thrombosis risk. In the absence of bleeding, supportive care is sufficient. If there is bleeding and it is too early to repeat DDAVP, VWF concentrate can be given. Plans for coming off ECMO should be frequently discussed, as permitted by the hemodynamic stability. Once ECMO is removed, AVWS reverses rather quickly.

Additional adjunctive efforts to minimize bleeding, like maintaining safe platelet counts in the complicated patients with systemic and multiorgan issues and optimizing anticoagulation to avoid bleeding, are important management components.

Underlying mechanical, malignant, and autoimmune conditions leading to AVWS also make this condition just as amenable to reversal. With surgical correction, chemotherapy, or immunosuppression, AVWS also improves. For significant immunological diseases like lupus, systemic therapy with intravenous immunoglobulins or plasmapheresis or agents like steroids or cyclophosphamide may be indicated [10]. Whenever underlying issues can be addressed, steps toward such therapies should be considered an integral part of AVWS management.

Outcomes and Follow-Up

Most of the patients that develop AVWS due to a treatable condition, can revert to normal VWF levels. For patient with Wilms tumor or thrombocythemic issues, chemotherapy-related remission can also normalize VWF levels. For underlying cardiac issues, once corrective surgery is performed and the shearing anatomy is gone, VWF defects also improve. Normalization of the multimer pattern and improvement in the VWF:Ag/RCo ratio confirm reversal of the defect. For patients that are on circulatory support devices like VAD or ECMO, AVWS is promptly and completely reversed after device is explanted. The immune-mediated AVWS may be more difficult to treat and be persistent, but can improve with effective immunosuppression.

Due to etiologies in AVWS being heterogeneous, there is need for individualizing care. Most patients have a positive outcome with regard to disease reversal after correction of the underlying issue and, thus, have a good prognosis. Follow-up frequency can be based on the disease activity and bleeding risk.

In the absence of bleeding issues, follow-up can be annually for patients with persistent AVWS. Once steps toward correction for the underlying issue are taken, one immediate follow-up and another a few months out, with repeat VWF panel at the latter,

should be planned. By 1 year from correction, almost all patients show reversal of the AVWS. Being a complex and heterogeneous disease, patients with AVWS should be cared for by hematologists with expertise in this disease or at a hemophilia treatment center (HTC).

Clinical Pearls and Pitfalls
- A high level of suspicion in the correct clinical setting and appropriate timing of laboratory evaluation are essential to establish the correct diagnosis of acquired VWD in a timely manner.
- Anticoagulant and platelet inhibition therapy can make correct diagnosis difficult in patients with underlying complex cardiac conditions and in those who are on vascular support devices.
- Although multimer testing is helpful in identifying AVWS, for acute bleeding in sick patients, there may not always be sufficient time to wait for multimer distribution results. It is prudent to then make the diagnosis based on patient's personal and family history, new onset of VWF defects, and decreased VWF:RCo to VWF:Ag ratio.
- For patients who develop AVWS while on mechanical support with VAD and ECMO, the VWF profile defects and related bleeding risk normalize soon after they come off such devices.
- DDAVP/desmopressin may be successfully used for small procedures in AVWS.
- Angiodysplasia and related GI bleeding can also be seen in patients with AVWS, and this phenomenon in Heyde syndrome has contributed to identification of role of VWF in angiogenesis. Once the underlying cardiac defect is corrected, the angiodysplasia also improves.

References

1. Franchini M, Lippi G. Acquired von Willebrand syndrome: an update. Am J Hematol. 2007;82(5):368–75.
2. Heilmann C, Geisen U, Beyersdorf F, Nakamura L, Benk C, Berchtold-Herz M, et al. Acquired von Willebrand syndrome in patients with ventricular assist device or total artificial heart. Thromb Haemost. 2010;103(5):962–7.
3. Callaghan MU, Wong TE, Federici AB. Treatment of acquired von Willebrand syndrome in childhood. Blood. 2013;122(12):2019–22.
4. Nichols WL, Hultin MB, James AH. Von Willebrand disease (VWD): evidence- based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). Haemophilia. 2008;14:171–232.
5. Loscalzo J. From clinical observation to mechanism–Heyde's syndrome. N Engl J Med. 2012;367(20):1954–6.
6. Veyradier A, Jenkins CS, Fressinaud E, Meyer D. Acquired von Willebrand syndrome: from pathophysiology to management. Thromb Haemost. 2000;84(2):175–82.
7. Budde U, van Genderen PJ. Acquired von Willebrand disease in patients with high platelet counts. Semin Thromb Hemost. 1997;23(5):425–31.
8. Tiede A. Diagnosis and treatment of acquired von Willebrand syndrome. Thromb Res. 2012;130(Suppl 2):S2–6.
9. Tiede A, Rand JH, Budde U, Ganser A, Federici AB. How I treat the acquired von Willebrand syndrome. Blood. 2011;117(25):6777–85.
10. Kumar R, Steele M. Acquired bleeding disorders in children. In: Blanchette VSBV, Revel-Vilk S, editors. SickKids handbook of pediatric thrombosis and hemostasis, vol. 1. 2nd ed. Basel: Karger; 2017. p. 134–56.