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Diagnostic Challenges in Acquired von Willebrand Disease: A Complex Case of Prostate Carcinoma

Paul-Emile Claus[a, c], Inge Van Haute[a], Eline Verhoye[a], Dries Deeren[b], Els Moreau[a]

Abstract

We report an 80-year-old man suffering from ulcerative colitis and a prostate adenocarcinoma. Due to melena, colon biopsies were taken. Diffuse bleeding and a cardiac infarction complicated this procedure. Laboratory studies showed a normal platelet count and a prolongation of the activated partial thromboplastin time (aPTT). Von Willebrand factor (VWF) antigen level and ristocetin cofactor activity were low. Several disorders are known to be associated with acquired von Willebrand disease (AVWD), the commonest being hematoproliferative and cardiovascular disorders. Non-hematologic neoplasms causing AVWD are rarely documented. The underlying mechanisms differ among these disorders or may overlap. These include development of autoantibodies and mechanical destruction of VWF under high shear stress. Absorption of VWF on or inside malignant cells is believed to be the main mechanism in non-hematologic malignancies. In this report, we give a concise overview of the underlying disorders and the mechanisms that we encountered in this complex case.

Keywords: Acquired von Willebrand disease; Pathophysiology; Melena; Prostate carcinoma; von Willebrand factor

Introduction

Von Willebrand factor (VWF) is a large multimeric glycoprotein that is synthesized by endothelial cells, subendothelial connective tissue and megakaryocytes. The protein consists of numerous monomers, each containing a number of specific domains with a specific function responsible for binding of factor VIII or adhesion and aggregation of platelets. The size of VWF is regulated by the metalloproteinase ADAMTS13, which cleaves the VWF molecule. Qualitative and quantitative abnormalities of VWF result in different inherited types of von Willebrand disease [1]. To date, there are six types of von Willebrand disease: type I (partial quantitative deficiency of VWF), type 2 (qualitative deficiency of VWF) which is divided into four distinct types (2A, 2B, 2M and 2N) and type 3 (total quantitative deficiency of VWF). Hereditary von Willebrand disease (HVWD) is the most common congenital bleeding disorder with a worldwide prevalence of 1-2% [2]. In contrast, acquired von Willebrand disease (AVWD) is much more rare and mainly occurs in a later stage of life without family history of bleeding. Patients with AVWD mostly present with mild to moderately severe mucocutaneous bleeding similar to that reported in HVWD. It is almost always associated with other diseases. This makes the diagnosis of AVWD very complex and leads to an underestimation of its prevalence.

Case Report

We present an 80-year-old male who suffered from ulcerative colitis as documented by colon biopsies in 2012 and was treated with mesalazin. In 2013, due to lower urinary tract symptoms and an initial PSA of 9 ng/mL, investigations revealed a local Gleason 7 prostate adenocarcinoma. During 1 year, the patient was given hormonal therapy consisting of an antiandrogen and a gonadotropin-releasing hormone (GnRH) analogue and he received several radiotherapy sessions. Surgery was not performed. Approximately 1 year later, he was readmitted in our hospital with recurrent melena. A coloscopy was done during which new biopsies were taken. There was persistent bleeding at the biopsy sites and shortly after the procedure, the patient developed a cardiac infarction leading to urgent coronary artery bypass grafting (CABG). Diffuse bleeding also complicated this procedure. There was no family history of bleeding disorders. The patient did not smoke but was known to be a heavy alcohol drinker. He was on mesalazin, pantoprazol, atorvastatin, metformin and hormonal therapy for his prostate carcinoma.

Laboratory studies few days prior to the CABG procedure showed an isolated normocytic anemia. He had a prolonged activated partial thromboplastin time (aPTT) that did not correct in a mixing study. The prothrombin time (PT) was normal.

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[a]Clinical Laboratory, AZ Delta Hospital, Rode-Kruisstraat 20, Roeselare, Belgium
[b]Department of Hematology, AZ Delta Hospital, Rode-Kruisstraat 20, Roeselare, Belgium
[c]Corresponding Author: Paul-Emile Claus, Clinical Laboratory, AZ Delta Hospital, Rode-Kruisstraat 20, Roeselare, Belgium.
Email: paul-emile.claus@azdelta.be

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Table 1. Laboratory Findings in Our Patient

Analysis (unit)	Value	Normal range
Hemoglobin (g/dL)	9.9	13.7 - 17.1
MCV (fL)	85.1	84.0 - 98.3
MCH (pg)	30.4	27.6 - 32.9
White blood cell count (cells/µL)	4,790	4,200 - 9,800
Platelet count (cells/µL)	213,000	162,000 - 351,000
Serum iron (µg/dL)	36	50 - 165
Iron-binding capacity (µg/dL)	191	250 - 480
Ferritin (µg/L)	690	30 - 400
PT (%)	98.0	70.0 - 116.0
aPTT (s)	72.1	28.0 - 39.0
LDH (U/L)	345	240 - 480
Troponin T (ng/mL)	0.425	0.000 - 0.030

Further analysis revealed a low factor VIII level of 7% (normal 60-150%) with a low factor VIII activity of 15.8% (normal 50-150%) and normal factor IX and factor XI levels. He had a low VWF antigen level of 10% (normal 50-150%) and ristocetin cofactor activity of 5.5% (normal 50-150%). Factor VIII antibodies were negative. Unfortunately, the type of von Willebrand disease was not determined by VWF multimer analysis. Autoimmune studies revealed a positive p-ANCA and antinuclear antibodies. Rheumatoid factor tested negative. Other test results are summarized in Table 1.

Methylprednisolone and intravenous immunoglobulins were started. A few days later, we already noticed a normalization of the aPTT (32.9 s) and an increase of the factor VIII level (153%). The VWF antigen level and ristocetin cofactor activity both returned to normal (105 and 93.2%, respectively). The cardiac infarction was believed to be evoked by the anemia that occurred due to the persistent melena. The patient's clotting parameters remained normal so that methylprednisolone and intravenous immunoglobulins could be stopped. The hormonal therapy for his prostate carcinoma was stopped after 1 year. Active surveillance has shown an undetectable PSA of $\leq$ 0.02 ng/mL and new bleeding symptoms have not occurred since then.

Discussion

AVWD is associated with a variety of underlying diseases that are well documented [3]. The pathogenic mechanisms that operate in these different disorders are very heterogeneous. They may act independently or can overlap. Most cases of AVWD are seen in patients with lymphoproliferative (30-48%) and myeloproliferative (15-18%) disorders. On the second place, we find cardiovascular disorders (12-21%), followed by neoplasia (5-6%), immune deficiencies (2-6%) and other conditions (9-28%) including drug-induced AVWD, infections, systemic diseases and idiopathic AVWD. The frequencies that were reported during an international registry on AVWD correlated well with the data collected from 123 publications [4]. A smaller study conducted on 187 patients with different disorders and who suffered from AVWD stated that lymphoproliferative disorders were less frequent (2%) in favor of myeloproliferative (43%) and cardiovascular disorders (40%).

The major pathophysiological mechanism in lymphoproliferative disorders is the development of autoantibodies against VWF, usually of the IgG type. These may bind to the functional epitopes of VWF and neutralize its activity, or they may be directed against non-functional regions of VWF and form immune complexes, accelerating the clearance of VWF from the circulation [5].

In myeloproliferative disorders, other mechanisms can occur besides anti-VWF autoantibodies. Essential thrombocythemia is more commonly associated with AVWD than polycythemia vera and chronic myeloid leukemia. In these cases, an increased platelet count causes a paradoxical situation by resulting in both a prothrombotic and bleeding tendency. An increase in the number of platelets circulating in the blood in combination with the shear stress to which blood passing through the capillaries is subjected, stimulates the adsorption of larger VWF multimers onto the platelets' membrane. This results in the removal of VWF multimers from the circulation and subsequent degradation [6].

This same mechanism may be responsible for the reduction of VWF in cardiovascular disorders. Due to several factors, the blood shear stress may rise which leads to activation of the platelets and adsorption of the VWF multimers. High shear stress can also induce a direct mechanical destruction or proteolysis of the multimers [7]. The main cardiovascular disorders causing AVWD are congenital and acquired ventricular and atrial septal defects, aortic stenosis and mitral valve prolapse. Cases of cardiac infarction associated with AVWD are not described. However, it is well known that severe cardiac infarctions may cause septal and valvular defects which may increase blood shear stress. It is important to note that AVWD in these situations is difficult to diagnose because VWF concentrations often stay high, especially in the acute state of these disorders. Ristocetin cofactor activity and collagen binding activity are more sensitive and will decrease more rapidly during proteolysis of VWF multimers.

AVWD associated with immune deficiencies is caused by the formation of autoantibodies, which can be specific or non-specific, as seen in lymphoproliferative disorders. The antibodies are predominantly IgG, but IgM and IgA antibodies have also been reported. These inhibitors mainly interfere in the binding of VWF to the platelets' membrane. They can be directed against different functional and non-functional epitopes of VWF. Other inhibitors recognize the factor VIII/VWF complex which leads to low VWF and factor VIII activity.

In solid tumors selective adsorption of VWF on or inside the malignant cells can occur due to aberrant expression of glycoprotein Ib or glycoprotein IIb/IIIa receptors on their surface. This phenomenon has been documented in several reports using specific immunohistochemical staining techniques [8]. The molecular basis however remains unknown. Several cases of Wilms' tumor associated with AVWD have been reported [9]. Other underlying neoplasms that have been described are peripheral neuro-ectodermal tumors, adrenal carcinoma and Ew-

ing sarcoma. In most cases of AVWD associated with a solid tumor, response to high-dose intravenous immunoglobulins was poor [10]. Treatment of the underlying disease by tumor resection or chemotherapy has proven to be most effective. As far as we know, there have been neither case reports nor larger studies describing AVWD associated with prostate carcinoma.

Conclusion

In this case, we encountered several complex comorbidities that can cause AVWD through different pathophysiological mechanisms. Our patient has been suffering from ulcerative colitis for at least 2 years. Ulcerative colitis is an autoimmune disorder characterized by infiltration of T lymphocytes in the colon. The presence of p-ANCA and antinuclear antibodies leads to the assumption that autoantibodies against VWF may have developed as well. A search for anti-VWF antibodies is recommended when AVWD is associated with autoimmune disease, lympho- and myeloproliferative disorders, cases with a solid, non-hematologic tumor or no detectable underlying disorder. The presence or absence of neutralizing antibodies can easily be detected by performing mixing experiments of patient plasma and normal plasma. Unfortunately, these mixing studies have several drawbacks and may fail to detect low-titer anti-VWF antibodies and non-neutralizing antibodies. As we did not find trustworthy data of the mixing test and since antibodies were not detected, it would be precipitate to state that this patient suffered from AVWD caused by his ulcerative colitis.

Nor do we believe that the AVWD was provoked by his cardiac infarction. The patient already presented with persistent bleeding before he complained of any symptoms of a cardiac infarction. However, an intensive CABG procedure may rapidly increase blood shear stress and aggravate the ongoing reduction of VWF.

Eventually, we would like to discuss prostate carcinoma as a possible causative factor of AVWD. We found several reports of prostate cancer associated with acquired hemophilia A caused by the development of FVIII inhibitors [11]. Nonspecific inhibitors to the VIII/VWF complex may also occur, reducing VWF activity. The hypothesis that malignant prostate gland cells might express aberrant glycoprotein Ib or IIb/IIIa receptors on their surface has in our view insufficiently been investigated. It is unlikely that VWF can be adsorbed by aberrant receptors on malignant cells in local prostate cancer since these cells are not present in the blood circulation. Some studies state that anti-VWF autoantibodies may also occur in solid, non-hematologic tumors as part of a paraneoplastic autoimmune syndrome [12]. Our patient was treated with methylprednisolone and intravenous immunoglobulins to which he responded well with normalization of the aPTT, VWF antigen level and ristocetin cofactor activity. Active surveillance has shown a good evolution of the tumor disease and bleeding symptoms have not occurred since then.

References

1. Shetty S, Kasatkar P, Ghosh K. Pathophysiology of acquired von Willebrand disease: a concise review. Eur J Haematol. 2011;87(2):99-106.
2. Kumar S, Pruthi RK, Nichols WL. Acquired von Willebrand disease. Mayo Clin Proc. 2002;77(2):181-187.
3. Federici AB, Rand JH, Bucciarelli P, Budde U, van Genderen PJ, Mohri H, Meyer D, et al. Acquired von Willebrand syndrome: data from an international registry. Thromb Haemost. 2000;84(2):345-349.
4. Budde U, Bergmann F, Michiels JJ. Acquired von Willebrand syndrome: experience from 2 years in a single laboratory compared with data from the literature and an international registry. Semin Thromb Hemost. 2002;28(2):227-238.
5. 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.
6. Budde U, Scharf RE, Franke P, Hartmann-Budde K, Dent J, Ruggeri ZM. Elevated platelet count as a cause of abnormal von Willebrand factor multimer distribution in plasma. Blood. 1993;82(6):1749-1757.
7. Mohri H. Acquired von Willebrand syndrome: its pathophysiology, laboratory features and management. J Thromb Thrombolysis. 2003;15(3):141-149.
8. Facon T, Caron C, Courtin P, Wurtz A, Deghaye M, Bauters F, Mazurier C, et al. Acquired type II von Willebrand's disease associated with adrenal cortical carcinoma. Br J Haematol. 1992;80(4):488-494.
9. Baxter PA, Nuchtern JG, Guillerman RP, Mahoney DH, Teruya J, Chintagumpala M, Yee DL. Acquired von Willebrand syndrome and Wilms tumor: not always benign. Pediatr Blood Cancer. 2009;52(3):392-394.
10. Federici AB. Use of intravenous immunoglobulin in patients with acquired von Willebrand syndrome. Hum Immunol. 2005;66(4):422-430.
11. Girardi Dda M, Silva DR, Villaca PR, Souza CE, da Fonseca LG, Bastos DA, Hoff PM. Acquired hemophilia A in a patient with advanced prostate cancer. Autops Case Rep. 2015;5(2):55-59.
12. Franchini M, Lippi G. Acquired von Willebrand syndrome: an update. Am J Hematol. 2007;82(5):368-375.