Letter to the Editor

Diagnostic Challenges in Acquired von Willebrand Syndrome: A Complex Case of Prostate Carcinoma Associated-Acquired von Willebrand Syndrome

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We read with great interest the recent article by Federici et al, regarding the diagnostic and therapeutic approaches to patients with acquired von Willebrand syndrome (AVWS).[1] AVWS is associated with a variety of underlying diseases that are well-documented. In our hospital, we encountered a complex case of prostate carcinoma associated-AVWS (see ►**Fig. 1** for timeline). Despite a thorough search of the literature, we failed to find a similar case or a clear pathophysiological explanation.

We present an 80-year-old male who suffered from ulcerative colitis as documented by colon biopsies in 2012 and who was subsequently treated with mesalazine. In 2013, due to lower urinary tract symptoms and an initial prostate-specific antigen (PSA) of 9 ng/mL, follow-up investigations revealed a local Gleason 7 prostate adenocarcinoma. The patient was given hormonal therapy consisting of an antiandrogen and a gonadotropin-releasing hormone analogue for the next year in addition to several radiotherapy sessions. Surgery was not performed. In April 2014, he was readmitted to our hospital with recurrent melena. There was no family history of bleeding disorders. A colonoscopy was performed during which new biopsies were taken. This procedure was complicated by persistent bleeding at the biopsy sites. Laboratory studies showed an isolated normocytic anemia. He also had a prolonged activated partial thromboplastin time (aPTT) that did not correct in a mixing study. The prothrombin time was normal. 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 von Willebrand factor (VWF) antigen (VWF:Ag) level of 10% (normal, 50–150%) and ristocetin cofactor activity (VWF:RCo) of 5.5% (normal, 50–150%) (►**Table 1**). Factor VIII antibodies were tested for and not identified. Unfortunately, the type of VWD was not determined by VWF multimer analysis. Also, tests for potential VWF antibodies and VWF collagen binding activity (VWF:CB) were not available in our center. Methylprednisolone was started with initially insufficient response; thus, high dose intravenous immunoglobulins and VWF concentrate were administered a few days later. Four days after the colonoscopy, the patient developed a cardiac infarction for which urgent coronary artery bypass grafting (CABG) was necessary. In the interest of performing safe surgery, the cardiac surgeons couldn't operate immediately, but instead waited until the patient's hemostasis parameters returned to normal. At approximately 2 days afterwards, therapy with immunoglobulins was started, a normalization of the aPTT (32.9 seconds) and an increase of the factor VIII level (153%) was achieved, and the VWF:Ag and VWF:RCo levels both returned to normal (105 and 93.2%, respectively). The CABG procedure could then safely be performed. No major bleeding complications occurred. Postoperatively, he recovered well at the intensive care unit and his hemostasis parameters remained normal so that methylprednisolone and intravenous immunoglobulins could be stopped. The hormonal therapy for his prostate carcinoma was stopped in June 2014. Active surveillance has since shown an undetectable PSA of $\leq$0.02 ng/mL and new bleeding symptoms haven't occurred since then.

VWF is a large multimeric glycoprotein that is synthesized by endothelial cells, subendothelial connective tissue, and

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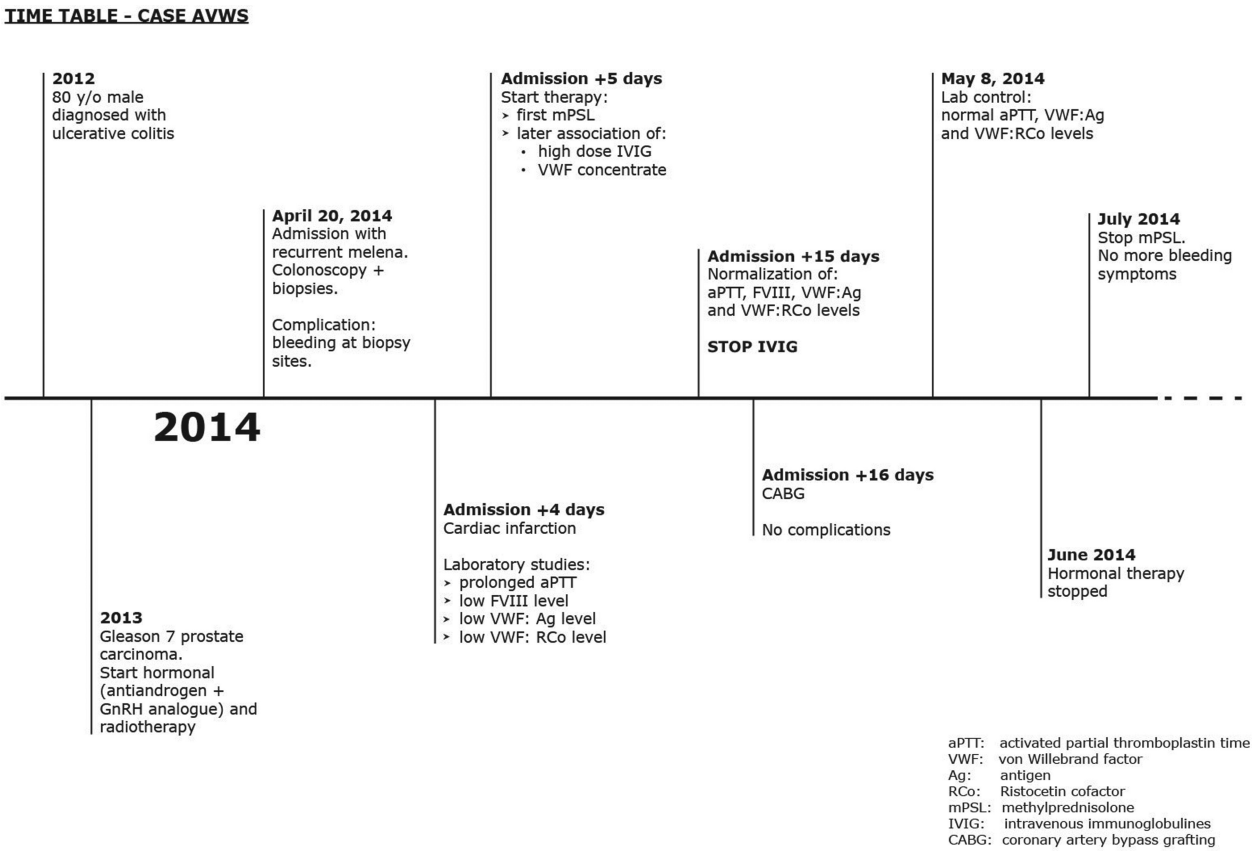

Fig. 1 Time table: case acquired von Willebrand syndrome.

Table 1 Laboratory findings in our patient

Analysis (unit)	Values	Normal range
Hemoglobin (g/dL)	**9.9**	13.7–17.1
MCV (fL)	85.1	84.0–98.3
MCH (pg)	30.0	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 (sec)	**72.1**	28.0–39.0
Factor VIII activity (%)	**15.8**	50–150
Factor IX (%)	137	70–130
Factor XI (%)	109	60–150
VWF:Ag (%)	**10**	50–150
VWF:RCo (%)	**5.5**	50–150
LDH (U/L)	345	240–480
Troponin T (ng/mL)	**0.425**	0.000–0.030

Abbreviations: Ag, antigen; aPTT, activated partial thromboplastin time; LDH, low density lipoprotein; MCH, mean cell hematocrit; MCV, mean cell hematocrit; PT, prothrombin time; RCo, ristocetin cofactor; VWF, von Willebrand factor.
Note: Abnormal results are boldfaced.

megakaryocytes. The protein consists of numerous monomers, each containing several specific domains with a specific function responsible for binding of factor VIII or adhesion and aggregation of platelets. Qualitative and quantitative abnormalities of VWF result in different inherited types of von Willebrand disease (VWD). There are six types of VWD according to the latest classification criteria: type 1 (partial quantitative deficiency of VWF), type 2 (qualitative deficiency/defect of VWF) which is subdivided into four distinct types (2A, 2B, 2M, and 2N), and type 3 (total quantitative deficiency of VWF).[2] Hereditary VWD is the most common congenital bleeding disorder with a worldwide prevalence reported to be as high as 2%.[3] In contrast, AVWS is seemingly rarer and mainly occurs in the later stage of life without family history of bleeding.[1,4] Patients with AVWS mostly present with mild to moderately severe mucocutaneous bleeding similar to that reported in congenital VWD. AVWS is almost always found associated with other diseases. This makes the diagnosis of AVWS very complex and leads to a probable underestimation of its prevalence. The pathogenic mechanisms that operate in the different disorders are very heterogeneous. They may act independently or can overlap. Most cases of AVWS are seen in patients with lymphoproliferative (30–48%) and myeloproliferative (15–18%) disorders. Next prevalent are cardiovascular disorders (12–21%), followed by neoplasia (5–6%), immune deficiencies (2–6%), and other conditions (9–28%) including drug-induced AVWS, infections, systemic diseases, and idiopathic AVWS.[1,4,5] The frequencies that were reported during an international registry on von Willebrand disease (AVWD) correlated well with the data collected from 123 publications. A smaller study conducted on 187 patients with different disorders and who suffered from AVWS 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 nonfunctional regions of VWF and form immune complexes, accelerating the clearance of VWF from the circulation.[6]

In myeloproliferative disorders, other mechanisms can occur besides anti-VWF autoantibodies. Essential thrombocythemia is more commonly associated with AVWS 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.[7]

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.[8] 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 AVWS have not been 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 AVWS in these situations is difficult to diagnose because VWF concentrations often stay high, especially in the acute state of these disorders. VWF:RCo and VWF collagen binding activity (VWF:CB) are more sensitive and will decrease more rapidly during proteolysis of VWF multimers.

AVWS associated with immune deficiencies is caused by the formation of autoantibodies, which can be specific or nonspecific, 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 platelet membrane. They can be directed against different functional and nonfunctional 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.[9] The molecular basis, however, remains unknown. Several cases of Wilms' tumor associated with AVWS have been reported.[10] Other underlying neoplasms that have been described are peripheral neuroectodermal tumors, adrenal carcinoma, and Ewing sarcoma. In most cases of AVWS associated with a solid tumor, response to high-dose intravenous immunoglobulins was poor.[11] Treatment of the underlying disease by tumor resection or chemotherapy has proven to be most effective.

We do not believe that the AVWS in our case was provoked by the 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. The hypothesis that malignant prostate gland cells might express aberrant glycoprotein Ib or IIb/IIIa receptors on their surface has, in our view, been insufficiently 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. We found several reports of prostate cancer associated with acquired hemophilia A caused by the development of FVIII inhibitors.[12] Nonspecific inhibitors to the factor VIII:VWF complex may also occur, reducing VWF activity. Some studies state that anti-VWF autoantibodies may also occur in solid, nonhematologic tumors as part of a paraneoplastic autoimmune syndrome.[13] Our patient was treated with methylprednisolone and high dose intravenous immunoglobulins to which he responded well with normalization of the aPTT, VWF:Ag, and VWF:RCo, suggesting a potential immune-related cause. Unfortunately, as previously

noted, tests for potential VWF antibodies were not available in our center and thus this could not be directly proven. Active surveillance of his tumor disease has also shown a good evolution and bleeding symptoms haven't occurred since. Thus, we would like to propose prostate carcinoma as a possible causative factor of AVWS in this patient, albeit through an unclear pathogenesis.

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