Allopurinol-induced acquired von Willebrand syndrome

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ABSTRACT

Acquired von Willebrand syndrome (AVWS) is a relatively infrequent but often overlooked finding when testing for von Willebrand factor (VWF) levels in a patient with mucocutaneous bleeding. Known causes include cardiovascular disorders, hematologic and solid tumors, autoimmune disorders, hypothyroidism, and drugs. An incoercible oral bleeding after a two-teeth removal in a patient with a mechanical aortic valve eventually raised suspicion about an AVWS that was confirmed through laboratory testing. Substitution therapy with an exogenous VWF factor was required to control the bleeding. Known causes of AVWS, including Heyde's syndrome, were ruled out. VWF levels finally normalized two days after suspension of allopurinol, which the patient received for symptomatic hyperuricemia, leading to his complete recovery and early discharge without any other complications. AVWS is an underdiagnosed entity due to a lack of testing. Allopurinol has never been postured before as a possible etiology and should be evaluated when reaching a diagnosis.

Introduction

Von Willebrand factor (VWF) is a large multifunctional glycoprotein whose role in hemostasis is critical, as it acts as a bridging molecule for platelet adhesion and aggregation, as well as a carrier for factor VIII in the circulation.[1-3] Deficiency or dysfunction of VWF results in a bleeding susceptibility condition known as von Willebrand syndrome (VWS), which can either be congenital, resulting from mutations in the VWF gene, or acquired.[1-3] Acquired von Willebrand syndrome (AVWS) is a rare disorder with a diverse and not yet fully understood pathophysiology. Several mechanisms have been proposed, which could be summarized in four: antibody-mediated clearance, adsorption onto the surface of cells or drugs, proteolytic degradation caused by shear stress, and a decrease in its synthesis or secretion.[2-4] The etiology of AVWS is broad, with various associated pathologies reported, including lymphoproliferative and myeloproliferative disorders, solid tumors, autoimmune diseases, cardiac disorders, hypothyroidism, and drug-induced cases.[2-4]

Allopurinol is a xanthine oxidase inhibitor used to lower serum levels of uric acid by diminishing its production. Common indications are symptomatic hyperuricemia, in order to prevent new episodes of gout, and hyperuricemia coexisting with renal insufficiency. The drug is typically initiated orally at a dose of 100 mg per day and then increased gradually at weekly intervals until the target uric acid level is reached.[4]

Case report

We report the case of a Caucasian 73-year-old male patient with multiple medical priors, from which a mechanical aortic

valve (implanted to address severe stenosis) on oral anticoagulation therapy with acenocoumarol stood out. He also had multiple cardiovascular risk factors (hypertension, dyslipidemia, a past smoking and drinking habit, and symptomatic hyperuricemia, for which he received allopurinol), a sinus node dysfunction for which he carried a pacemaker and a radiotherapy-treated prostate cancer (in remission at the time of the events).

The patient was admitted to the emergency department following incoercible oral bleeding after the removal of two teeth on the right maxillary hemiarch. Hemifacial edema on his ipsilateral cheek was also present (Figure 1). He had suspended acenocoumarol and started bridge therapy with low-molecular-weight heparin before the intervention. Heparin dose was lowered and antibiotic therapy with amoxicillin-clavulanate was initiated on admission.

The patient showed no response to local hemostatic interventions throughout the initial six days of hospitalization, as mild but persisting bleeding kept troubling the postoperative period. The cessation of heparin treatment failed to alleviate the bleeding. VWF was finally measured on the seventh day of hospitalization, showcasing a significant decrease in antigen levels (VWF:Ag 35.2 IU/dL). This decrease was further evident in the assessment of VWF activity (VWF: RCo 12.1 IU/dL, VWF: GPIb <4 IU/dL). The propeptide ratio was sightly incremented (VWF: pp/VWF: Ag 3.55; reference value <2.60). Multimeric analysis revealed a decrease in intermediate and high molecular weight FVW multimers and an increase in low and very high molecular weight FVW multimers [IMWM, HMWM, LMWM, and VHMWM, respectively (Table 1)]. Analysis of VWF multimers was performed with the Hydragel 11 VWF multimers kit (H5VWM; Sebia Hispania, Barcelona, Spain). Agarose gel electrophoresis was performed with the Hydrasys 2 Scan instrumentation, using preformed 2% agarose gels, direct immunofixation, visualization with peroxidase-labelled antibody, and densitometry according to the manufacturer's recommendations. Samples were diluted according to their VWF: Ag levels as follows: <20%: 1/4; 20-50%: 1/6; 150-300%: 1/10; >300%: 1/20. The percentage of LMWM, IMWM, HMWM and VHMWM were assessed using Phoresis software (Sebia) with peaks 1-3 designated as LMWM, peaks 4-7 as IMWM, and peaks >7 as HMWM according to the manufacturer's recommendations; those with supranormal levels were categorized as VHMWM. A normal plasma was included on each gel as a control.

These findings suggested an acquired type 2A von Willebrand syndrome. Amoxicillin-clavulanate was suspended and proper replacement therapy with exogenous VWF was initiated. VWF levels were monitored before and three hours after the administration of a 50 IU per kg dose, excluding the possibility of a a rapid clearance pattern as the recovery rate was nearly normal (VWF: GPIb increased from 4.2 to 57.7 IU/dL). Trough levels were also satisfactory, with VWF: GPIb remaining at 31.8 IU/dL nine hours after administering a 25 IU per kg dose.

Multiple tests were performed throughout the patient's hospitalization to determine the underlying cause of the disease. Valve function was evaluated through echocardiography, revealing no notable abnormalities. The levels of thyroid-stimulating hormone, prostate-specific antigen, and beta-2 microglobulin levels were

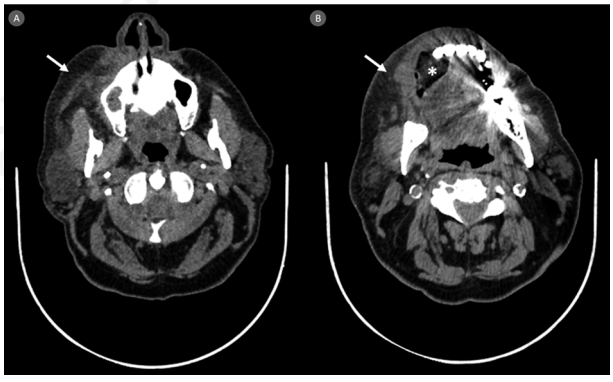
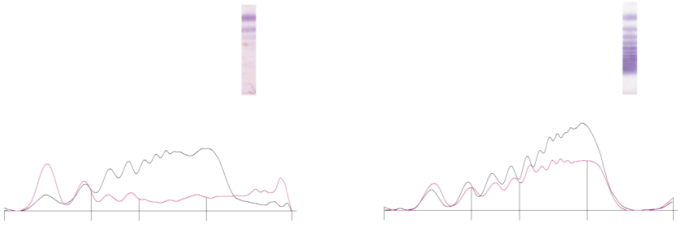


Figure 1. Axial contrast-enhanced computed tomography on admission. Right hemifacial subcutaneous tissue thickening (arrows). Postoperative changes on the right maxillary hemiarch (asterisk in panel B).

Table 1. Multimer von Willebrand factor pattern before (1st measurement) and after (2nd measurement) the cessation of allopurinol.

	1st measurement, %	2nd measurement, %	Reference values
LMWM	34.1	14.0	(8.48-15.20)
IMWM	14.6	18.3	(16.65-21.11)
HMWM	17.7	49.2	(48.49-55.21)
VHMWM	33.6	18.5	(14.28-20.58)
Electrophoresis			

LMWM, low molecular weight multimer; IMWM, intermediate molecular weight multimer; HMWM, high molecular weight multimers; VHMWM, very high molecular weight multimers.

within normal range. The autoantibody screening panel yielded negative results. Serum biomarkers did not suggest the presence of liver dysfunction. Hematologic neoplasms commonly associated with the condition were ruled out through examinations of the blood smear, lymphocyte populations, proteinogram, immunoglobulin levels, and molecular testing for V617F *JAK-2* mutation and *BCR::ABL* rearrangement. No positive findings for von Willebrand disease-related genetic mutations were detected through next-generation sequencing. A computed tomography scan was conducted, revealing no liver alterations or solid tumors, except for a small polyp in the cecum, which was successfully removed endoscopically and showed no signs of malignancy.

Having exhausted every complementary testing that could lead to a diagnosis, the possibility of a drug-induced condition was considered. Amoxicillin-clavulanate was ruled out, as it was initiated when the bleeding was already present, and then suspended and reintroduced during the patient's hospitalization, with no changes in his clinical status. Allopurinol was suspended on day 17 after admission. VWF levels improved significantly two days later, allowing termination of substitution treatment and clinical and analytical stabilization (VWF: Ag and VWF: GPIb reached 168 IU/dL and 109 IU/dL respectively within 24 hours after stopping exogenous VWF; Figure 2). Multimer levels were also normalized (Table 1). During immediate follow-up after discharge, alternative therapy with febuxostat was initiated and regular anticoagulation was restarted. The patient did not develop any other complications on this matter and remained in complete response.

Discussion

AVWS is an often overlooked and relatively infrequent finding when testing for VWF levels in a patient with mucocutaneous bleeding.[1,2] Its association with aortic stenosis, and more particularly with mechanical valves, is well-known and described in multiple case reports and revisions.[4] This prior helped raise suspicion on the possibility of an AVWS in our patient, after ruling out the possibility of an anticoagulation excess but was not its ultimate cause. Clinicians should also test for the presence of hypothyroidism, autoimmune diseases, and hematologic and solid tumors at diagnosis.[4]

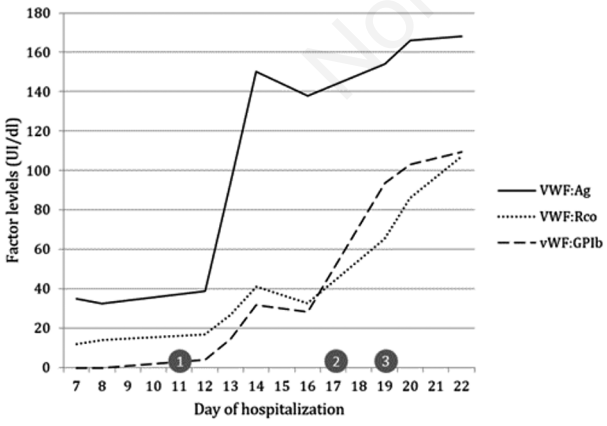


Figure 2. Evolution of von Willebrand factor levels during the patient's hospitalization (count starts at day seven, when they were first measured). 1. Day 11: initiation of substitution therapy with intravenous von Willebrand factor, 2400 IU every 12 hours. 2. Day 17: withdrawal of alopurinol. 3. Day 19: withdrawal of von Willebrand factor. VWF, Von Willebrand factor; Ag, antigen levels; Rco, ristocetin cofactor activit.

There are several drugs known to be involved in the decrease in VWF levels. Valproic acid, ciprofloxacin, griseofulvin, tetracyclines, thrombolytic agents, hydroxyethyl starch (HES), high-dose recombinant factor VIII, and pesticides have been previously reported.[2-3] No clear pathogenic mechanisms have been proposed except for HES (absorption of multimers of VWF into its large molecules) and ciprofloxacin (increased proteolysis of the FVW by specific proteases). Causality was established based on the normalization of all hemostatic parameters after suspension of the medicine.[3]

AVWS type 2A is the most commonly described form of the disease when associated with drug toxicity,[3] which was consistent with our patient's antigen levels and VWF activity along with the loss of IMWM and HMWM. However, VHMWM were paradoxically incremented. This has been described in some cases of congenital type 1 VWD, associated with an increment of FVW synthesis trying to compensate for its rapid clearance.[6] The latter mechanism could explain the phenomenon observed in our patient. The administered exogenous VWF molecule do not seem to have been affected by the possible proteolysis, which could account for the normal recovery pattern we observed when testing for post-administration efficacy, but this is only speculation.

Allopurinol has not previously been associated with the occurrence of AVWS. The Naranjo adverse drug reaction probability scale yielded a low grade (four points),[7] indicating a possible adverse event, although this score may be influenced by the predominant role of pharmacodynamics in its calculation. To prevent iatrogenic effects, the drug was not reintroduced, which represented the main limitation in establishing causality. According to the WHO-UMC categorization,[7] this association would be more accurately described as a probable or likely adverse event of the medication.

Conclusions

AVWS is an underdiagnosed entity. Its diagnostic workup requires a high level of suspicion and well-designed labs or a comprehensive network of facilities. Multimeric analysis is crucial when diagnosing AVWS to determine its potential underlying physiopathology mechanism. The possibility of a drug-induced AVWS must always be considered in our differential diagnosis and alopurinol should be ruled out as a possible cause.

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