Acquired von Willebrand Disease in a Patient with a Left Ventricular Assist Device: Measuring Anti-Factor Xa to Titrate Anticoagulation

Trent Rook, BS; Steven Swavely, BS
Pennsylvania State University College of Medicine, Hershey, PA

ABSTRACT

This case illustrates that those with left ventricular assist devices (LVADs) have the potential to develop an acquired von Willebrand Disease (avWD), which can subsequently alter the patient’s partial thromboplastin time (PTT). There is a growing body of recent literature suggesting that the use of anti-factor Xa blood levels in place of PTT is more appropriate management, as demonstrated by this patient. Educating future physicians on how to properly monitor and anti-coagulate such a patient is clinically important.

A 60-year-old gentleman with ischemic cardiomyopathy, status-post LVAD placement, presented with hematuria. His echocardiogram demonstrated a thrombus obstructing the normal function of the LVAD. A heparin drip was initiated with an initial PTT in therapeutic range of 45-55 seconds. Despite adequate treatment, his symptoms failed to resolve and on further investigation his anti-factor Xa level was found to be subtherapeutic. Once the anti-factor Xa level was adjusted appropriately, the hemoglobinuria and intravascular hemolysis resolved. The corresponding PTT was higher than expected at 75-85 seconds. The patient returned to baseline and was discharged home in stable condition.

Despite being potentially hypocoagulable with avWD, those with heart assist devices are commonly anticoagulated to prevent severe morbidity and mortality resulting from clot formation due to the LVAD.

CASE PRESENTATION

A 60-year-old male with a past medical history of ischemic cardiomyopathy status post LVAD placement two years prior, pulmonary carcinoid tumor, hyperlipidemia, hypertension, morbid obesity, gout, obstructive sleep apnea, severe chronic obstructive pulmonary disease (COPD) on home oxygen as needed, and hypothyroidism status post Graves’ disease presented to the Emergency Department as a referral from an outside hospital for blood in his urine. Around noon that day, the patient noticed his urine was a dark amber color that progressively darkened as the day continued, which caused him to seek care at the outside hospital’s Emergency Department. The patient’s past surgical history included a coronary bypass graft, an implanted biventricular pacer, and LVAD placement. His only known allergy was to acetaminophen, which re-
sults in an anaphylactic reaction. The patient’s medications included allopurinol, alprazolam, aspirin, ipratropium bromide/albuterol, warfarin, docusate, furosemide, gabapentin, hydralazine, magnesium oxide, methylprednisolone, metolazone, oxycodone, potassium chloride, pravastatin, pantoprazole, spironolactone, levothyroxine, and zolpidem. He had a 20-pack/year history of smoking, and denied any alcohol or illicit drug usage. Family history was insignificant for cardiovascular or clotting disorders. Review of systems was significant for hematuria and chronic respiratory symptoms. Pertinent positives on physical exam included the absence of palpable pulses, which is a normal finding in post-LVAD patients, and the presence of muffled LVAD mechanical sounds with distant heart tones that were of regular rate and rhythm on cardiac auscultation. On further evaluation, he was found to have intravascular hemolysis (lactate dehydrogenase [LDH] of 4419 U/L and plasma hemoglobin of 95 g/dL) and an echocardiogram with findings significant for LVAD pump dysfunction and a left ventricle that was not unloaded, which was consistent with a thrombus obstructing the normal function of the LVAD. The patient was placed on a heparin drip of 1000 units/hr. The hemoglobinuria did not resolve and the LDH and plasma hemoglobin failed to normalize, despite PTT measurements in the therapeutic range of 45-55 seconds.

In light of this anomaly, anti-factor Xa levels were then used as a surrogate marker for appropriate anticoagulation level, with a goal of therapeutic heparin level 0.3-0.7 U/mL. As initial labs revealed a subtherapeutic anti-factor Xa level despite the appropriate PTT levels, the heparin dosage was increased (Figure 1). Once the anti-Xa level was appropriate, the hemoglobinuria and intravascular hemolysis resolved. The corresponding PTT was higher than expected at 75-85 seconds. Based on the amount of heparin required, warfarin dosing was calculated and appropriately bridged and discharged once the patient reached a new goal INR of 2-2.5.

Figure 1. Results of sequential testing showing a discordance between the patient’s PTT (therapeutic level 45-55 seconds) and his anti-factor Xa level (therapeutic level 0.3-0.7 IU/mL). As seen on initial testing, the anti-factor Xa level was subtherapeutic despite a PTT within the therapeutic range. As such the unfractionated heparin was rapidly increased to compensate for the severe deficit. This resulted in a supratherapeutic value necessitating fine-tuning of unfractionated heparin dosing. Given the clinical improvement and the patient’s propensity for a subtherapeutic coagulation profile, the decision was made to maintain a final steady-state that was slightly supratherapeutic as seen above.
DISCUSSION

LVADs have become a mainstay of therapy for individuals with heart failure as a means of bridge to transplantation, a bridge to recovery in acute heart failures, or as an alternative to heart transplantation as a result of a shortage of heart donors. While LVADs have their merits, they are not without risk; this risk includes recurrent severe bleeding (44% within 56 days post-operative). Hence, there is a delicate balance between remaining properly anticoagulated to avoid thrombus formation due to the foreign body LVAD and bleeding risk. These bleeding events cannot be entirely explained by the administration of prophylactic anticoagulation; rather, it is hypothesized that this population is at increased risk of developing avWD. LVADs represent the newest potential risk factor of a growing list of documented causes of avWD including (in order of prevalence): lymphoproliferative and myeloproliferative disorders, cardiovascular defects like aortic stenosis, and neoplasias. Unlike congenital vWD, which results from a mutation in the gene for von Willebrand factor (vWF), the increased shearing stress of LVADs causes a quantitative loss of the high-molecular weight vWF multimers necessary for clotting. vWF multimers bind to the collagen of damaged vessel walls and subsequently allow platelet adherence via their GPIb/IX receptor, promoting clot formation. Studies performed using electrophoresis on patients with LVAD-associated bleeding showed a decrease in large vWF multimers, compared to a matched sample. Thus, patients with congenital or acquired vWD have increased bleeding tendencies.

Despite being potentially hypocoagulable with avWD, those with heart assist devices are commonly anticoagulated to prevent severe morbidity and mortality resulting from clot formation due to the LVAD. Recent literature suggests that anticoagulation should be titrated to a therapeutic anti-factor Xa range for monitoring unfractionated heparin in patients with LVADs, as the PTT is disproportionately prolonged due to avWD. Von Willebrand Factor (vWF) is an essential glycoprotein involved in hemostasis. In the normal population, vWF binds with factor VIII, thus protecting it from degradation. In patients with vWD, there is a deficiency of vWF that exposes factor VIII to more rapid breakdown. Factor VIII is involved in the intrinsic pathway of the coagulation cascade, of which PTT is a surrogate laboratory marker. Decreases in blood factor VIII lead to an elevation in the PTT. Heparin also affects the intrinsic pathway of the coagulation cascade by activating antithrombin III, which then inactivates thrombin and factor X, among other proteases.

While PTT can be used to trend heparin, it is an indirect marker for heparin’s effect on the coagulation cascade, whereas monitoring anti-factor Xa levels are a more direct measure, which provides an obvious advantage over using PTT for anticoagulation monitoring. This is clinically important because a patient who seems properly anticoagulated may in fact be subtherapeutic, exposing them to the risk of clots. The primary disadvantage of using such a system is lower availability and higher cost because it is not currently the standard of care for heparin monitoring; its use is becoming more widespread due to variation in PTT values. In the event of LVAD obstruction leading to malfunction and subsequent active hemolysis, this is especially important. Consequently, though these individuals may appear to be therapeutically anticoagulated, as demonstrated by our patient and his seemingly appropriate coagulation profile, they may be at increased risk of thrombosis as a result of inaccurate standard testing parameters.
LEARNING POINTS

1. In the post-operative setting of LVAD placement, partial thromboplastin time (PTT) may be falsely prolonged due to avWD.

2. Anti-factor Xa levels are more appropriate for correlating warfarin dosing for chronic anticoagulation in LVAD patients.

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REFERENCES


