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Case Report

Antithrombin III Deficiency in Patients Requiring Mechanical Circulatory Support

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Keywords

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- Ventricular assist device
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Abstract

Introduction: Antithrombin or antithrombin III is a vitamin K-independent, natural anticoagulant that is the major inhibitor of thrombin. With the binding of heparin, a conformational change in antithrombin occurs that increases the inactivation of thrombin by antithrombin by 4000-fold. Antithrombin deficiency can be hereditary or acquired; the acquired form is frequently encountered in patients requiring mechanical circulatory support.

Cases: A retrospective chart review was performed of patients requiring mechanical circulatory support, 2 patients were identified as being antithrombin deficiency and received antithrombin replacement therapy. Patient 1 required extracorporeal membrane oxygenation (ECMO) for cardiogenic shock secondary to myocardial infarction. The ECMO oxygenator repeatedly clotted, which triggered an investigation into the failure of anticoagulation. The clots dissolved after replacement of the antithrombin III. Patient 2 required biventricular assist device placement for cardiogenic shock secondary to myocardial infarction. On day 5 both the right and left ventricle devices developed clot and the hematologic work-up diagnosed antithrombin III deficiency. After replacement of the antithrombin III the clot in the device chamber resolved.

Conclusions: Routine monitoring of antithrombin levels in patients requiring mechanical circulatory support is advisable and cost efficient. Institutions that routinely care for patients requiring mechanical circulatory support should have protocols for triggering the monitoring of antithrombin levels as well as triggers for therapeutic intervention when patients are found to be antithrombin deficient.

ABBREVIATIONS

ATIII: Antithrombin III**; BiVAD:** Biventricular Assist Device; **ECMO:** Extracorporeal Membrane Oxygenation; **ICD:** Implantable Cardioverter-Defibrillator; **MCS**: Mechanical Circulatory Support; **POD**: Postoperative Day; **PTT**: Partial Thromboplastin Time; **VAD**: Ventricular Assist Device.

INTRODUCTION

Formation of clots within the circuit of mechanical circulatory support (MCS) such as extracorporeal membrane oxygenation (ECMO) or ventricular assist device (VAD) is a life-threatening emergency and requires emergent intervention. Unfractionated heparin is a commonly used anticoagulant for MCS because of its proven efficacy, easy titration, and reversibility if needed. Heparin binds with anti-thrombin III (ATIII) and then the ATIII-heparin complex inhibits factor Xa and inhibits the activation of prothrombin [1]. ATIII deficiency can result in heparin resistance, which can be a challenge for patients requiring MCS. We present 2 patients with ATIII deficiency, diagnosed while on the MCS. Both patients developed significant clots in the devices and which quickly resolved with ATIII replacement.

CASE PRESENTATION

Patient 1

A 56 year old male with a past medical history of chronic obstructive pulmonary disease, ischemic cardiomyopathy with implantable cardioverter-defibrillator (ICD) placement, coronary artery disease with prior stents placed in the left anterior descending coronary artery in 2004 and 2005, congestive heart failure, hypertension, hyperlipidemia, and polycythemia was transferred to our facility from an outside hospital where he initially presented with a complaint of several syncopal episodes

and multiple discharges of his ICD. At the outside hospital a cardiac catheterization was attempted, during which the patient had an episode of pulseless electrical activity. After initial resuscitation and placement of an intra-aortic balloon pump, the patient was transferred to our facility for further management. Upon arrival, laboratory data showed a white blood cell count of 13.6 B/L, hemoglobin of 13.8 g/dL, platelets of 144 B/L, prothrobin time/international normalized ratio (PT/INR) of 15.7sec/1.28, partial thromboplastin time (PTT) of 38sec. His initial echocardiogrphy showed an ejection fraction of 5-10%. At this time the patient was requiring norepinephrine at 0.28 mcg/kg/min and the patient was developing end-organ injury (acute renal failure, lactic acidosis and pulmonary edema). After being assessed by the cardiothoracic surgery team, the patient was placed on ECMO. Cardiac catheterization at that time showed complete occlusion of the left anterior descending artery, no intervention was applied, and intravenous heparin was started after completion of the catheterization. On postoperative day (POD) 3, despite being adequately anticoagulated using 1000-1550 units/hour of heparin at a target PTT level of 55-65 sec, the oxygenator was noted to contain extensive clot for which the circuit was exchanged. This problem recurred on POD# 4, requiring a second exchanged of the oxygenator. On POD# 6, the ECMO circuit was again noted to contain extensive clot (Figure 1 left). Laboratory studies revealed antithrombin III (ATIII) level of 52% (normal 84-134%) and anti-factor Xa level of 0.10 IU/mL. The patient received 2000 units of antithrombin III (ThrombateIII, Talecris Biotherapeutics, Research Triangle Park, NC) intravenously and an additional 2000 units on the following day. Subsequently, the clots in the ECMO circuit resolved (Figure 1 right). On POD# 10, the patient was taken to the operating room and underwent coronary artery bypass grafting with saphenous vein graft to left anterior descending, and weaning and removal of ECMO without incident. The echocardiogram on POD# 15 showed ejection fraction (EF) of 15%.

Patient 2

A 52 year old male with a past medical history of hypertension who, after experiencing chest pain presented to an outside hospital, where it was found that he had a massive acute myocardial infarction. An immediate cardiac catheterization was performed with planned percutaneous coronary intervention. Catheterization revealed extensive 3-vessel disease with the completely occluded th left anterior descending artery, thus the intervention was not attempted. The patient became hemodynamically unstable in the cardiac catheterization lab. After an intra-aortic balloon pump was placed he was taken emergently to the operating room. There was no graftable coronary artery and patient was in cardiogenic shock. At this time, a biventricular assist device (BiVAD) using BVS 5000 (Abiomed Inc, Danvers, MA) was placed. He was transferred to our facility for further management. Transesophageal echocardiography showed severe biventricular failure on BiVAD support. He was started on an intravenous heparin infusion with rates between 750-1600 units/hour and a goal PTT of 55-65 sec. On POD# 3, he returned to the operating room for a pump exchange due to clot formation in the device chambers. On POD# 5, despite intravenous heparin therapy, we noted again a large volume of white clot in both left and right devices. Laboratory studies revealed an ATIII level of 51%, and an anti-factor Xa level of 0.25 IU/mL, and repeated value was 30% and 0.03 IU/mL, respectively. 2500 units of ATIII were given intravenously in addition to the continuously administered intravenous heparin therapy. Within 48 hours, the clots in the VAD completely resolved.

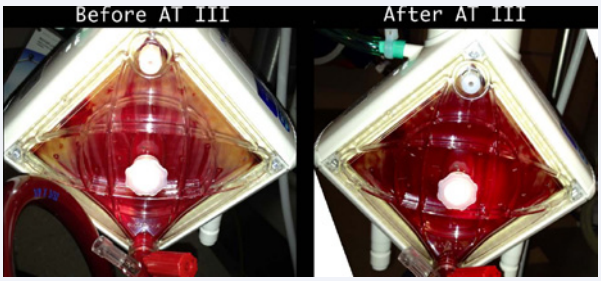

Figure 1 Photograph of ECMO oxygenator of case 1. Clots formed in the oxygenator (left) is resolved after treatment with antithrombin III (right).

DISCUSSION

ATIII or antithrombin (AT) is a vitamin K-independent, natural anticoagulant that is the major inhibitor of thrombin. With the binding of heparin, a conformational change in AT occurs that increases the inactivation of thrombin by AT by 4000-fold. Hereditary deficiency of AT is inherited in an autosomal dominant fashion with variable penetrance. Two types of AT deficiency have been described: Type I deficiency results from reduced synthesis of the AT. Homozygous AT type I deficiency is thought to be incompatible with life, and heterozygotes exhibit AT levels 40-60% of normal. Antigenic and functional activity of AT are reduced equally. Type II deficiency results from a molecular defect within the AT protein, thus functional activity is reduced by immunologic activity remains unchanged. Typical patients with both type I or II deficiency present with venous thromboembolism [2].

Acquired deficiency of AT is generally attributed to four different pathophysiologies; accelerated consumption, reduced synthesis, increased excretion, and drugs. Accelerated consumption can be seen in acute thrombotic conditions such as disseminated intravascular coagulation, sepsis and following major surgery. Patients requiring mechanical circulatory support are at an increased risk of developing AT deficiency for many of these reasons.

One widely available test for AT deficiency compares the amount of AT in a patient's plasma to the amount found in normal pooled plasma, approximately 140 μg/mL. A normal value for most laboratories is 75-120 percent. The cost of this laboratory test at our institution is $398.00. Additionally, the anti-factor Xa assay with values between 0.35-0.67 IU/mL that corresponds to PTT between 60-80 seconds can also be used to confirm the diagnosis. The cost of this test at our institution is $301.00. A recent survey of medical directors coordinators of Extracorporeal Life-Support Organization centers showed that in the institutions surveyed 51% routinely checked AT levels of patients requiring ECMO, and 31% occasionally checked these levels, while 40% routinely monitored anti-factor Xa levels and 25% measured anti-factor Xa occassionally. Furthermore, of

those that reported monitoring AT levels, 78% checked AT levels at least every 24 hours on all patients requiring ECMO [2,3]. Formation of a clot within a mechanical circulatory device can be catastrophic and frequently requires urgent intervention. As in the first case described above, in addition to the considerable time and effort applied in changing the ECMO circuit several times, the financial concerns must also be addressed. At our institution, the cost of a single ECMO circuit is $1,200 and the cost of the Abiomed ventricles is $40,000 each. In the second case, had the BiVAD required an exchange, the resources used in returning to the operating room would also have been significant. As demonstrated in the photo series, resolution of the clot burden was dramatic with the administration of ATIII. In patients with known AT deficiency, the correct dosing of AT depends on the specific patient's pre-therapy AT levels. The loading dose for a non-pregnant patient is [(100 - baseline AT activity level)/2.3] x body weight (kg) = units of AT required. The maintenance dose is also based on the baseline AT levels; [(100 -baseline AT activity level)/10.2] x body weight (kg) =units of AT required per day. The cost of Thrombate III (Grifols USA LLC, Los Angeles, CA) is $2.98/IU.

Patients requiring mechanical circulatory support present unique challenges, we have described two incidences of AT deficiency leading to substantial use of resources in the care of these patients. In any patient requiring mechanical circulatory support where there is evidence of a failure of anticoagulation therapy, a high clinical suspicion for AT deficiency can be very beneficial. Laboratory testing for AT deficiency (AT-III level, Anti-factor Xa) should be initiated immediately when a suspected failure of anticoagulation is encountered. Additionally, it may be advisable for institutions that treat patients requiring mechanical circulatory support to have a protocol for regarding the regular monitoring of AT levels in these patients and the triggers of values or events that prompt either further laboratory investigation or therapy with AT. With prompt recognition of the inherited AT deficiency and initiation of intravenous AT considerable morbidity and mortality can be avoided, and overall costs of operating and maintaining the mechanical circulatory devices can be reduced.

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