



## Case Report

### Perioperative and Postoperative Management in Patients with Alpha-2-Antiplasmin Deficiency: A Case Study of 67-Year-Old Male Undergoing Operative Distal Femur Repair

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#### Abstract

**Introduction:** Alpha-2-antiplasmin deficiency is a rare autosomal recessive condition characterized by increased fibrinolysis which can subsequently lead to uncontrolled hemorrhage. First described in Japan in 1969 by Masateru Kohakura, alpha-2-AP deficiency is rare with fewer than 50 published case studies to date. Individuals with alpha-2-AP deficiency will have normal coagulation parameters including platelet count, bleeding time, Prothrombin Time (PT), activated Partial Thromboplastin Time (aPTT), and clotting factor titers. In alpha-2-AP deficiency patients, clots are able to form normally but degrade in an accelerated fashion prior to the initiation of tissue and vascular repair. Diagnosis of alpha-2-AP deficiency thus requires a high index of suspicion and can be confirmed with specific functional and immunological antiplasmin assays. Here we present a case of a 67-year-old male with known history of homozygous alpha-2-AP deficiency undergoing intramedullary fixation of a distal femur fracture, followed by a discussion of the literature on Perioperative and postoperative strategies for individuals with  $\alpha$ 2-AP deficiency.

**Case Discussion:** A 67-year-old male with known history of homozygous alpha-2-AP deficiency presented to our institution with a displaced distal left femur fracture status post a fall from standing height. He has a past medical history of coal workers pneumoconiosis, hypertension, treated hepatitis C infection, and hypothyroidism

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as well as prior right humeral fracture requiring surgical correction and previous intracranial hemorrhage in 2013 from a horse accident, both successfully managed with antifibrinolytic therapy. Immediate pre-operative management for bleeding risk included infusion of FFP and 1 gram of tranexamic acid IV bolus. He then received a continuous infusion of tranexamic acid intraoperatively. He underwent uneventful intramedullary fixation of the left distal femur. After completion of the infusion, he was placed on tranexamic acid 1300 mg q 8 hours. Unfortunately, on post-operative day 7, patient developed a new Left Lower extremity deep venous thrombosis despite prophylactic LMWH.

**Discussion:** Patients with alpha-2-AP much like those with hemophilia have increased bleeding tendencies during surgical procedures. Generally, adequate hemostasis can be managed with administration of anti-fibrinolytic agents. As in our case, there remains the potential for thrombotic events related to antifibrinolytic therapy and the benefits versus risks of treatment will need to be considered in every surgical case in patients with diagnosis of homozygous alpha-2-AP deficiency. Since it is a rare entity, there is limited medical literature to utilize as guidelines in managing such patients and the approach to post-operative hemorrhaging and DVT prophylaxis in individuals with defects in the fibrinolysis pathway should be considered on a case-by-case basis taking into consideration additional risk factors for both bleeding and thrombosis.

#### Introduction

Alpha-2-antiplasmin ( $\alpha$ 2-AP) deficiency is a rare autosomal recessive condition characterized by increased fibrinolysis which can subsequently lead to uncontrolled hemorrhage [1]. First described in Japan in 1969 by Masateru Kohakura in a 16 year old boy with repeated unexplained bleeding [2].  $\alpha$ 2-AP deficiency is rare with fewer than 50 published case studies to date [3-14]. Homozygous  $\alpha$ 2-AP deficiency is seen in consanguineous families and may initially present with umbilical bleeding [1]. Bleeding tendencies can be pronounced in the heterozygous state as well, although heterozygous individual's may have normal levels of  $\alpha$ 2-AP [15,16]. While manifestations of bleeding are similar to hemophilia patients, those individuals with  $\alpha$ 2-AP deficiency will have normal coagulation parameters including platelet count, bleeding time, Prothrombin Time (PT), activated Partial Thromboplastin Time (aPTT), and clotting factor titers. In  $\alpha$ 2-AP deficiency patients, clots are able to form normally but degrade in an accelerated fashion prior to the initiation of tissue and vascular repair. Diagnosis of  $\alpha$ 2-AP deficiency thus requires a high index of suspicion and can be confirmed with specific functional and immunological antiplasmin assays, which would confirm either Type I (quantitative; decrease in  $\alpha$ 2-AP activity and antigen) or Type II (qualitative; decrease in  $\alpha$ 2-AP activity but with normal antigen levels) deficiencies [17].

The formation of a fibrin clot represents the final step in secondary hemostasis representing a common end point of the intrinsic and extrinsic coagulation pathways [18]. The fibrin meshwork exists in a delicate equilibrium controlled by factors promoting fibrin formation as well as the reverse process of fibrinolysis, which controls clot

formation to a minimum necessary to facilitate tissue repair. Tissue type Plasminogen Activator (tPA) and urokinase type Plasminogen Activator (uPA) play primary roles in fibrinolysis by converting protein plasminogen to an active serine protease, plasmin. Plasmin function is to cleave fibrin and is inhibited by  $\alpha$ 2-AP [19]. This interplay is depicted in figure 1.  $\alpha$ 2-AP forms a direct complex with plasmin via factor XIIIa, inhibits adsorption of plasminogen to fibrin, and strengthens the local fibrin network through cross linking.  $\alpha$ 2-AP is mainly synthesized in the liver, but some production has been observed in the kidney and brain. It has a half-life of 2.6 days [1]. Acquired  $\alpha$ 2-AP can be seen in liver disease, amyloidosis, and in iatrogenic states during fibrinolytic therapy [16]. Bleeding episodes in those with phenol typically significant  $\alpha$ 2-AP are typically well controlled with oral antifibrinolytic agents, such as aminocaproic acid or tranexamic acid which act by preventing plasminogen from binding fibrin [1].

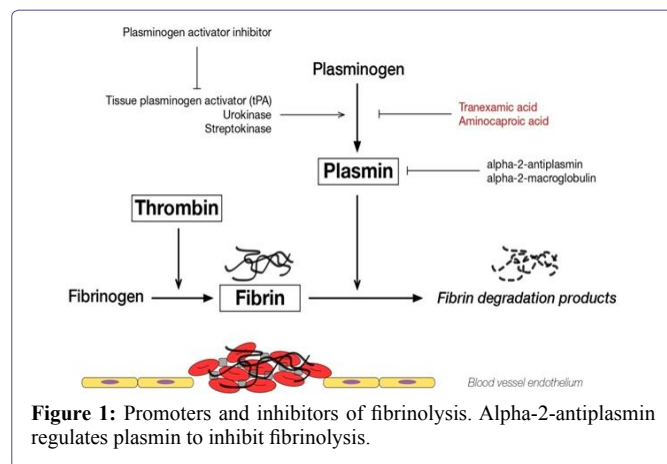


Figure 1: Promoters and inhibitors of fibrinolysis. Alpha-2-antiplasmin regulates plasmin to inhibit fibrinolysis.

Patients with  $\alpha$ 2-AP deficiency represent unique challenges in the operating room and during recovery from surgical procedures. Here we present a case of a 67-year-old male with known history of homozygous  $\alpha$ 2-AP deficiency undergoing intramedullary fixation of a distal femur fracture, followed by a discussion of the literature on perioperative and postoperative strategies for individuals with  $\alpha$ 2-AP deficiency.

## Case Discussion

A 67-year-old male with known history of homozygous  $\alpha$ 2-AP deficiency presented to our institution with a displaced distal left femur fracture status post a fall from standing height. Patient was diagnosed with alpha-2-antiplasmin deficiency at the age of 33 after repeated spontaneous and provoked bleeding episodes requiring Fresh Frozen Plasma (FFP) to control. Since his diagnosis, patient has been treated with oral antifibrinolytic agents including aminocaproic acid and tranexamic acid on an as needed basis with adequate control. He has a past medical history of coal workers pneumoconiosis, hypertension, treated hepatitis C infection, and hypothyroidism as well as prior right humeral fracture requiring surgical correction and previous intracranial hemorrhage in 2013 from a horse accident, both successfully managed with antifibrinolytic therapy. Patient has one sister with homozygous  $\alpha$ 2-AP deficiency and two sons who are heterozygous for the condition, both of whom have normal serum levels of  $\alpha$ 2-AP.

Patient weighed 111 kilograms at presentation. As expected, our patient had normal coagulation laboratory tests at admission. His

I.N.R. was 1.1 with a Prothrombin Time (PT) of 14.1 seconds and an activated Partial Thromboplastin Time (aPTT) of 30 seconds. Immediate pre-operative management for bleeding risk included infusion of two units of FFP and 1 gram of tranexamic acid IV bolus over 10 minutes (100 mg/mL infused at 1 mL/minute). Post infusion coagulation parameters remained normal. It would have been ideal to have  $\alpha$ 2-AP activity levels before, during, and after the treatment; however, the testing for  $\alpha$ 2-AP activity is not a readily available test and could not be medically justified. He then received a continuous infusion of 1 gram of tranexamic acid intraoperatively (100 mg/mL infused at 1.25 mL/hour for 8 hours). He underwent uneventful intramedullary fixation of the left distal femur. After completion of the infusion, he was placed on tranexamic acid 1300 mg q 8 hours. Patient was also placed on Low-Molecular Weight Heparin (LMWH) 30 mg twice a day for Deep Venous Thrombosis (DVT) prophylaxis. He demonstrated good hemostasis with no postoperative hemorrhaging and was discharged in stable condition on post-operative day 2 to a rehabilitation facility.

Unfortunately, on post-operative day 7, patient developed a new Left Lower extremity deep venous thrombosis despite prophylactic LMWH. At that time, his LMWH dose was increased to 100 mg bid with continuation of home dose tranexamic acid until repeat duplex ultrasound obtained post-operative day 11 demonstrated no evidence of thrombotic extension. His tranexamic acid was discontinued at that time and he was treated with prophylactic LMWH 30 mg BID for a total of six weeks. Follow up duplex ultrasound after therapy showed no evidence of residual thrombosis.

## Discussion

Patients with  $\alpha$ 2-AP much like those with hemophilia have increased bleeding tendencies during surgical procedures. Generally, adequate hemostasis can be managed with administration of anti-fibrinolytic agents. As in our case, there remains the potential for thrombotic events related to antifibrinolytic therapy and the benefits versus risks of treatment will need to be considered in every surgical case in patients with diagnosis of homozygous  $\alpha$ 2-AP deficiency. Since it is a rare entity, there is limited medical literature to utilize as guidelines in managing such patients. It can be even more difficult when the diagnosis of  $\alpha$ 2-AP deficiency is not known. One report describes the case of a 6-year-old boy with a history of severe bleeding after an elective adenoidectomy. Standard perioperative tests for coagulation parameters remained within normal limits, but patient had profound bleeding after his procedure which required two repeat attempts of surgical hemostasis in the operating room. He was discovered to have homozygous  $\alpha$ 2-AP deficiency with a serum  $\alpha$ 2-AP concentration of 24 percent (normal > 60 percent) [8].

Shahian and Levine reported a case of open aortic valve replacement and coronary bypass in an individual with known heterozygous  $\alpha$ 2-AP deficiency with serum  $\alpha$ 2-AP concentration of 52 percent. Patient underwent infusion of 3000 mL of FFP, which increased perioperative  $\alpha$ 2-AP levels to 78 percent [6]. Morimoto et al describes management of intraoral bleeding in those with  $\alpha$ 2-AP deficiency with 7.5-10 mg/kg of tranexamic acid orally every 6 hours starting 3 hours before procedure to be continued for 7 days [20]. There are no published recommendations for aminocaproic acid dosing in this setting. As recommended by our Hemophilia Treatment Center, our patient received two units of FFP and 1g of IV tranexamic acid bolus pre-operatively with a continuous infusion of 1g tranexamic acid over eight hours intraoperatively and transition to oral tranexamic acid 1300 mg

q 8 hours. The incidence of thrombosis and pulmonary embolism is not known for aminocaproic acid administration, but for tranexamic acid, the incidence for either entity is < 1% [21].

The guidelines for DVT prophylaxis in patients with  $\alpha$ 2-AP deficiency are also not established given the rarity of this condition. In xenograft models of Pulmonary Emboli (PE),  $\alpha$ 2-AP was shown to play a critical role in resistance to thrombolysis [22] and its inhibition led to thrombolysis in a comparable manner to tPA administration [23], perhaps even with synergistic effects with tPA in decreasing mortality from PE [24]. These findings open the possibility of utilizing  $\alpha$ 2-AP in a therapeutic capacity for thrombotic events. Despite the antithrombotic tendencies inherent in those with  $\alpha$ 2-AP deficiency, orthopedic procedures on weight bearing bones and joints in particular result in higher postoperative risk of DVT given the likelihood of post-operative immobility. Similarly, in patients with hemophilia, pharmacologic thromboprophylaxis is also considered controversial. At least one source does not recommend thromboprophylaxis for those hemophilia patients with an inhibitor given the high risk of bleeding but does recommend thromboprophylaxis after orthopedic procedures in those without inhibitor [25].

In our patient, prophylactic LMWH at 30g bid in conjunction with tranexamic acid was sufficient in preventing post-operative hemorrhage, but was unsuccessful in preventing DVT. It is unknown whether full dose therapeutic LMWH would have been more successful in preventing the DVT without compromising post-operative bleeding risk. Heparin products work by binding antithrombin and accelerating its activity by 1000 fold. The result is decrease in Factor Xa and IIa (activated Thrombin) influence in the coagulation system. This seemingly predates the formation of Fibrin and hence the fibrinolytic pathway as well. In reality, these opposing forces that balance hemostasis are occurring simultaneously. In  $\alpha$ 2-AP deficiency, Plasmin is left activated and able to degrade Fibrin leading to clot dissolution. Inhibition of the fibrinolytic pathway with tranexamic acid can lead to unopposed fibrin longevity with possible propagation to pathologic thrombosis. The approach to post-operative DVT prophylaxis in individuals with defects in the fibrinolysis pathway should be considered on a case-by-case basis taking into consideration additional risk factors for bleeding and thrombosis such as thrombocytopenia, extent of surgical trauma, immobility, malignancy, obesity, and concurrent medications. Recognizing that both entities are increased in this patient population is paramount. Although this situation is rare, it is our practice to utilize anti-fibrinolytic agents to correct the known hereditary defect while administering standards of care anticoagulation to minimize the thrombotic risk. As this case demonstrates, even with careful consideration, morbidity can occur.

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