Received: 15 February 2024 | Accepted: 20 February 2024

https://doi.org/10.1016/j.rpth.2024.102384

CASE REPORT

Perioperative management of venous recanalization in a patient with inherited antithrombin deficiency: case report

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Handling Editor: Mike Makris

Abstract

Background: Inherited antithrombin (AT) deficiency (ATD) is a severe thrombophilia causing venous thromboembolism, which can be complicated by postthrombotic syndrome (PTS). Venous recanalization, used to treat PTS, often requires a temporary withdrawal of anticoagulant therapy. In ATD patients, there is a risk of insufficient perioperative anticoagulation due to altered heparin response.

Key Clinical Question: There is no consensus on how to manage perioperative anticoagulation in ATD patients.

Clinical Approach: Warfarin-unfractionated heparin transition could be a more reliable strategy than low-molecular-weight heparin transition because unfractionated heparin anti-Xa activity not only reflects heparin-bound AT but also AT's activity, which correlates strongly with therapeutic anticoagulation. Biological monitoring could thus decrease the number of plasma-derived AT supplementation.

Conclusion: This study describes a successful perioperative management of anticoagulation for venous recanalization that could be suggested to type 1 ATD patients with PTS.

KEYWORDS
antithrombin deficiency, perioperative anticoagulation management, postthrombotic syndrome, unfractionated heparin, venous recanalization, venous thromboembolism

Essentials

- Antithrombin deficiency (ATD) is a risk factor of thrombosis and postthrombotic syndrome.
- No consensus exists on the management of perioperative anticoagulants in ATD patients.
- Careful management of perioperative anticoagulation can ensure successful venous recanalization.
- The current approach of vitamin K antagonist–unfractionated heparin transition for venous recanalization in patients with ATD can be proposed.

Nicolas Gendron and Lina Khider contributed equally to this work.

1 | INTRODUCTION

Inherited antithrombin (AT) deficiency (ATD) is a severe thrombophilia associated with high risk of venous thromboembolism (VTE), mostly deep vein thrombosis (DVT) and pulmonary embolism. It is a rare disease with a prevalence of 1/5000 in the general population [1,2] and of 1% to 2% among VTE patients. The relative risk of first VTE with ATD is 15 times higher than in the general population and the risk of recurrence is 4 times higher [1,2]. AT belongs to the family of serine protease inhibitors (serpins), which irreversibly inhibits activated coagulation factors, mainly factor (F)Xa and factor (F)IIa. There are 2 types of ATD : quantitative (type 1), which represents 80% of patients, and qualitative (type 2) [1,3]. In quantitative deficiencies, AT concentration is decreased. In qualitative type 2, AT anticoagulant activity is impaired or null, with subtypes depending on the functional defect, usually associated with the location of the pathogenic mutation [3]. Postthrombotic syndrome (PTS) is a form of chronic venous insufficiency that occurs secondary to DVT. It is associated with a significant impact on quality of life and with significant health care expenses [4]. Typical PTS symptoms are leg heaviness, pain, edema, pruritus, and venous claudication. Incidence of PTS, which usually appears within 2 years following a DVT, varies between 20% and 50% in all venous thromboses taken together [5] and is more frequent in case of proximal DVT. Venous recanalization (VR) is indicated in cases of PTS with chronic residual proximal venous obstruction when anticoagulant therapy is not completely effective [6]. This procedure is indicated mostly in the treatment of obstructive and occlusive unilateral iliofemoral lesions in patients with residual venous symptoms impairing their quality of life [5,6]. The long-term results are very encouraging, since all studies show a technical success rate of >90%, a clinical improvement of 99%, and more than 70% of patients are completely asymptomatic after recanalization [7]. To the best of our knowledge, there is no consensus or literature on perioperative anticoagulation management in ATD patients, including mechanical VR. Altered heparin responsiveness and increased VTE risk are important to consider for ATD patients undergoing anticoagulant transition or bridging. We hereby present a case of successful anticoagulation transition for VR in a patient with type 1 ATD and PTS.

2 | METHODS

2.1 | Patient

The study was performed in accordance with the Declaration of Helsinki and the ethics committee approved the study (N°20222-09-06). The patient included was informed of the research protocol by letter, allowing him to express his opposition to the use of his data, according to French legislation and the institutional review board.

2.2 | Mechanical VR

Due to the extensive chronic venous occlusion, the intervention consisted of mechanical recanalization and stenting of the inferior vena cava, with Y-stenting in both common iliac veins and right external iliac vein, in order to restore full patency of the proximal venous drainage. It was performed on anticoagulation using unfractionated heparin (UFH) in the angiographic suite under general anesthesia.

2.3 | Laboratory assays

ATD plasmatic phenotype was determined using AT Stachrom-ATIII (Diagnostica Stago) for heparin's cofactor AT activity (ATCof) and for AT antigen level (normal range, 80%-120%). UFH therapy was monitored using a chromogenic assay measuring anti-Xa activity (liquid anti-Xa reagent, Diagnostica Stago). All assays were performed on STAR-Max 3 coagulometer (Diagnostica Stago). The exons and intron–exon boundaries of *SERPINC1* (gene ID: 462) were studied by direct sequencing, as previously reported [8]. GenBank NM_000488.3 was used as reference sequence. American College of Medical Genetics and Genomics guidelines were followed to establish variant pathogenicity [9].

2.4 | Case study

A 45-year-old man (body mass index: 22.9 kg/m^2, 70 kg) with quantitative ATD and history of personal and familial VTE (Figure) was admitted in our institution for vena cava VR. ATD was explored and a pathogenic variant, c.1171C>T, located in the exon 6 of *SERPINC1*, inducing the introduction of a premature stop codon, was identified. This variant was previously described [10,11] with ATCof of around 50%.

His personal history of VTE began at the age of 9 years with an unprovoked DVT (inferior vena cava, common iliac veins, portal vein, and suprahepatic veins) associated with a mesenteric infarction, which resulted in a small bowl resection and long-term oral anticoagulation with vitamin K antagonist (VKA) since then. Between 1999 and 2017, he had 4 recurrent superficial vein thrombosis while on VKA therapy. Patient did not require anticoagulation interruption or AT supplementation. In 2019, the patient was diagnosed with severe bilateral PTS with a Villalta score of 15. Before admission, a perioperative anticoagulation protocol was suggested with VKA-heparin transition (Figure A). Warfarin was interrupted 4 days before the interventional radiology procedure with an international normalized ratio of 2 1 day before VR. Additionally, baseline ATCof was 48%, enabling us to expect a positive response to UFH without requiring AT supplementation. Patient was subsequently administered UFH at therapeutic dose of 500 IU/kg/day (Figure B), and anti-Xa activity was monitored

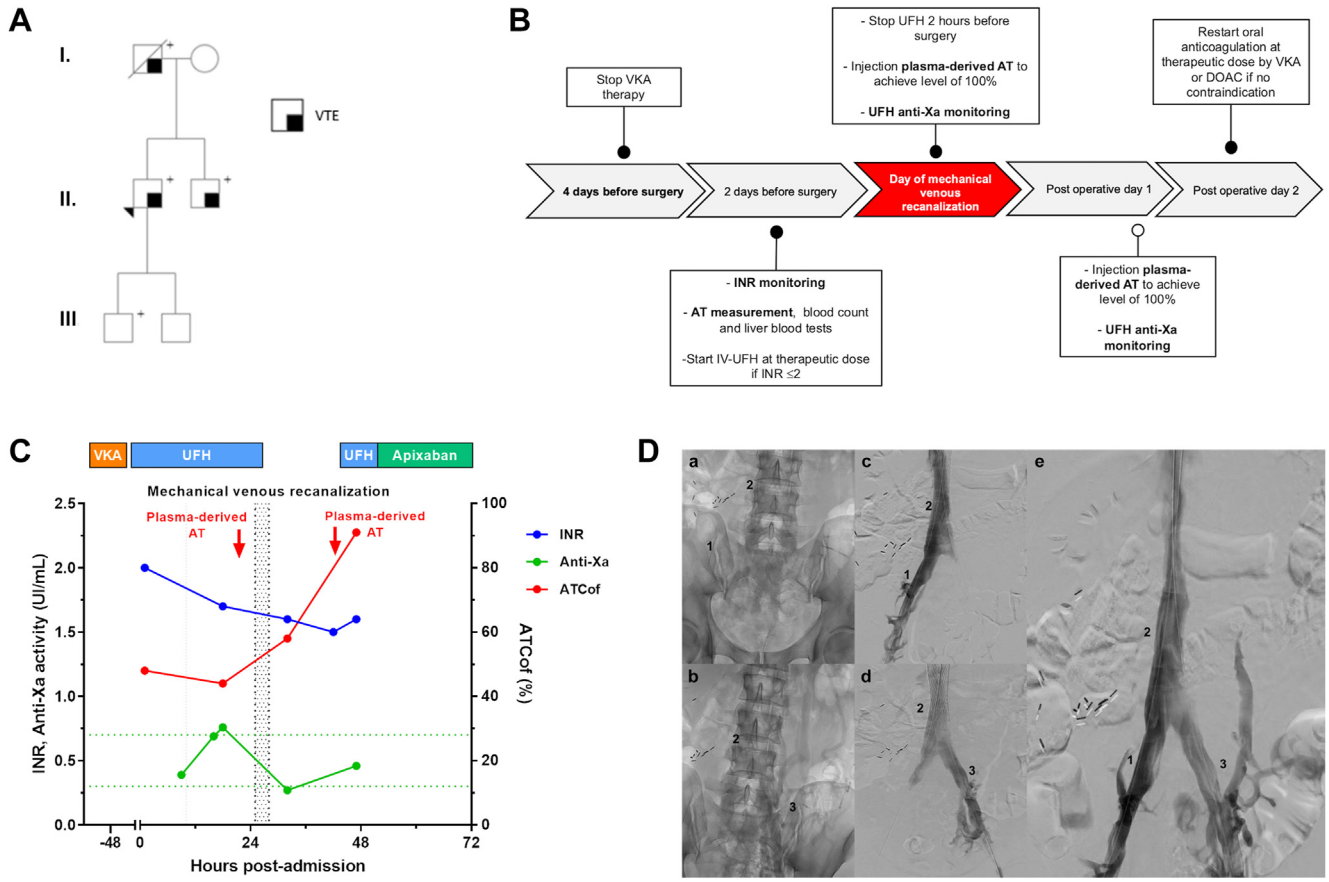

FIGURE Perioperative management of venous recanalization in a patient with antithrombin deficiency. (A) Genealogical tree of the patient with type 1 antithrombin deficiency. Patient (proband) I.1 Father: fatal pulmonary embolism at age of 40 years II.3 Brother: history of pulmonary embolism. (B) Anticoagulation management of mechanical venous recanalization with suggested unfractionated heparin (UFH)-transition protocol. (C) Anticoagulation management of the patient for mechanical venous recanalization. (D) Prevenous and postvenous recanalization imagery. A 20 mm × 80 mm Sinus XL (Optimed○R) stent was deployed in the infrarenal inferior vena cava, extended by 2 additional stents into the common iliac veins: a 14 mm × 120 mm stent on the right and a 14 mm × 100 mm stent on the left. Furthermore, the configuration was expanded with a 14 mm × 60 mm stent in the left external iliac vein. All stents underwent reshaping using balloons of appropriate size corresponding to their diameters.

A) Diagnostic phlebography via right pedal approach. Right iliac veins and inferior vena cava are threadlike or occluded.

B) Diagnostic phlebography via left pedal approach. Left iliac veins and inferior vena cava are threadlike or occluded.

C) Post recanalization result of the inferior vena cava and right iliac veins.

D) Post recanalization result of the inferior vena cava and left iliac veins.

E) Final result with recovered patency of the inferior vena cava and iliac veins.

1. Right common iliac vein.[2.] Inferior vena cava.[3.] Left common iliac vein.

anti-Xa, anti-activated factor X activity; AT, antithrombin; ATCof, cofactor AT activity; DOAC, direct oral anticoagulant; INR, international normalized ratio; VKA, vitamin K antagonist; VTE, venous thromboembolism.

with therapeutic target of 0.3 to 0.7 IU/mL during anticoagulant transition. The patient had an elevated anti-Xa activity 4 hours before surgery (0.76 UI/mL). Accordingly, on the day of VR, intravenous UFH was discontinued. Plasma-derived AT concentrate was administered (30 UI/kg, 2100 IU) to ensure that AT level reached 80% 1 hour before entering the angiographic suite. VR was performed, along with angioplasty and extensive Y-stenting of the subhepatic vena cava, bilateral primitive iliac veins, and the right external iliac vein. The intervention was a success, with good permeability of the inferior vena cava and the 2 common iliac veins up to their bifurcation and without complications. Four hours after the intervention, ATCof was 58% (which can be explained by its consumption during VR) and anti-Xa was 0.27 IU/mL. UFH at therapeutic dose (500 IU/kg/day) was reintroduced for thromboprophylaxis, combined with an additional AT infusion (30 UI/kg, 2100 IU). ATCof reached 91% with UFH anti-Xa activity measured at 0.46 IU/mL. The patient expressed a preference for treatment with direct oral anticoagulants (DOACs), leading to a switch from UFH to apixaban 5 mg twice a day on postoperative day 2, along with aspirin 75 mg per day for 6 months for prevention of in-stent thrombosis as suggested [12]. Two weeks later, apixaban was

switched to rivaroxaban due to patient's history of bowel resection as apixaban is predominantly absorbed in the small bowel while rivaroxaban is absorbed in the stomach [13]. At the 3-month and 6-month follow-up visits, a significant improvement was observed with Villalta scores of 8 and 4, respectively, and Doppler ultrasound showed perfect patency.

3 | DISCUSSION

Perioperative anticoagulation transition using UFH and plasma-derived AT concentrate supplementation while closely monitoring UFH anti-Xa activity was a successful strategy for VR in this case. VKA-UFH transition could be a more reliable strategy than low-molecular-weight heparin transition because UFH anti-Xa activity correlates strongly with therapeutic anticoagulation [14,15]. Without closely monitoring UFH anti-Xa activity, circulating heparin levels in patients are undetermined, making it difficult to predict the exact number of AT infusions needed to assure UFH efficacy and to prevent thrombosis. Moreover, since plasma-derived AT concentrate is a product prepared from human plasma, it is costly. Additionally, its repeated administrations can lead to infectious diseases due to the transmission of infective pathogens. Therefore, VKA-UFH transition could limit the number of AT infusions to those strictly necessary. Another transition strategy could have involved the use of direct thrombin inhibitors such as argatroban, bilavirudin, or dabigatran to minimize time off oral therapy and avoid AT supplementation [16]. However, argatroban and bivalirudin are indicated for heparin-induced thrombocytopenia, and monitoring relying on activated partial thromboplastin time and/or anti-IIa activity can be complicated [16,17]. Moreover, physicians and nurses are generally more comfortable using UFH. Preprocedure transition with a DOAC such as dabigatran or oral FXa inhibitors (apixaban or rivaroxaban) could also have been considered. However, for VR, anticoagulant therapy with short half-life is needed in case of perioperative bleeding event. To the best of our knowledge, guidelines for AT replacement in ATD patients exist only in the setting of pregnancy and acute VTE [18]. Furthermore, the Summary of Product Characteristics allows for the use of AT supplementation and heparin in case of inherited ATD when treating VTE, but it does not specify a threshold below which ATD would necessitate such AT supplementation [19]. There is an unmet need for guidelines to manage ATD patients undergoing perioperative anticoagulant bridging or transition, particularly for VR. Our objective was to suggest a protocol that may be helpful when managing future ATD patients who have to undergo VR. Whether the patient has VKA or DOAC anticoagulation, the key element of our protocol is to monitor anti-Xa activity when transitioning with UFH. We also advise to interrupt UFH 2 to 4 hours before surgery and administer plasma-derived AT at a weight-adjusted dose. Postoperative oral anticoagulation may then be resumed after the intervention. DOAC therapy for VTE patients with ATD is still a topic of debate, but available data reported in the literature are encouraging [1]. Since VR is a recent surgical procedure, the vast majority of patients are currently treated with DOACs; therefore, in our center, DOACs are used for secondary prevention of venous stenting during 6 months [20] in association with aspirin 75 mg per day as suggested [12]. In this specific case, our patient needs long-term anticoagulation.

This protocol does not apply to all ATD patients but rather to type 1 ATD patients and to other invasive procedures requiring continuation of therapeutic anticoagulation. It mandates an individualized approach according to the patient's history, the availability of anticoagulants, and laboratory monitoring.

CONCLUSION

To conclude, this case study highlights that perioperative anticoagulation transition using UFH and plasma-derived AT supplementation in ATD patients, while closely monitoring UFH anti-Xa activity, was a successful strategy for VR. This careful management of anticoagulant therapy allowed the procedure to be successful and enabled the patency to persist over time. This outcome is reassuring and encourages the possibility of providing VR to patients with severe thrombophilia.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AUTHOR CONTRIBUTIONS

N.M., E.M., M.S., N.G., and L.K. were involved in the clinical management and the inclusion of the patient. J.B., C.R., L.M., and N.G. perform the experiments. J.B., C.R., and L.K. analyzed the data. J.B., C.R., N.M., M.S., N.G., and L.K. wrote the manuscript. All authors reviewed the manuscript.

RELATIONSHIP DISCLOSURE

N.G. and L.K. acknowledge the following without any relation to the current manuscript: L.K. has received speaker honoraria or consultancy fees from Bayer and Bristol-Myers Squibb; N.G. discloses consulting fees or travel awards by Bayer, Bristol-Myers Squibb/Pfizer, LEO-Pharma, LFB, and Stago Diagnostica. All other authors have nothing to disclose with the present study.

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