



## Case Report

## Successful administration of recombinant human antithrombin in a pregnant Japanese woman with hereditary antithrombin deficiency

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## ARTICLE INFO

## Article history:

Accepted 21 June 2019

## Keywords:

Hereditary antithrombin deficiency

Pregnancy

Prophylaxis

Recombinant human antithrombin

Venous thromboembolism

## ABSTRACT

**Objective:** Hereditary antithrombin (AT) deficiency increases the risk of venous thromboembolism (VTE) in pregnant woman. We report the first case of administration of recombinant human antithrombin (rhAT) to a pregnant Japanese woman with AT deficiency.

**Case report:** A 30-year-old woman, gravida 2 para 0, was referred to our hospital because of AT deficiency. Unfractionated heparin was administered from 13 weeks of gestation and rhAT was administered from labor onset. A cesarean section was performed and the patient and her baby were healthy, with no sequelae.

**Conclusion:** We concluded that rhAT was effective for preventing VTE during delivery, with no potential infection risks.

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## Introduction

Antithrombin (AT) plays a crucial role in regulating coagulation, primarily by inhibiting thrombin and factor Xa [1]. Hereditary AT deficiency is therefore associated with an increased risk of venous thromboembolism (VTE) [2,3], and Egeberg reported the first case of AT deficiency associated with VTE in 1965 [4]. The risk of VTE increases with age and the presence of other risk factors, such as surgery, pregnancy and postpartum period, use of low-dose estrogen or progesterone, trauma, and immobility [5]. The risk of VTE in women with hereditary AT deficiency appears to be highest during the immediate postpartum period, and anticoagulation therapy may be warranted during this period [6,7]. AT replacement therapy is also effective in patients with AT deficiency during high-risk situations [8]. Until recently, only human plasma-derived AT (hpAT) concentrates were available for use in AT replacement therapy; however, the use of recombinant human antithrombin (rhAT), which is not derived from human blood, eliminates the potential infection risks associated with hpAT [9].

There have been no previous reports of rhAT administration in pregnant women with hereditary AT deficiency in Japan, and we here present a patient who was treated successfully with rhAT without VTE or other sequelae.

## Case presentation

A 30-year-old woman, gravida 2 para 0, was referred to our hospital at 24 weeks of gestation because of hereditary AT deficiency. Her family history included a mother, uncle, and aunts with AT deficiency, and she had been diagnosed with hereditary AT deficiency based on her ATIII activity level 10 years previously (Fig. 1). She had also experienced an asymptomatic cerebral infarction at 24 years old. Thromboprophylaxis with self-injection of unfractionated heparin 20,000 U/day was started from 13 weeks of pregnancy. Her serum ATIII activity level was only 30%–40%, but no thrombosis occurred during the pregnancy and her serum d-dimer level did not increase. She was admitted for programmed labor at 39 weeks of gestation to allow her ATIII activity level to be controlled during delivery. Self-injected unfractionated heparin was stopped and 3000 U rhAT (ACOALAN® Injection, Japan Blood Products Organization, Japan) was administered intravenously every 24 h (about 50 U/kg/day) from the start of labor. No allergic or immunologic reactions against rhAT were observed. Three days after labor induction, the patient underwent a cesarean

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section because of arrested labor, and gave birth to a male child weighing 3120 g, with an Apgar score of 9 at 5 min. The blood loss was 584 g. Self-injection of unfractionated heparin 20,000 U/day was restarted on postpartum day 1 and rhAT was stopped on postpartum day 3. The patient's ATIII activity increased to 80%–120% during administration of rhAT, with no thromboembolism during delivery or the postpartum period. The ATIII activity and d-dimer levels throughout the clinical course are summarized in Fig. 2. Self-injection of unfractionated heparin was re-started for 6 weeks according to the American College of Chest Physician Guidelines on antithrombotic therapy. The patient and her baby were healthy with no sequelae or adverse events at a follow-up visit 4 weeks after delivery.

## Discussion

Pregnancy is considered as a hypercoagulable state because of increased levels of coagulation factors, decreased free protein S, acquired activated protein C resistance, and impaired fibrinolysis [10]. The risk of maternal VTE is generally increased during pregnancy and the postpartum period, and guidelines established for managing pregnant patients with AT deficiency [11] recommend that pregnant women at moderate to high risk of VTE should receive antepartum prophylaxis with prophylactic or intermediate-dose low molecular weight heparin (LMWH). However, LMWH is only approved for the prevention of VTE during the immediate postoperative period in Japan, and we therefore administer unfractionated heparin instead of LMWH.

Hereditary AT deficiency is a rare condition and adequate guidelines relating to AT replacement therapy are therefore lacking. AT replacement therapy using hpAT has traditionally been used in pregnant women with AT deficiency [8]; however, hpAT is plasma-derived and has been associated with fluctuations in its blood supply and a theoretical risk of transmission of blood-borne infectious agents [12]. In contrast, rhAT has been reported to be safe and effective [1,13]. The structure of rhAT is identical to that of hpAT, except for differences in side-chain glycosylation that cause rhAT to have a higher affinity for heparin and a shorter half-life than hpAT [1]. Although rhAT was approved in Japan in 2017, the substitution of rhAT in pregnant woman with hereditary AT deficiency has not previously been reported in Japan.

AT substitution plus LMWH were reported to produce the best maternal and neonatal outcomes, with no incidences of maternal

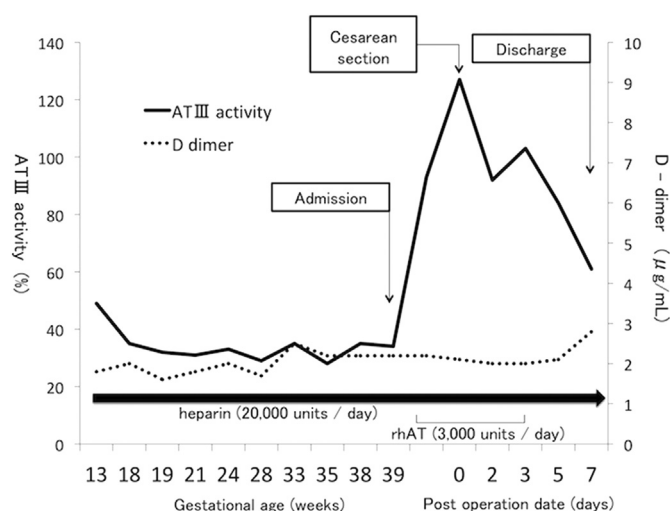


Fig. 2. Antithrombin III (ATIII) activity and d-dimer levels throughout the clinical course.

VTE [14]. Among a cohort of 21 pregnant women with AT deficiency who received rhAT for VTE prevention, Paidas et al. reported no confirmed VTEs during rhAT therapy or within the first week after rhAT discontinuation [1]. In the current case, we substituted LMWH from 13 weeks of gestation week and administered rhAT during delivery, with no adverse events or VTE. We suggest that the timing of rhAT administration is important, and although previous researchers have reported various timings of administration of AT, the appropriate timing remains obscure. Further studies are therefore needed to determine the appropriate timing of rhAT administration.

In conclusion, hereditary AT deficiency is a high-risk complication during pregnancy. The current cases suggests that rhAT could effectively prevent VTEs in pregnant patients, with no adverse effects in the mother or neonate.

## Conflicts of interest

All authors have no conflicts of interest.

## Acknowledgements

We thank Susan Furness, PhD, from Edanz Group ([www.edanzediting.com/ac](http://www.edanzediting.com/ac)) for editing a draft of this manuscript.

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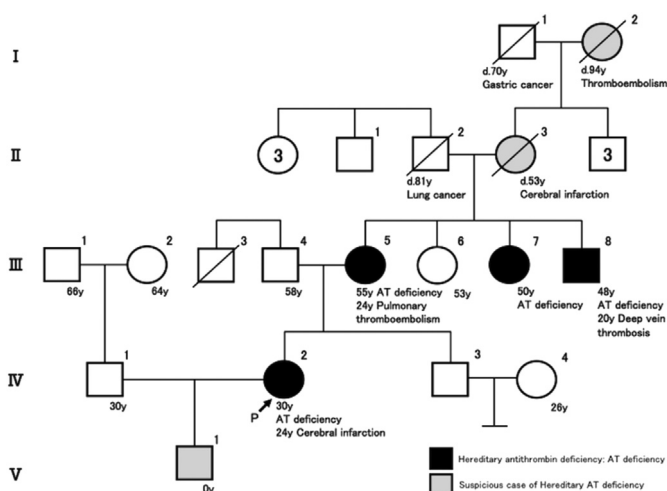


Fig. 1. Family tree of the current patient with hereditary antithrombin deficiency.

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