Successful treatment with rivaroxaban of an extended deep vein thrombosis complicated by pulmonary embolism in a patient with familial antithrombin III deficiency: a case report

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Background
Patients with low levels of antithrombin III (AT III) are at an increased risk of developing arteriovenous thromboembolic disease.

Case summary
We report a case of a 28-year-old woman who presented with a 1-week history of spontaneous right calf pain and swelling. A heterozygous AT III deficiency, phenotypically expressed as deep vein thrombosis, was reported in the patient’s mother and sister. Blood workup revealed residual AT III activity at 58% with normal protein C and protein S levels. Computed tomographic angiography (CTA) revealed subsegmental bilateral pulmonary embolism (PE) and deep vein thrombosis in the right leg extending into the inferior vena cava up to the confluence of the left renal vein. Placement of an inferior vena cava filter was not considered. Given the patient’s haemodynamic stability, anticoagulant therapy with 15 mg of rivaroxaban twice a day was initiated instead. Echocardiography after 10 days of treatment revealed complete resolution of the thrombus located in the inferior vena cava, while CTA revealed complete resolution of the PE.

Discussion
Patients with AT III deficiency are likely to be heparin-resistant and will require higher heparin doses or the administration of AT III replacement therapy for the treatment of thrombosis, both of which are associated with an increased risk for haemorrhagic complications. Direct factor Xa inhibition by rivaroxaban provided an alternative mechanism for anticoagulation, which was found to be particularly useful in this patient with familial AT III deficiency, deep vein thrombosis, and PE.

Keywords
Antithrombin III deficiency • Venous thromboembolism • Xa factor inhibitor • Case report
Inherited antithrombin III (AT III) deficiency is an autosomal dominant disorder with an estimated prevalence of 0.02–0.2% in the healthy population. Affected patients have a significantly increased risk of venous thromboembolism (VTE), including deep venous thromboembolism (DVT) and pulmonary embolism (PE). The first-line therapy for VTE is continuous administration of heparin or fondaparinux. However, patients with AT III deficiency are also known to be resistant to anticoagulation by heparin and, thus, exhibit greater propensity for thrombus progression than individuals without the disease; this phenomenon can be attributed to the decreased activity of AT III.

Direct oral factor Xa (FXa) inhibitors have recently been proven to be effective for the treatment of VTE. However, studies regarding their use in patients with AT III deficiency are lacking. Thus, there are currently no guidelines or consensus statements regarding the optimal duration of oral anticoagulant therapy for primary and secondary prevention of VTE recurrences in patients with AT III deficiency.

In this article, we report a case of PE and DVT in a female patient with inherited heterozygous AT III deficiency, in which treatment with rivaroxaban was highly effective.

Timeline

Four years prior to consultation: The patient’s mother and sister were diagnosed with deep vein thrombosis secondary to heterozygous antithrombin III deficiency.

Two years prior to consultation: The patient was diagnosed with inherited heterozygous AT III deficiency.

On the day of consultation: The patient was admitted to our intensive cardiac care unit for right calf pain and swelling of 1 week duration. Echocardiography revealed deep vein thrombosis with possible pulmonary embolism (PE). Computed tomographic angiography (CTA) confirmed the presence of the PE. Subsequently, treatment with rivaroxaban 15 mg BID was initiated.

One week after admission: Repeat echocardiography was done which revealed partial resolution of both the PE and deep vein thrombosis. Patient was subsequently discharged from the hospital.

Ten days after admission: Repeat echocardiography revealed complete resolution of the PE, which was subsequently confirmed with CTA.

Three weeks after admission: Rivaroxaban dosing was reduced to 20 mg OD.

Three months after admission: Clinical re-evaluation showed no recurrence of deep vein thrombosis. The patient was still maintained on rivaroxaban.

Six months after admission: Clinical re-evaluation still showed no recurrence of deep vein thrombosis. The patient was still maintained on rivaroxaban.

Nine months after admission: Clinical re-evaluation showed no recurrence of deep vein thrombosis. The patient was still maintained on rivaroxaban.

One year after admission: No signs of deep venous thromboembolism recurrence were found on clinical re-evaluation. The patient was advised to maintain rivaroxaban treatment and to follow-up with a cardiologist at least once a year.

Learning points

• Patients with low antithrombin III (AT III) levels may be heparin-resistant and are at an increased risk for arteriovenous thromboembolic disease; such patients require higher heparin doses or AT III replacement therapy for treatment of thrombotic disease, both of which are associated with an increased risk for haemorrhage.

• Direct factor Xa inhibition by rivaroxaban was found to be particularly useful in this patient presenting with familial AT III deficiency, deep vein thrombosis, and pulmonary embolism.

Case presentation

A 28-year-old woman with familial heterozygous AT III deficiency was referred to our institution for right calf pain and swelling of 1 week duration. The patient’s sister and mother, both of whom are known to have inherited AT III deficiency by genotypic examination, both have a history of DVT and PE. However, no further details regarding the genetic profile of the patient and her relatives were available. There was no history of oral contraception use or other precipitating factors for the development of DVT and PE.

The patient’s vital signs upon admission were as follows: heart rate of 90 b.p.m., blood pressure of 120/75 mmHg, respiratory rate of 24 breaths/min, and an oxygen saturation of 98% at room air.

Physical examination revealed prominent S2 heart sounds at the pulmonic area. Electrocardiogram showed normal sinus rhythm but with an incomplete right bundle branch block. D-dimer levels are routinely assessed in the emergency department as part of the chest pain protocol despite its low positive predictive value for PE especially in patients with high clinical probability of the disease. For this patient, her D-dimer serum levels were measured and revealed to be 27.25 mg/L (normal range: 0.00–0.50 mg/L). Residual AT III activity was measured to be at 58% (normal range: 83–118%), whereas protein C and protein S plasma levels were both found to be within the normal range.
normal range. No anti-beta-2-glycoprotein, antiphospholipid, anti-prothrombin, or antcardiolipin antibodies were detected in this patient. Echocardiography (Figure 1) revealed a floating thrombus within the inferior vena cava measuring 7 cm × 1 cm, extending to the perirenal region with a low echocardiographic probability of pulmonary hypertension (tricuspid regurgitation Vmax 1.98 m/s; normal interventricular septal motion; no pulmonary artery dilatation). Contrast enhanced computed tomography (CT) of the chest, abdomen, pelvis, and lower limbs revealed bilateral subsegmental PE (Figure 2) and deep vein thrombosis of the right leg extending into the inferior vena cava up to the left renal vein. Based on the family history and clinical findings, the patient was diagnosed with PE and DVT in the setting of an inherited heterozygous AT III deficiency.

The 2014 Guidelines released by the European Society of Cardiology for the diagnosis and management of acute PE recommend providing haemodynamic and respiratory support, anticoagulation therapy, thrombolytic treatment, surgical embolectomy, percutaneous catheter-directed treatment, and venous filters for treating the acute phase of PE. After a thorough assessment, haemodynamic and respiratory support was deemed unnecessary for this patient. Furthermore, due to the absence of clinical evidence pointing to cardiogenic shock, thrombolytic treatment, surgical embolectomy, and percutaneous catheter-directed treatment were not considered as first-line therapies for this patient. Placement of an inferior vena cava filter was not considered since there were no absolute contraindications to the administration of anticoagulant drugs and because PE did not recur after the administration of appropriate anticoagulation treatment. Because of the patient’s low AT III activity, achievement of adequate anticoagulation would have taken too much time with the use of heparin, fondaparinux, or vitamin K antagonist therapies.

After the patient was admitted and written informed consent was obtained using our institutional consent form, now archived in her medical records, she was administered rivaroxaban 30 mg daily (15 mg tablets taken twice a day) for 3 weeks, after which the dose was reduced to 20 mg once a day according to clinical trials.

Because the patient’s condition was classified as Class I according to the PE severity index, she was discharged after 1 week but was maintained on treatment with rivaroxaban 20 mg once a day. Ten days after treatment, repeat echocardiographic examination revealed complete resolution of the thrombus located in inferior vena cava (Figure 3). Because the treatment of this patient deviated from traditional practices, a repeat CT scan of the chest was performed and documented complete disappearance of the PE (Figure 4).

The patient received regular follow-up examinations for 1 year after discharge, with repeat echocardiography and compression venous ultrasonography performed every third month; during this time, the patient was maintained on 20 mg of rivaroxaban daily. No recurrence of PE or DVT was found. The patient was then advised to have an annual check-up with a cardiologist.

**Discussion**

This case demonstrates the efficacy of an FXa inhibitor for the treatment of VTE in a patient with inherited AT III deficiency. Patients with
AT III deficiency are known to have a substantially increased risk for developing VTE, with thrombotic events occurring in 67% of patients between ages 10 and 35. Approximately 50–90% of patients with AT III deficiency experience an episode of VTE during their lifetime. Due to the lack of clinical studies, haematologists differ in their recommendations regarding the treatment of VTE in patients with AT III deficiency. The efficacy and safety of rivaroxaban for the treatment of VTE was reported in the 2010 EINSTEIN study. However, its efficacy in patients with inherited AT III deficiency has yet to be established.

To the best of our knowledge, this is one of the first cases that demonstrates the efficacy of the direct FXa inhibitor rivaroxaban as first-line treatment for the acute phase of VTE and for the prevention of recurrences in a patient with AT III deficiency. This case report may raise some clinically relevant issues about VTE therapy in patients with AT III deficiency.

The anticoagulant effects of FXa inhibitors are not influenced by AT III activity.

AT III is a single-peptide plasma α-glycoprotein that functions as a potent inhibitor of blood coagulation by inhibiting thrombin (its primary target) and factors Xa, IXa, and VIIa (Figure 5).

Rivaroxaban, a direct FXa inhibitor, acts directly on the coagulation cascade without the participation of AT III, thus providing a potent anticoagulant effect even for patients with AT III deficiency. Moreover, FXa inhibitors may result in a faster onset of anticoagulation compared to heparin or vitamin K antagonists. Because the anticoagulation effect of heparin is mediated through the potentiation of endogenous AT III activity, patients with AT III deficiency may experience resistance to heparin therapy and require higher doses to achieve adequate anticoagulation. In the same manner, delays in the anticoagulation effects of vitamin K antagonists may also be observed. Thus, the use of an FXa inhibitors in the setting of thrombosis can rapidly induce anticoagulation even in patients with low or absent AT III activity, thereby avoiding the risks associated with heparin resistance and preventing thrombus progression.

The efficacy of AT III replacement therapy for patients with inherited AT III deficiency has been described in some case reports. However, there are currently no randomized clinical trials that assess the efficacy of AT III replacement therapy, and therefore, no consensus regarding the use AT III concentrates in affected patients is available. The possible use of other direct oral anticoagulants, especially other FXa inhibitors, for the treatment and prevention of VTE in patients with AT III deficiency is worth discussing. Fukuda et al. suggested that edoxaban, another FXa inhibitor, might be effective in patients with low plasma AT III concentrations, while Kawano and Maemura reported a case demonstrating the efficacy of edoxaban as treatment for VTE in a cancer patient with AT III deficiency. From the results of these studies, it is possible that other FXa inhibitors may be effective treatments for VTE in patients with AT III deficiency.

There are several types of inherited AT III deficiencies, and each is classified into three broad categories.

Type I is primarily a quantitative defect, presenting with decreased concentrations and activity levels of AT III due to a reduction in the synthesis of biologically normal protease inhibitor molecules. Type II AT III deficiency is a qualitative disorder and arises from substitution mutations that result in dysfunctional copies of AT III. This classification is further divided into three variants according to the site of mutation as determined by genotypic analysis. Type II RS involves mutations in the reactive site or the cleavage zone of the AT III by thrombin (between Arg 393 and Ser 394) or the adjacent amino acids. Type II HBS involves the heparin binding site of
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AT III thus affecting its interaction with heparin. Type II pleiotropic effect involves multiple mutations that result in dysfunction of both the reactive and binding sites. The patient in this case report was classified as Type I heterozygous AT III deficiency based on AT III activity, antigen assay, and genotype assessment. Type I inherited AT III deficiency is associated with a greater risk for VTE than the Type II variant and other thrombophilias. However, there are currently no guidelines or consensus statements regarding the duration of oral anticoagulant therapy for primary and secondary prevention of VTE in patients with AT III deficiency. The risk of VTE recurrence in patients with AT III deficiency who are not on maintenance anticoagulation is high. This patient did not have any VTE recurrence after 1 year with maintenance rivaroxaban. Hence, direct FXa inhibitors may be effective in preventing VTE and PE recurrence in patients with AT III deficiency. Despite the lack of clinical studies or recommendations regarding the duration of anticoagulant prophylaxis in patients with AT III deficiency, this patient may require lifelong oral anticoagulation to prevent recurrence of her symptoms.

Conclusion

Rivaroxaban has shown to be effective for the treatment and prevention of VTE recurrence in a patient with inherited AT III deficiency. However, further studies on a larger series of patients are needed to validate the efficacy of FXa inhibitors for the prevention of VTE recurrence in this specific patient population.

Lead author biography

Dr Enrico Di Girolamo was graduated in 1997 from the School of Cardiology, “G. D’Annunzio” University, Chieti, Italy. Practitioner in the Intensive Cardiac Care Unit since 1999. Chief of the Arrhythmology Unit of the “SS. Annunziata” Hospital, Chieti, Italy since 2014. He has worked in the field of Cardiology and Arrhythmology since 1999 and his interests include syncope, catheter ablation of atrial and ventricular arrhythmias as well as cardiac implantable devices. He has authored several original manuscripts in cardiovascular research, translational and clinical cardiovascular medicine, and has published in the Journal of the American College of Cardiology, Circulation and Heart Rhythm, among many others.

Supplementary material

Supplementary material is available at European Heart Journal - Case Reports online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author(s) confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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