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The novel *SERPINC1* missense mutation c.1148 T > A (p.L383H) causes hereditary antithrombin deficiency and thromboembolism in a Chinese family: a case report

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Abstract

Background Hereditary antithrombin deficiency, an autosomal-dominant thrombotic disease caused by a *SERPINC1* gene deficiency, is extremely rare, although it is the leading cause of hereditary thrombophilias. Herein we report a novel *SERPINC1* gene mutation in a Chinese family and one case of pulmonary embolism associated with the mutation. We also discuss the latest diagnostic and treatment strategies for antithrombin deficiency.

Case presentation The 33-year-old Chinese male proband had a pulmonary embolism and there was no evidence of thromboembolism in the other family members. In the pulmonary embolism case, treatment with nadroparin calcium combined with warfarin failed; however, rivaroxaban was effective. No emboli were evident in the follow-up computed tomography pulmonary angiography. Antithrombin activity fluctuated approximately 50% during hospitalization and follow-up. The antithrombin activity of the proband, his 58-year-old father, and his 5-year-old son was significantly low (44–48%). A novel missense variant c.1148 T > A (p.L383H) in the *SERPINC1* gene was identified in these three family members. The pathogenesis predictions from Mutation-Taster, Provean, and SIFT were "disease-causing," "deleterious," and "damaging," respectively.

Conclusion The novel c.1148 T > A (p.L383H) pathogenic mutation in the *SERPINC1* gene updated the gene mutation spectrum of hereditary antithrombin deficiency. Direct oral anticoagulation with rivaroxaban may be a more effective and selective anticoagulant in patients with hereditary antithrombin deficiency over warfarin or heparin.

Keywords Hereditary antithrombin deficiency, *SERPINC1*, Pulmonary embolism, Novel genetic variant, Rivaroxaban

Background

Afflicting almost 10 million people worldwide per year, venous thromboembolisms (VTE), including deep vein thromboses and pulmonary embolisms (PE), contribute substantially to the global burden of disease. PE is the third most common cause of cardiovascular death [1, 2]. Thrombophilia, which is defined as a predisposition to thrombosis, may be inherited (primary) or acquired (secondary). Classical inherited thrombophilia includes loss-of-function mutations in the genes encoding the physiological anticoagulants antithrombin (AT), protein C, and protein S, as well as gain-of-function variants in

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the genes encoding factor V Leiden and prothrombin [3]. The overall incidence of inherited thrombophilia is difficult to estimate, and its most common form is a factor V Leiden mutation. Hereditary AT deficiency, first described in 1965, causes an autosomal-dominant thrombotic disease with incomplete penetrance and variable expression. Its prevalence in white individuals of European ancestry is 0.02–0.04%, and the incidence and recurrence rates of venous thromboembolism (VTE) are 1–2% and 2–5%, respectively [4].

The AT protein is encoded by the serpin family C member 1 (*SERPINC1*) gene, which consists of 432 mature circulating amino acids that are cleaved from its 464-amino-acid precursor. It is a single-stranded glycoprotein synthesized by hepatocytes, exerting its anticoagulant effect as a plasmatic serine protease inhibitor by inactivating coagulation factors IIa, IXa, Xa, XIa, and XIIa [5]. A mutation in the *SERPINC1* gene can lead to quantitative (type I) and qualitative (type II) types of AT deficiency. A type I deficiency is defined as a reduced functional protein with a parallel decrease in the plasma antigen, whereas a type II deficiency exhibits an impaired inhibitory activity resulting from dysfunctional AT with a normal antigen level [4].

In this study, we identified a novel missense *SERPINC1* genetic variant c.1148 T > A (p.L383H) leading to a hereditary AT deficiency in a Chinese family. We report one case of acute PE owing to this novel mutation. In addition, we discuss the diagnostic and anticoagulant therapy for this hereditary AT deficiency.

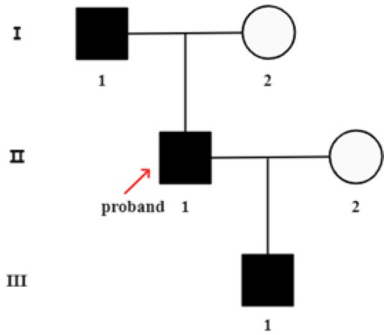

Fig. 1 Family pedigree. The proband is indicated by a red arrow. Family members confirmed to have a hereditary antithrombin deficiency are represented by the black squares

Case presentation

The 33-year-old male proband (family pedigree II-1 in Fig. 1) was admitted on 16 September 2020 (day 1). He presented to our department with a primary complaint of chest pain with a low fever (37.9 °C) of 5 days duration and hemoptysis for 1 day. His pertinent medical history included time spent in a sauna 1 day before the onset of symptoms. Subsequently, 5 days before admission, he was diagnosed with pneumonia in our hospital emergency department on the basis of his symptoms and a computed tomography (CT) scan of the chest showing a slight inflammation or infection-like shadow in the left lower lung (Fig. 2A). Antibiotic treatment failed and his chest pain increasingly worsened. After admission, laboratory tests showed an AT activity of 53% (reference interval, 80–120%), D-dimer of 10.72 mg/L (reference interval, 0–0.5 mg/L), a fibrinogen degradation product of 9.6 mg/L (reference interval, 0–5 mg/L), and an oxygenation index of 230.2. Subsequently, acute PE

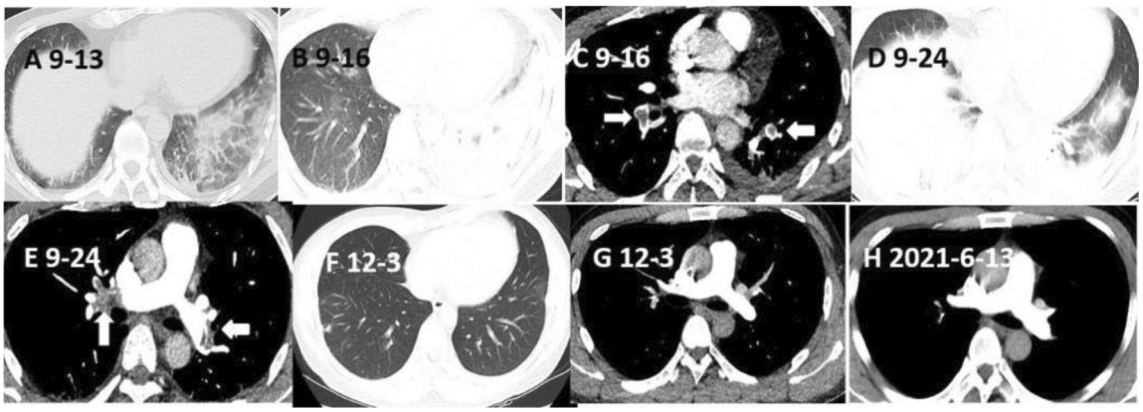

Fig. 2 Dynamic changes on a computed tomography scan of the lungs and computed tomography pulmonary angiography (**A–G** obtained in 2020 and **H** in 2021; white arrows mark the filling defects of a pulmonary embolism). The slight "infection-like" shadow (actually a pulmonary infarction) in the left lower lung was observed in our emergency department (**A**) and was worse on admission, 5 days later (**B**). Meanwhile, a pulmonary embolism was confirmed by the presence of filling defects (**C**). The pulmonary infarction worsened (**D**) with newly formed emboli (**E**) in the right lung region after traditional anticoagulant treatment. After admission and treatment, the emboli and infarction disappeared during follow-up with sufficient anticoagulation therapy with rivaroxaban (**F–H**)

was confirmed by CT pulmonary angiography (CTPA) demonstrating multiple filling defects in the branches of the pulmonary arteries (Fig. 2B, C). Nadroparin calcium (4100 IU every 12 hours) combined with warfarin (2.5 mg every day) were started and moxifloxacin was given on the basis of his increased white blood cell count (11.3×10^9/L, reference interval, $3.5–9.5\times10^9$/L) and C-reactive protein (125.0 mg/L, reference interval, 0–4 mg/L).

However, hemoptysis worsened on day 3 and warfarin was discontinued owing to an international normalized ratio of 2.2. On day 5, nadroparin calcium was replaced with a direct-acting oral anticoagulant (DOAC) (rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg every day). On day 6, the patient experienced severe chest pain, which was relieved gradually with a fentanyl patch. Meanwhile, a repeat CTPA (on 24 September 2020) showed new emboli and a pulmonary infarction in the right lung region, indicating previous insufficient and ineffective anticoagulation (Fig. 2D, E). Protein C and protein S activity was normal, and no thrombus was observed in the iliac and bilateral lower extremity veins on ultrasound imaging.

On day 19, the patient was discharged without symptoms; a repeat chest CT scan showed that the infarction shadow was almost completely absorbed. Rivaroxaban was administrated orally 20 mg every day as maintenance anticoagulation for 6 months and then at 10 mg every day for 3 months until July 2020. On 3 December 2020, a repeat CTPA showed a punctate filling defect in the right pulmonary artery; no emboli were evident in the subsequent follow-up examinations (Fig. 2F–H). AT activity fluctuated approximately 50% during hospitalization and follow-up and was 47% on 9 January 2022.

Family evaluation

Peripheral blood samples were collected from the proband and four other family members on 9 January 2022; prothrombin time, activated partial thromboplastin time, thrombin time, AT activity (chromogenic assay), D-dimer, and fibrinogen levels were measured using an automatic coagulation instrument. All tests were performed in accordance with the manufacturer's instructions. We also collected information on VTE events in these family members. This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Soochow University. Informed consent was obtained from each participant in accordance with the Declaration of Helsinki.

DNA sequence analyses

To identify novel variants, all exons and flanking introns of seven genes associated with thrombophilia (SERPINC1, SERPIND1, PROC encoding protein C, and PROS1 encoding protein S) were analyzed by high-throughput next-generation sequencing technology (Biotecan Pharmaceuticals Co, Ltd, Shanghai, China). The key process was to collect peripheral anticoagulated blood from five family members, extract genomic DNA, perform target region amplification, perform amplification product magnetic bead purification, conduct a polymerase chain reaction of the adapter sequence, purify the magnetic beads, and perform concentration detection and sequencing.

Bioinformatic analyses

Gene databases (1000 Genomes Project catalog, Exome Aggregation Consortium, Esp6500, and gnomAD) were used to query the mutation spectrum. Mutation-Taster (gene level), Provean, and SIFT (protein level) were used to predict the pathogenic consequences of the *SERPINC1* gene mutation.

Results

VTE events investigation in the family

Except for the proband, who had the acute PE, there were no evident thrombotic events in the other family members. The prothrombin time, activated partial thromboplastin time, thrombin time, D-dimer, and fibrinogen levels of all the family members were all within the reference intervals. The AT activity of the proband, his father, and his son was below the reference intervals, and it was normal in his mother and wife (Table 1). The proband's paternal grandparents had died many years earlier.

DNA sequence analyses

The *SERPINC1* gene is located on chromosome 1q23-25.1 and encodes AT. The full length of the genomic DNA is 13,578 base pairs (bp) containing 7 exons and 6 introns [6]. A DNA sequence analysis of the *SERPINC1* gene revealed a point mutation in exon 5 that resulted in the 1148th base mutating from T to A, subsequently generating a missense mutation of leucine at position 383 to histidine (SERPINC1: Chr1:173,878,695:NM_000488.3:e

Table 1 Antithrombin activity and genetic mutation analysis

Family members	Antithrombin activity (%)	c.1148 T > A	PROC	PROS1
Father (I-1)	47	Homozygote	Wild	Wild
Mother (I-2)	90	Wild	Wild	Wild
Proband (II-1)	47	Heterozygote	Wild	Wild
Wife (II-2)	96	Wild	Wild	Wild
Son (III)	51	Heterozygote	Wild	Wild
Reference range	80–120	Wild	Wild	Wild

xon5:c.1148 T > A: p. L383H) in the proband, his father, and his son. His mother and wife do not harbor this missense mutation; their *SERPINC1* genes are wild type. In addition, the mutated *SERPINC1* gene in his father is homozygous, and the proband and his son are heterozygous. There were no mutations in the *SERPIND1*, *PROC*, or *PROS1* genes.

Bioinformatic analyses

This novel mutation was not found in the 1000 Genomes Project catalog, Exome Aggregation Consortium, Esp6500, or gnomAD databases. After searching the gene databases of OMIM, HGMD, Clinvar, and PubMed, there was also no record of the mutation. The pathogenesis predictions of the L383H mutation by Mutation-Taster, Provean, and SIFT were "disease causing with pathogenic probability being 0.99999851200991," "deleterious," and "damaging," respectively.

Discussion

In clinical practice, it is important to have a high index of suspicion for the possibility of misdiagnosing PE as pneumonia. In the current case, the patient had pneumonia symptoms and an infection-like change on a chest CT scan; thus, a diagnosis of pneumonia was made in the emergency department. However, the patient's progressive chest pain and subsequent hemoptysis while on antibiotics could not be explained by the pneumonia diagnosis. Subsequently, a PE was confirmed owing to a significantly increased D-dimer and CTPA. In addition, during the hospitalization, a worsening infection-like shadow on chest CT scans was consistent with the dynamic change of emboli. Thus, the shadow was found to constitute a pulmonary infarction.

This young patient had no history of a malignant tumor, surgery, trauma, medication, or other systemic abnormalities indicating a PE. His AT activity fluctuated around a significantly low level (50%) during hospitalization and the follow-up period. This finding indicates a possibility that the PE was a result of an inherited thrombophilia caused by an AT deficiency. In the subsequent investigation, obviously decreased AT activity was measured in the paternal family members (father, proband, son) (Table 1). Ultimately, an inherited AT deficiency with a missense mutation (c.1148 T > A: p.L383H) in the *SERPINC1* gene was confirmed in these family members. To date, more than 486 mutations in the *SERPINC1* gene have been associated with AT deficiency (http://www.hgmd.cf.ac.uk/ac/gene.php?gene=SERPINC1), including reports of novel *SERPINC1* gene mutations [7–10]. Checking several population gene databases and using bioinformatics tools, we found that the mutation had not been previously reported, despite its high pathogenicity prediction.

Congenital AT deficiency is associated with early and recurrent thrombosis, presenting an almost 14-fold higher risk of VTE compared with nondeficient individuals. Common sites for deep vein thrombosis are in the lower extremities or pulmonary arteries; less commonly, they occur in the cerebral sinus, vena cava, and mesenteric, renal, and hepatic (portal vein or intrahepatic portal branches) veins [11–13]. In particular, spontaneous thromboses can occur more easily in AT-deficient carriers with external prothrombotic factors, such as immobilization, trauma, surgery, hormonal contraception, and pregnancy [14]. Therefore, in the present PE case, we speculated that the sauna, sweating, and hemoconcentration may have caused the vascular endothelial injury and the subsequent "rapid" formation of a pulmonary artery thrombus. AT deficiency is regarded as the most severe thrombophilia, and these patients should be followed closely. To appropriately manage anticoagulation and thromboprophylaxis in both symptomatic and asymptomatic carriers, a workup for AT deficiency diagnosis, including functional (AT activity), biochemical (clinical type), and genetic (molecular), is recommended [1, 5].

Acute thromboembolism and anticoagulants may influence AT activity assays and lead to a false diagnosis; thus, the assays should be repeated 3 months after the acute thrombosis event and after holding one or two doses of DOACs whenever possible [3, 15]. After the functional assay has been performed, antigen-level assays are useful to define type I (quantitative, approximately 80% of cases) versus type II (qualitative) AT deficiencies. A type II AT deficiency can further be stratified into reactive site (type IIa), heparin-binding site (type IIb), and pleiotropic effect (type IIc) subtypes. As far as the genetic diagnosis is concerned, sequencing mutation analysis of the *SERPINC1* gene return positive findings in up to 80% of the constitutional abnormalities of AT deficiency; however, variations of other genes involved in AT transcription, folding, or posttranslational modification might affect protein levels or function, leading to associated AT deficiencies [15]. In addition, the current guidelines do not recommend the extensive use of all the thrombophilic assays because of their low clinical utility in terms of therapeutic changes once a positive result is obtained. However, the incidence of AT deficiency is thought to be underestimated, and an increasing amount of evidence supports the clinical benefit of a direct sequencing analysis in cases of suspected AT deficiency [15, 16]. In our study, the consistently significantly lower AT activity of the proband during follow-up and subsequent family AT deficiency diagnoses with the novel *SERPINC1* mutation (c. 1148 T > A: p.L383H) were confirmed.

In consideration of the significantly higher risk of VTE and the recurrence in congenital thrombophilia, patients with AT deficiency should be considered for anticoagulant therapy for the treatment and primary or secondary prevention of VTE and an even longer duration of prophylaxis [3]. Anticoagulation therapy in patients with an inherited AT deficiency generally follows the standard management for VTE and congenital thrombophilias but with the addition of AT supplementation therapy aiming to achieve a normal AT activity level. AT replacement combined with heparin can be used for the treatment of acute thromboembolism, especially in severe or recurrent VTE. Even patients with asymptomatic AT deficiency should receive primary thromboprophylaxis with heparin and/or AT supplementation in highly thrombogenic circumstances, including immobilization, surgery, pregnancy, and the postpartum period. Currently, there are two kinds of available human AT products, plasma-derived and recombinant AT, which were approved by the US Food and Drug Administration in 1991 and 2009, respectively [15]. The enzymatic activity of AT is significantly enhanced ($\geq$1000-fold) when an exogenous cofactor of heparin or heparin analogue binds to the heparin-binding site. In our PE case, anticoagulation therapy in the early stage (nadroparin calcium combined with warfarin) failed to stop the progression of pulmonary thrombosis, which partly contributed to the insufficient AT. Thus, the heparin analogue could not exert its inhibitory function efficiently.

Regarding anticoagulant therapy for the treatment or secondary prevention of VTE, there has been little guidance on whether traditional therapy should be modified in the presence of thrombophilia. In the 2012 antithrombotic guideline for VTE disease from the American College of Chest Physicians, only vitamin K antagonist (VKA) therapy (warfarin) was recommended for patients with antiphospholipid syndrome, although thrombophilias were not mentioned; thus, VKA therapy was historically implemented in many patients with VTE and thrombophilia. However, VKA therapy is challenging owing to the need for frequent laboratory monitoring, a narrow therapeutic range, complex dosing regimens, and common drug–drug and drug–food interactions [3]. In theory, DOACs (such as dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban) affecting either factor IIa or factor Xa should be effective in patients with thrombophilia. A variety of randomized, controlled clinical trials on DOACs compared with warfarin for the treatment and prophylaxis of VTE have been conducted and yielded positive results. Therefore, there is a preference for DOACs over VKA therapy in the 2016 antithrombotic guidelines for VTE and an increasing interest in using DOACs in patients with VTE and an underlying thrombophilia [3]. Recently, several series of case reports, prospective studies, and dynamic cohort studies with subanalyses focusing on patients with severe thrombophilia, including inherited AT deficiencies, offered reassuring conclusions concerning DOACs (mainly apixaban and rivaroxaban) and their efficacy and safety in this population [4, 17–20]. The 2019 European Society of Cardiology [21] and the American Chest Physicians 2021 guidelines [22] recommend DOACs over VKAs for antithrombotic therapy for VTE, although they do not yet provide guidance for patients with thrombophilia owing to limited data. However, all these results are encouraging, and DOACs are now widely used to prevent and treat VTE. In the end, thromboembolic risk differs according to the type of inherited deficiency, genotypic characterization, and its severity; therefore, whether extended, long-term, or indefinite, anticoagulation therapy should be considered on a case-by-case basis, taking personal and familial history of thrombosis into consideration.

Conclusion

Taken together, the rarest thrombophilia deficiencies are associated with a severe clinical phenotype, including AT, protein C, and protein S deficiencies. We identified a novel and definitely causative *SERPINC1* missense mutation c.1148 T>A (p.L383H) leading to congenital AT deficiency in a Chinese family, which updates the mutation spectrum of the *SERPINC1* gene and adds to our understanding of the molecular basis for AT deficiency. Although the substantial evidence supporting the widespread use of DOACs (mainly rivaroxaban) in congenital AT deficiency is lacking and difficult because of the very low incidence rate, the currently available data from case studies and clinical trials demonstrate the efficacy, safety, and advantages of DOACs in treating this population as an alternative to VKAs and heparin.

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Author contributions

Fangkai He wrote the manuscript and took care of the patient. Yang Wang, Weiwei Ning, and Chao Liu edited the manuscript and took care of the patient. Xiaojun Guan and Yao Yao wrote and edited the manuscript. All authors approved the final manuscript and consented to publish the manuscript.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate
This study was approved by the ethics committee of the First Affiliated Hospital of Soochow University, and informed consent and permission to use the illustrations was obtained from the patients.

Consent for publication
Written informed consent was obtained from the patient and his next-of-kin for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

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