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Contents

Thrice Monthly Volume 11 Number 20 July 16, 2023

MINIREVIEWS

ORIGINAL ARTICLE

Clinical and Translational Research

Retrospective Cohort Study

Retrospective Study

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 20 July 16, 2023

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 20 July 16, 2023

Contents

ABOUT COVER

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CASE REPORT

Antithrombin III deficiency in a patient with recurrent venous thromboembolism: A case report

Jia-Qing Luo, Shuai-Shuai Mao, Jin-Yi Chen, Xue-Ying Ke, Yue-Feng Zhu, Wei Huang, Hai-Ming Sun, Zhen-Jie Liu

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Abstract

BACKGROUND

Antithrombin III (AT3) deficiency, an autosomal dominant disease, increases the likelihood of an individual developing venous thromboembolism (VTE). Long-term anticoagulation treatment is required for those suffering from AT3 deficiency.

CASE SUMMARY

A man aged 23, who had a history of deep venous thrombosis (DVT), experienced recurrent pain and swelling in his right lower extremity for three days following withdrawal of Rivaroxaban. He was diagnosed with DVT and antithrombin III deficiency as genetic testing revealed a single nucleotide variant in *SERPINC1* (c.667T>C, p.S223P). The patient was advised to accept long-term anticoagulant therapy.

CONCLUSION

Inherited AT3 deficiency due to *SERPINC1* mutations results in recurrent VTE. Patients may benefit from long-term anticoagulant therapy.

Key Words: Antithrombin; Venous thrombosis; SERPINC1; Single nucleotide variant; Anticoagulant therapy; Case report

Core Tip: Hereditary thrombophilia can be attributed to mutations in genes such as *PROS, PROC, SERPINC1*, and *F5*. Compared to mutations in other genes, mutations of *SERPINC1* consistently lead to a more pronounced thrombophilia. Patients with this type of mutation are often advised to take warfarin as a therapeutic measure. However, evidence on the efficacy of direct oral anticoagulants is inadequate. Following identification of the *SERPINC1* mutation, our patient was advised to take Rivaroxaban for 5 years to prevent the possibility of thrombus recurrence. This report may supply proof of the efficacy of direct oral anticoagulants in individuals suffering from hereditary thrombophilia.

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INTRODUCTION

Venous thromboembolism (VTE), consisting of pulmonary embolism (PE) and deep venous thrombosis (DVT), is a significant public health hazard. Approximately 20% of patients have unprovoked VTE. Moreover, 10%~40% of unprovoked VTE patients were diagnosed with inherited thrombophilia[1,2]. Inherited antithrombin III (AT3) deficiency is a particularly concerning form of inherited thrombophilia. AT3 belongs to the serine protease inhibitor superfamily (SERPIN). AT3 is a major inhibitor of plasma serine protease, and it works to inactivate clotting factors like thrombin, as well as factors Xa, IXa, XIa, and XIIa. Different mutations in *SERPINC1* are responsible for Inherited AT3 deficiency, a thrombotic disorder which is inherited in an autosomal dominant fashion[3]. It is estimated that between 0.02%-0.25% of the general population and 2%-5% of those with VTE have inherited AT3 deficiency[4,5]. AT3 deficiency is classified into two phenotypes based on the plasma levels of functional and antigenic AT. Type I is distinguished by a decrease in both functional and antigenic AT, whereas Type II presents with a decrease in functional AT but normal antigenic AT. Type II deficiency is categorized into three groups based on the location of the mutation: Reactive site defects, heparin binding site defects, and pleiotropic defects[4]. We present a case of AT3 deficiency caused by a *SERPINC1* mutation, which was characterized by recurrent DVT.

CASE PRESENTATION

Chief complaints

A 23-year-old man complained of recurrent right lower extremity pain and swelling for three days.

History of present illness

Approximately six months after withdrawing Rivaroxaban, the patient experienced recurrent right lower extremity pain and swelling.

History of past illness

One year ago, the patient came to the hospital complaining of right lower extremity pain for a week. Laboratory examinations before treatment showed the followings: D-dimer level 5.74 μg/mL, hemoglobin level 135 g/L, hematocrit 40.3%, erythrocyte sedimentation rate 6 mm/h, platelet count 241 × 10^9/L, fibrinogen level 2.28 g/L, prothrombin time 15 s, active partial thromboplastin time 51.9 s, and the functional AT level AT3 50.5%. Doppler ultrasound revealed venous thrombosis in the right femoral and popliteal veins. After two weeks of initial therapy with low-molecular-weight heparin, the patient left the hospital. He took Rivaroxaban 15 mg twice daily as continuous therapy for a week, which was then changed to Rivaroxaban 10 mg twice daily. The therapy was continued for seven months. The patient then decided to stop anticoagulation therapy.

Personal and family history

There was no record of trauma, malignancy, or other medical issues in his personal history. His parents had no history of thrombosis (Figure 1A).

Physical examination

During physical examination, his vital signs were recorded as follows: body temperature 36.0 °C, blood pressure 110/50

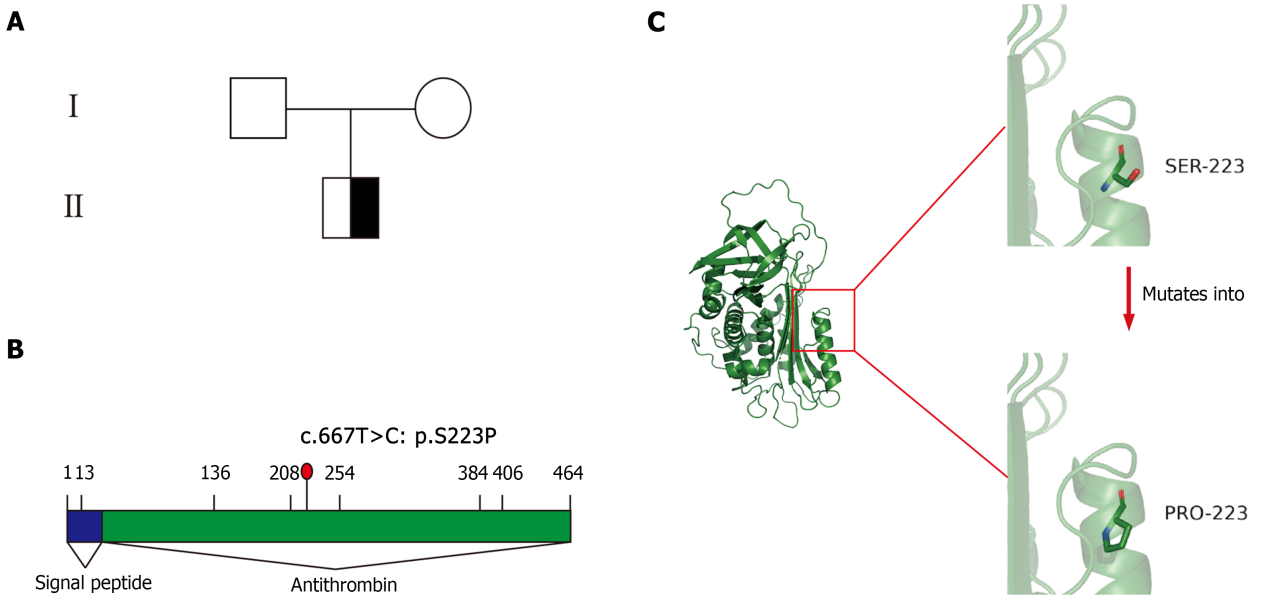

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Figure 1 Whole exome sequencing results. A: The patient's parents did not previously have thrombosis and refused to undergo genetic sequencing; B: The mutation was found in *SERPINC1* (c.667T>C); C: The protein change resulted in Serine (S) changed to Proline (P) at position 223 (p.S223P).

mmHg, heart rate 76 bpm, and respiratory rate 18 breaths/min. Furthermore, the right lower limb was swollen.

Laboratory examinations

The patient's functional AT level was 50.5%, indicating AT3 deficiency. Since there were no tests available to measure the antigenic AT level, it is not feasible to identify the subtype of AT3 deficiency in this patient.

Imaging examinations

Computed tomography pulmonary angiography indicated the presence of filling defects in both lobar and partial segmental arteries. Doppler ultrasound of the deep veins in both lower extremities revealed the presence of deep vein thrombosis in the right lower extremity, as well as thrombosis in the middle and lower sections of the right external iliac vein. By computed tomography pulmonary angiography and Doppler ultrasound, the patient was diagnosed with right lower extremity DVT and PE.

FINAL DIAGNOSIS

The patient was diagnosed with DVT, PE and AT3 deficiency.

TREATMENT

During the acute thrombosis, the patient was treated with low-molecular-weight heparin 4100 AxaIU every 12 h. As he was suffering from both DVT and PE, he was recommended to insert an inferior vena filter to prevent worse PE. Upon the discharge, he was advised to receive life-long anticoagulation therapy with Rivaroxaban 20 mg daily.

OUTCOME AND FOLLOW-UP

Over the 5-year follow-up period, no recurrent DVT was observed in this patient.

DISCUSSION

Due to failure to block the coagulation cascade, AT3 deficiency results in a greater risk of recurrent thrombosis[3]. The AT gene, located on chromosome 1 in the q23.1-23.9 region of the genome, is 13.5 kb long and has six introns and seven exons [6]. In 1983, the first variation resulting in AT3 deficiency was reported, and, to our knowledge, more than 200 mutations have been reported to be related to the risk of thrombosis[7]. Furthermore, the mutation profile of the *SERPINC1* gene

includes point mutations, splice site variants, small insertion/deletion mutations, and a few gross rearrangements[4]. The patient in this report had a point mutation. Moreover, the variant was known to result in AT3 deficiency. The AT3 activity in this patient was 50.5%. The decrease in AT3 activity supported the diagnosis.

AT3 deficiency is an autosomal dominant disorder. A heterozygous variant is linked to a heightened probability of venous thrombosis[7]. A heterogeneous variant was found following genome sequencing in this patient. Serine (S) changed to Proline (P) at position 223 (*c.667T>C, p.S223P*) on chromosome 1(Figure 1B and C). This variant was reported to be a missense change resulting in AT3 deficiency in 1984 and 2000[8,9]. In addition, this variant usually causes type I AT3 deficiency. The initial and recurrent VTE rates are different in type I and type II AT3 deficiency. Mitsuguro *et al*[10] discovered that individuals suffering from type I AT deficiency experienced more VTE occurrences compared to those with type II AT deficiency. Furthermore, Alhenc-Gelas *et al*[11] reported that among a large group of individuals with AT inherited deficiency, type I mutations demonstrated a greater likelihood of experiencing a first VTE, and type II deficiency had a lower risk for PE associated with DVT[11]. In this case, the patient was diagnosed with AT3 activity and a variant in the genotype. After withdrawing Rivaroxaban, he developed PE. We strongly advised the patient to take lifelong anticoagulant therapy.

Rivaroxaban is a selective factor Xa inhibitor. It is widely used in anticoagulation therapy. Many VTE patients prefer Rivaroxaban to warfarin, as it does not require monthly or weekly blood examinations. However, the guidelines did not mention the effects and security of Rivaroxaban in patients with inherited thrombophilia[12,13]. Moreover, few studies have focused on this issue. In our patient, Rivaroxaban seemed to be effective and safe during the six-month treatment. Recurrent VTE occurred quickly after the withdrawal of Rivaroxaban. Thus, Rivaroxaban may be effective in patients with AT3 deficiency. Some case reports have obtained similar outcomes[14-16].

CONCLUSION

When AT3 deficiency is suspected, gene detection is recommended. AT3-deficient patients with *SERPINC1* mutations can be recognized by genetic testing. The discovered mutation in *SERPINC1* (*c.667T>C, p.S223P*) seems to have clinical relevance in AT3 deficiency. Consequently, our patient was advised to modify his lifestyle and start on prolonged prophylactic treatment.

FOOTNOTES

Author contributions: Luo JQ and Mao SS contributed to manuscript writing and editing, and data collection; Chen JY, Ke XY, and Zhu YF contributed to data collection and analysis; Huang W, Sun HM and Liu ZJ contributed to conceptualization and supervision; All authors have read and approved the final manuscript.

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