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Case Report

Efficacy and safety of apixaban in a patient with systemic venous thromboembolism associated with hereditary antithrombin deficiency

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ABSTRACT

A 40-year-old man with progressively worsening dyspnea was admitted to our hospital. On physical examination, pulse oximetry results demonstrated 80% oxygen saturation in room air. The lungs sounded clear, and both extremities appeared normal, without pitting edema. His echocardiography revealed a pressure overload in the right ventricle. Suspecting the presence of pulmonary thromboembolism, we performed an enhanced computed tomography (CT). CT results revealed systemic venous thromboembolism (VTE) involving the superior mesenteric vein, inferior vena cava (IVC), right common iliac vein and pulmonary arteries, as well as splenomegaly and edema of the small intestine with ascites. After insertion of a retrievable IVC filter, we prescribed 10 mg of apixaban twice daily for the first 7 days, followed by 5 mg twice daily as long-term therapy. Confirming no exacerbation of the VTE symptoms, we removed the IVC filter 14 days after admission. Additionally, hereditary antithrombin deficiency was unraveled as the etiology of systemic VTE. Although an enhanced CT at 6 months follow-up showed that almost all previous VTE had dissolved, we decided to prescribe apixaban indefinitely. Fortunately, he has not experienced a recurrence of VTE or any bleeding events to date.

<**Learning objective:** Hereditary antithrombin (AT) deficiency is a thrombophilia, which has a high potential to develop venous thromboembolism (VTE). Direct oral anticoagulant (DOAC) therapy can substitute for conventional therapy, including parenteral anticoagulant plus warfarin. However, the efficacy and safety of DOAC treatments for patients with hereditary AT deficiency with systemic VTE have not yet been clarified. This report highlights the efficacy of a single apixaban prescription in achieving excellent outcomes in resolving systemic VTE with no bleeding events.>

Introduction

Antithrombin (AT) deficiency, a rare autosomal dominant disease, was reported as the first inherited thrombophilia in 1965 [1].?The disorder occurs in approximately 0.02%–0.25% of the overall population [2].?AT deficiency is classified into two types. Type I is characterized by decreased AT antigen levels and reduced AT activity known as classical hereditary AT deficiency; Type II involves a functional defect in AT activity with a normal range of AT antigen levels. Approximately 50%–90% of patients with classical hereditary AT deficiency develop thromboembolism by the age of 60 years; 60% of patients experience a first thromboembolism episode, particularly, between 14?and 30 years of age [2,3].?These thromboembolism episodes are characterized by repeated intravenous occurrences and a family history. Thus, patients with a history of thromboembolism usually take oral anticoagulants for their lifetime. In ordinary venous thromboembolism (VTE), such as deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE), conventional treatment comprises a parenteral anticoagulant: low-molecular-weight heparin (LMWH), unfractionated heparin, or fondaparinux administered for at least 5 days; warfarin is simultaneously initiated during this time and continued for at least 3?months. This regimen is challenging, because LMWH and fondaparinux require daily subcutaneous injections and warfarin requires coagulation monitoring with dose adjustments.

Apixaban, is a direct oral anticoagulant (DOAC) factor Xa inhibitor that has a rapid onset of action and predictable pharmacokinetics that allow a fixed-dose regimen. Recent studies supported the conclusion that apixaban has substantial potential

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to simplify the treatment of DVT and PTE by eliminating the need for initial parenteral anticoagulants and monitoring warfarin [4].? However, the efficacy and safety of apixaban against systemic VTE remain unknown.

We herein report the case of 40-year old man with AT deficiency associated with systemic VTE who achieved almost complete remission using apixaban.

Case report

A 40-year-old man presented with a 5-day history of progressively worsening dyspnea after returning from a 3-day hospital stay with a diagnosis of acute viral enterocolitis. Initially, his symptoms were epigastralgia and anorexia, which were cured completely with intravenous drips. On physical examination, pulse oximetry results demonstrated 80% oxygen saturation in room air; the blood pressure was 130?over 60 mmHg and heart rate was 122?bpm. The lungs were clear, and both extremities appeared normal. His electrocardiography results showed incomplete right bundle branch block and an echocardiography test revealed that the right ventricle suppressed the left ventricle through the septal myocardium during the diastole phase. Laboratory studies revealed the following: serum albumin levels, 3.8 g/dl [reference value (RV), 3.6–5.1 g/dl]; aspartate aminotransferase, 19?IU/l (RV, 5–38 IU/l); alanine aminotransferase, 29?IU/l (RV, 5–44 IU/l); lactate dehydrogenase, 191?IU/l (RV, 106–211 IU/l); creatine phosphokinase, 80?IU/l (RV, 14–170 IU/l); blood urea nitrogen, 10.0 g/dl (RV, 7–22 mg/dl); creatinine, 0.70 mg/dl (RV, 0.6–1.1 mg/dl); estimated glomerular filtration rate, 99.05 ml/min/1.73m^2; troponin T, 0.169 ng/ml (RV, 0–<0.1 ng/ml); brain natriuretic peptide, 260.4 pg/ml (RV, 0–18.4 pg/ml), and electrolytes were all normal. In terms of coagulation, prothrombin time-international normalized ratio (PT-INR), 1.00 (RV, 0.83–1.17); activated partial thromboplastin time, 33.8 s (RV, 26.0–36.0 s); fibrinogen, 569 mg/dl (RV, 150.0–450.0 mg/dl); fibrin degradation product (FDP), 116.3 μg/ml (RV, 0–5.0 μg/ml); D-dimer, 13.3 μg/ml (RV, 0–0.5 μg/ml); AT antigen level, 11.6 mg/dl (RV, 15–31 mg/dl); AT activity, 45% (RV, 81–123%); protein C activity, 67% (RV, 64–135%); protein S activity, 73% (RV, 64–149%), and anti-cardiolipin antibody (IgG), <8.0 U/ml (RV, 0–13 U/ml). The elevation in FDP and D-dimer levels accompanied with dyspnea suggested the existence of PTE. Results of enhanced computed tomography (CT) demonstrated multiple VTE in the superior mesenteric vein, inferior vena cava (IVC), right common iliac vein, and pulmonary arteries as well as splenomegaly and edema of the small intestine with ascites, thereby suggesting intestinal congestion. Interestingly, no DVT was found in either of his legs (Fig.?1). After insertion of a retrievable IVC filter, we prescribed 10 mg of apixaban twice daily for the first 7 days, followed by 5 mg twice daily for 6?months as long-term therapy;

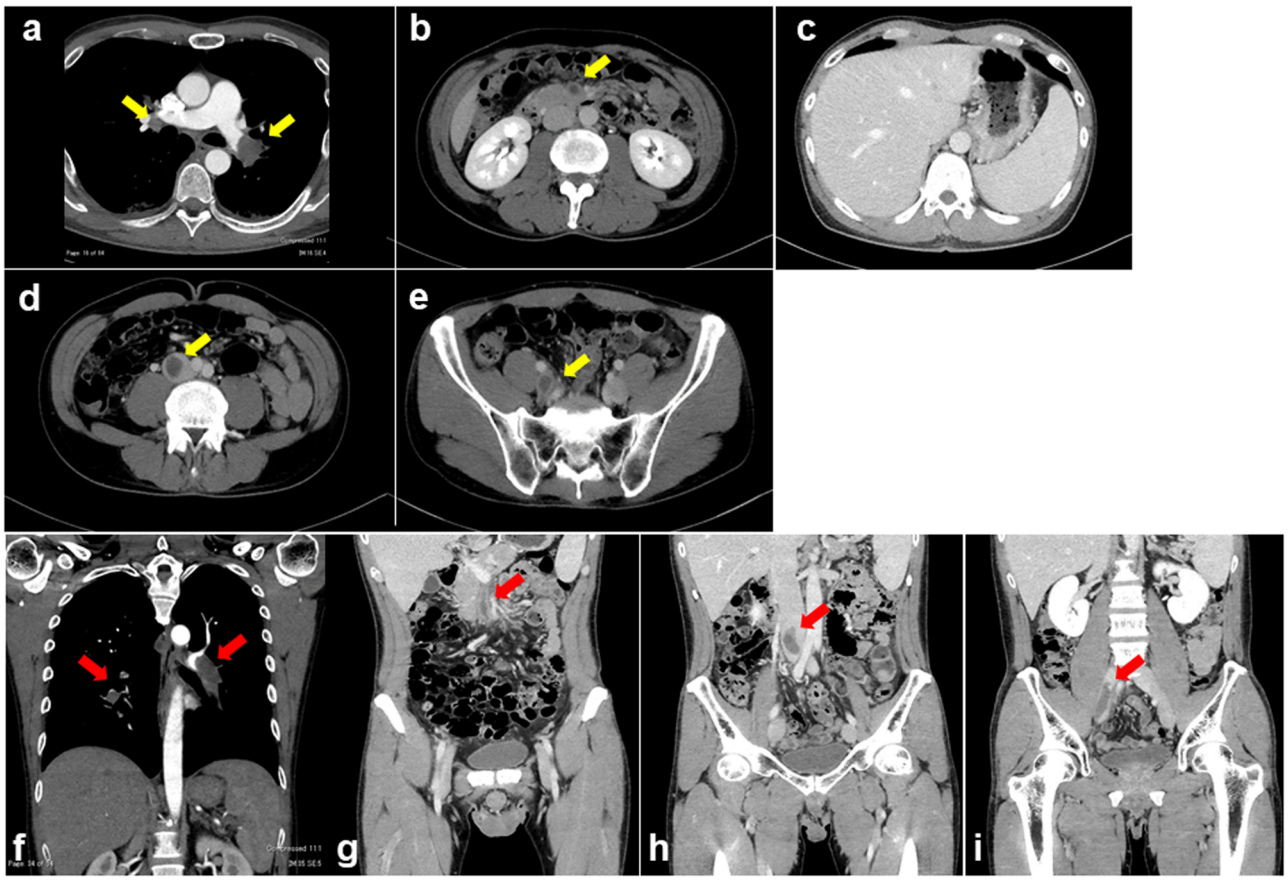

Fig. 1. Enhanced computed tomography (acute phase on admission). Five transverse plane images (a–e): (a) Large thrombi occlude both pulmonary arteries. (b) Superior mesenteric vein is occluded by thrombi. (c) Inferior vena cava is occluded by thrombi. (d) Right common iliac vein is occluded by thrombi. (e) Splenomegaly is presented because of interruption of venous return to the hepatic portal vein.
Four coronal plane images (f–i): (f) Large thrombi occlude both pulmonary arteries. (g) Superior mesenteric vein is occluded by thrombi. (h) Inferior vena cava is occluded by thrombi. (i) Right common iliac vein is occluded by thrombi.
Yellow and red arrows reveal the existence of thrombi.

the same treatment regimen within the Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy study [4].?Two weeks after the IVC filter insertion, there had been no exacerbation of the thromboembolism symptoms; thus, we removed the IVC filter. An enhanced CT at 6?months follow-up showed that almost every previous VTE has dissolved, although a few small PTEs remained (Fig.?2). Interestingly, the patient's father had suffered a complicated cerebral infarction in his forties. We prescribed apixaban indefinitely to prevent a recurrence of multiple VTE. He has not experienced a recurrence of PTE or any bleeding events to date under oral apixaban administration.

Discussion

In this present case, a 40-year-old man with systemic VTE associated with hereditary AT deficiency achieved almost complete remission after treatment with apixaban. His father had a history of cerebral infarction in his youth. Although we did not perform genetic examination to confirm whether his AT deficiency is inherited, we diagnosed that his AT deficiency was hereditary type I based on his family history and decreasing AT antigen level.

Apixaban is a DOAC with numerous advantages over warfarin, including a rapid pharmacological effect and a lower risk of bleeding. Additionally, the adjustment of appropriate warfarin dosage requires time and effort to control the range from 2.0?to 3.0?based on the PT-INR. Anticoagulant management in patients with thrombophilia, including AT deficiency tends to be further complicated to adjust appropriate dosage of anticoagulant agents [5].?Few reports have described the efficacy of rivaroxaban for treating AT deficiency [6,7].

Otherwise, no report has demonstrated the efficacy of apixaban to treat systemic VTE in patients with AT deficiency. Apixaban is more preferable than warfarin because (1) there is no need for anticoagulant monitoring, (2) apixaban is neither influenced by diet nor does it interact with other agents, and (3) there is a low risk of bleeding [8].

For antithrombotic therapy, sufficient anticoagulant effect of heparin could not have developed in our patient with AT deficiency because the anticoagulant effect of heparin depends on AT activity and antigen level in the blood. DOACs do not act through AT, Therefore, DOACs could be used as a complementary agent for treating patients with VTE who congenitally lack coagulation factors involving AT, such as those with thrombophilia. However, the appropriate level of DOACs required to achieve this goal remains unknown. Therefore, long-term anticoagulant therapy should be performed with due consideration of the risk of hemorrhagic complications.

Finally, there are few randomized controlled trials; therefore, the long-term efficacy and safety of IVC filters remains unclear.

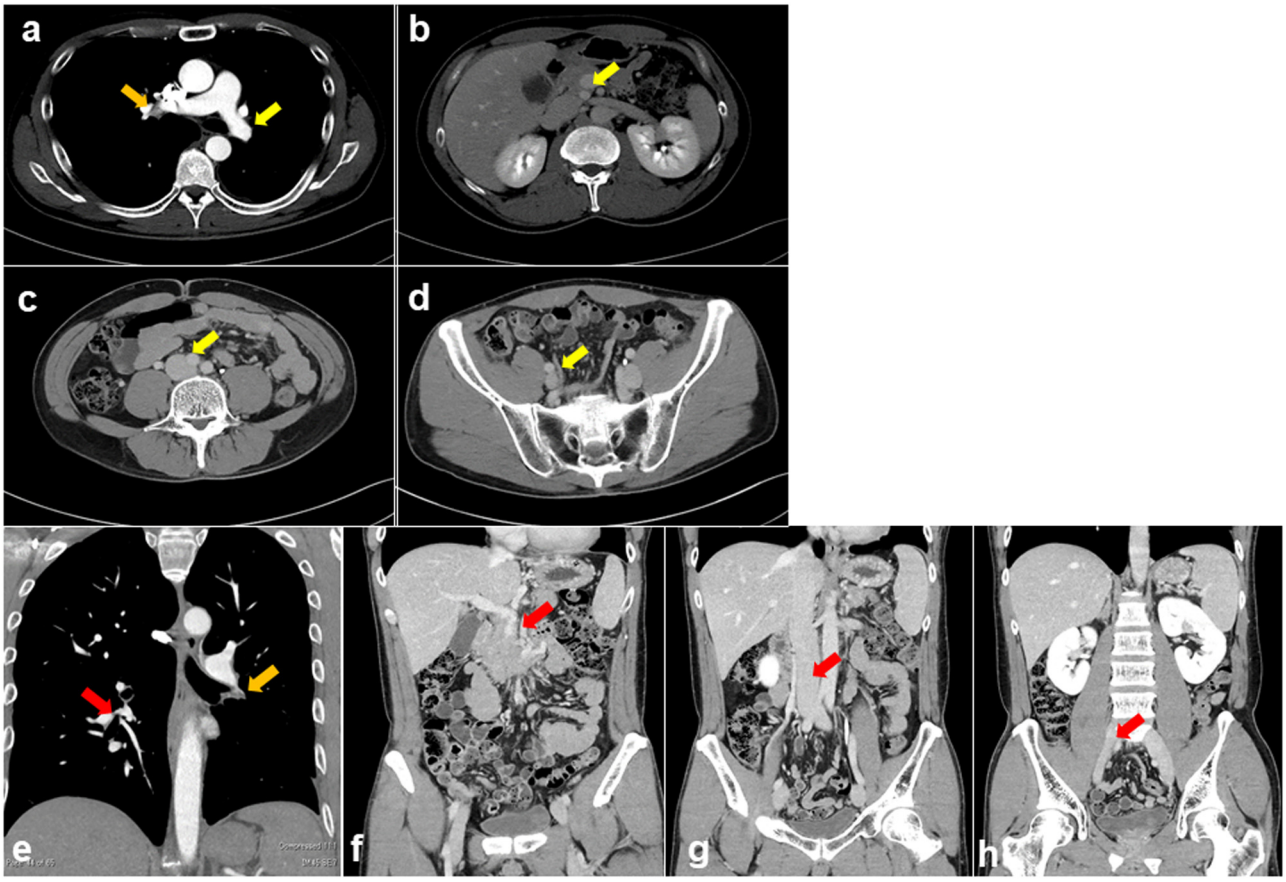

Fig. 2. Enhanced computed tomography (chronic phase after 6 months). Four transverse plane images (a–d): (a) Small thrombi still remain in the right pulmonary artery. Almost every thrombus is dissolved in every vein (b–d).
Four coronal plane images (e–h): (e) Small thrombi still remain in the left distal pulmonary artery. No thrombus is found in any vein (f–h).
Small thrombi indicated by orange arrows.
Yellow and red arrows indicate the existence of the previous thrombi. All thrombi have been dissolved.

However, a few prospective controlled studies have proved its efficacy in reducing subsequent PTE [9].?Moreover, Nonaka et?al. have reported the case of a patient with PTE accompanied with massive IVC thrombi that were successfully treated with aggressive catheter-directed thrombosis (CDT) and DOAC after an IVC filter deployment [10].?In this article, the authors decided to insert an IVC filter because the IVC thrombi were mobile and likely to flow away. Our patient showed many mobile thrombi in IVC and iliac veins, which were similar to the previously reported case [10].?Our patient was young; therefore, we had to avoid the next PTE event. According to the guidelines of the European Society of Cardiology, the severity grade of our patients' PTE was intermediate-high risk. Deployment of a retrievable IVC filter may be considered in patients with such a risk grade needing aggressive CDT and confirming mobile thrombi in large veins such as IVC, iliac, or superficial femoral veins. Additionally, it is advised to retrieve an IVC filter as soon as possible, after no necessity of continuing usage has been confirmed.

The present study has some limitations. We did not measure the AT antigen and activity levels when his condition was stable. To achieve an accurate diagnosis confirming that his AT deficiency is inherited, these levels must be measured. Unfortunately, we have not yet collected these data. Additionally, a 6-month follow-up CT is insufficient to assess the safety of apixaban over his lifetime. Further close observation is required in this case.

In conclusion, patients with hereditary AT deficiency have lesser AT activity and antigen level in AT than ordinary people. Therefore, using heparin as a parenteral therapy does not work to prevent thromboembolism in these patients. DOACs could be a breakthrough therapy to treat thromboembolism in patients with thrombophilia. Here we demonstrated the safety and efficacy of a single use of apixaban as an anticoagulant in a patient with systemic VTE associated with hereditary AT deficiency.

Conflict of interest

The authors declare that there is no conflict of interest.

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