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Fatal Cerebral Venous Thrombosis in a Pregnant Woman with Inherited Antithrombin Deficiency after BNT162b2 mRNA COVID-19 Vaccination

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Antithrombin deficiency is a high-risk factor for venous thromboembolism during pregnancy, whereas cerebral venous thrombosis is rare. Cerebral venous thrombosis related to coronavirus disease 2019 (COVID-19) vaccines has been reported; however, there are a few reports of cerebral venous thrombosis after a messenger RNA (mRNA) vaccination. A 25-year-old female in her sixth week of pregnancy presented with headache 24 days after BNT162b2 mRNA COVID-19 vaccination. The following day, she presented with altered sensorium and was diagnosed with severe cerebral venous thrombosis. She demonstrated heparin resistance and was found to have an inherited antithrombin deficiency. A heterozygous missense variant in *SERPINC1* (c.379T>C, p.Cys127Arg, 'AT Morioka') was detected by DNA analysis. Despite intensive care with unfractionated heparin, antithrombin concentrate, and repeated endovascular treatments, she died on the sixth day of hospitalization. Cerebral venous thrombosis in pregnant women with an antithrombin deficiency can follow a rapid and fatal course. Treatment with unfractionated heparin and antithrombin concentrate may be ineffective in severe cerebral venous thrombosis cases with antithrombin deficiency. Early recognition of antithrombin deficiency and an immediate switch to other anticoagulants may be required. Although the association between cerebral venous thrombosis and the vaccine is uncertain, COVID-19 vaccinations may require careful evaluation for patients with prothrombic factors.

Keywords: antithrombin deficiency; cerebral venous thrombosis; coronavirus disease 2019; messenger RNA vaccine; pregnancy
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Introduction

Both pregnancy and thrombophilia are known to be risk factors for cerebral venous thrombosis (CVT) (Ferro et al. 2004). CVT in pregnant or puerperium complicated with thrombophilia has a 38% possibility (Kashkoush et al. 2017). Among thrombophilia, antithrombin (AT) deficiency is a high-risk factor for venous thromboembolism during pregnancy (Gerhardt et al. 2016). However, only a few reports of CVT during pregnancy with AT deficiency exist (Özsener et al. 2001; McAuley et al. 2005; Sharpe et al. 2011).

CVT related to coronavirus disease 2019 (COVID-19) vaccines has been reported. Vaccine-induced immune thrombotic thrombocytopenia (VITT) is becoming recognized as an adverse event of the adenoviral vector vaccine (Sharifian-Dorche et al. 2021; Ahmed et al. 2022). In contrast, CVT after messenger RNA (mRNA) vaccination is rare (Cheng 2021; Dias et al. 2021; Fan et al. 2021; Yamaguchi et al. 2021; Zakaria et al 2021).

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We herein present a fatal case of CVT in a pregnant woman with an inherited AT deficiency after a BNT162b2 mRNA COVID-19 vaccination.

Case Presentation

A 25-year-old woman presented with nausea, anorexia, and headache 11 days after having a positive pregnancy test. She was confirmed to be six weeks pregnant and admitted to another hospital. She received the second dose of the BNT162b2 mRNA vaccine for COVID-19 24 days prior to hospitalization. On the following day, she presented with an altered sensorium. CVT was suspected based on the computed tomography (CT) scan of the head, and the patient was transferred to our hospital. On admission to our hospital, the patient was comatose and quadriplegic, with a convulsive seizure. The Glasgow Coma Scale score was 4 (E1V1M2). Laboratory testing revealed a normal platelet count of 258 × $10^3/\mu$L and an elevated D-dimer level of 5.97 μg/mL (reference range < 1.0 μg/mL). Other laboratory findings were unremarkable. A CT scan of the head showed a hemorrhagic infarction in the right thalamus and basal ganglia, intraventricular hemorrhage, and a high-density signal in the straight sinus (StS) and left transverse sinus (TS) (Fig. 1). Cerebral angiography revealed occlusion of the deep cerebral veins, StS, and left TS (Fig. 2a-c). We performed thrombectomy with an aspiration catheter and direct thrombolysis with urokinase (Fig. 2d). Massive thrombi were aspirated from the StS and left TS, resulting in recanalization of the StS (Fig. 2e, f). Despite perioperative administration of unfractionated heparin (UFH), neither the activated clotting time (ACT) nor activated partial thromboplastin time (APTT) was prolonged, suggesting heparin resistance (Fig. 3). The coagulation workup revealed reduced antithrombin (AT) activity at 44% (reference range 80%-130%) and low protein S (PS) activity at 27% (reference range 56%-126%). The patient and her family members had no history of thrombophilia or thrombosis. We administered UFH as a bolus and continuously with AT concentrate of 1,500 units/day. We diagnosed AT deficiency three hours after the admission and administered the AT concentrate four hours later. On the following day, APTT and ACT were still not prolonged (Fig. 3). A CT scan of the head showed worsening brain edema and acute hydrocephalus, requiring ventricular drainage (Fig. 4a, b). Susceptibility-weighted magnetic resonance imaging on the second day revealed the occlu-

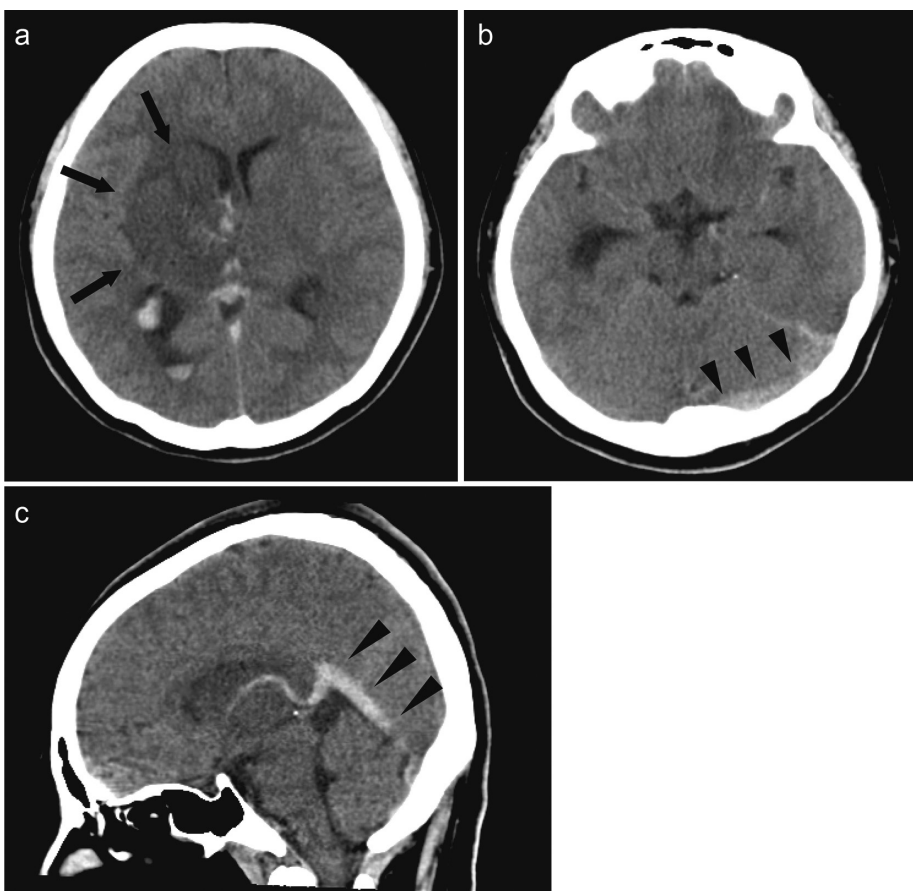

Fig. 1. Computed tomography scan of the head on admission.
(a) Hemorrhagic infarction on the right thalamus and basal ganglia (arrows) with intraventricular hemorrhage is observed. (b, c) High density in the left transverse sinus and straight sinus indicates cerebral venous thrombosis (arrowheads).

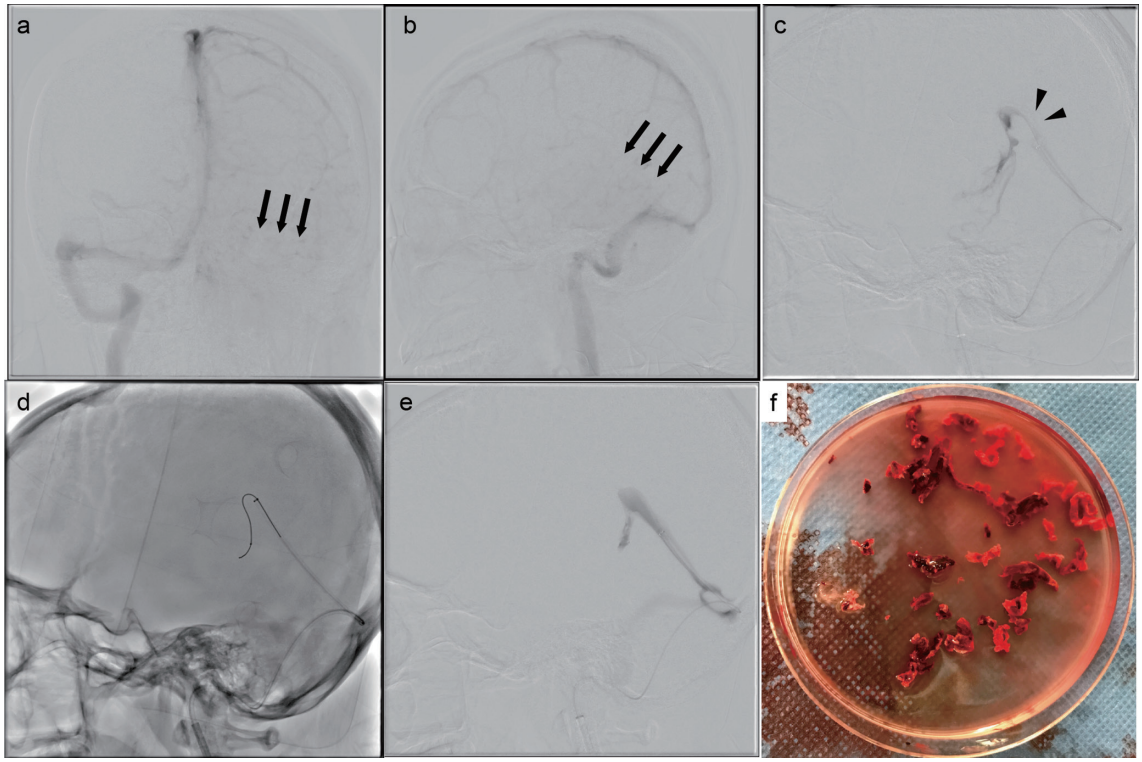

Fig. 2. Cerebral angiography and endovascular treatment.
(a, b) Cerebral angiography revealed the occlusion of the deep cerebral veins, straight sinus, and left transverse sinus (arrows). (c) A filling defect in the straight sinus suggests thrombus (arrowheads). (d) Thrombectomy with aspiration catheter and direct catheter thrombolysis with urokinase are performed. (e) A filling defect disappears, and recanalization of the straight sinus is achieved. (f) Massive thrombi are aspirated from the straight sinus and left transverse sinus.

sion of the deep cerebral veins with low intensity (Fig. 4c, d). The patient was intubated and on artificial ventilation. Although APTT and ACT were prolonged with high dose UFH on the second day of hospitalization (Fig. 3), her symptoms and brain edema did not improve. Thrombectomy and thrombolysis were performed again, and left TS recanalization was achieved. On the third day of hospitalization, we performed a therapeutic abortion after consulting with the patient's family to augment hypercoagulability secondary to pregnancy. Despite these treatments, the patient developed whole-brain edema and died on the sixth day of hospitalization (Fig. 4e, f). We were unable to perform an autopsy because the patient's family did not provide consent.

DNA analysis of AT and PS was performed at the Genetic Testing Laboratory of Kazusa DNA Research Institute (Kisarazu, Chiba, Japan) after obtaining familial consent. On evaluation for AT mutations, a heterozygous missense variant in the *SERPINC1* gene (c.379T>C, p.Cys127Arg, 'AT Morioka') was detected. This mutation causes type I AT deficiency (Ozawa et al. 1997). No PS mutations were detected. Low PS activity was the effect of pregnancy (Comp et al. 1986). The patient's sister and mother also had low AT levels of 45% and 52%, respectively, but they did not experience any thrombotic events during their pregnancies.

Consent was obtained from the patient's family for all procedures, including submission to the journal. The off-label use of endovascular devices for cerebral venous thrombosis and the questionnaire and methodology for this study were approved by the Human Research Ethics Committee of the Iwate Prefectural Central Hospital (Ethics approval number: 466).

Discussion

We presented a fatal case of CVT in a pregnant woman with inherited AT deficiency after a BNT162b2 mRNA COVID-19 vaccination. The course of the patient was rapid despite intensive care with UFH, AT concentrate, and repeated endovascular treatments. CVT in patients with AT deficiency during pregnancy is rare, and a fatal case has not been reported. This case indicated the difficulty of management in this setting.

For the initial treatment of CVT, intravenous UFH or low molecular weighted heparin is recommended regardless of the presence of intracranial hemorrhage (ICH) (Saposnik et al. 2011). This is based on a randomized controlled trial that showed a better outcome in the heparin group than in the placebo group (Einhäupl et al. 1991). An additional retrospective study assessing patients with ICH was performed in this report, showing that the mortality of the heparin group was lower. Other anticoagulants including direct oral

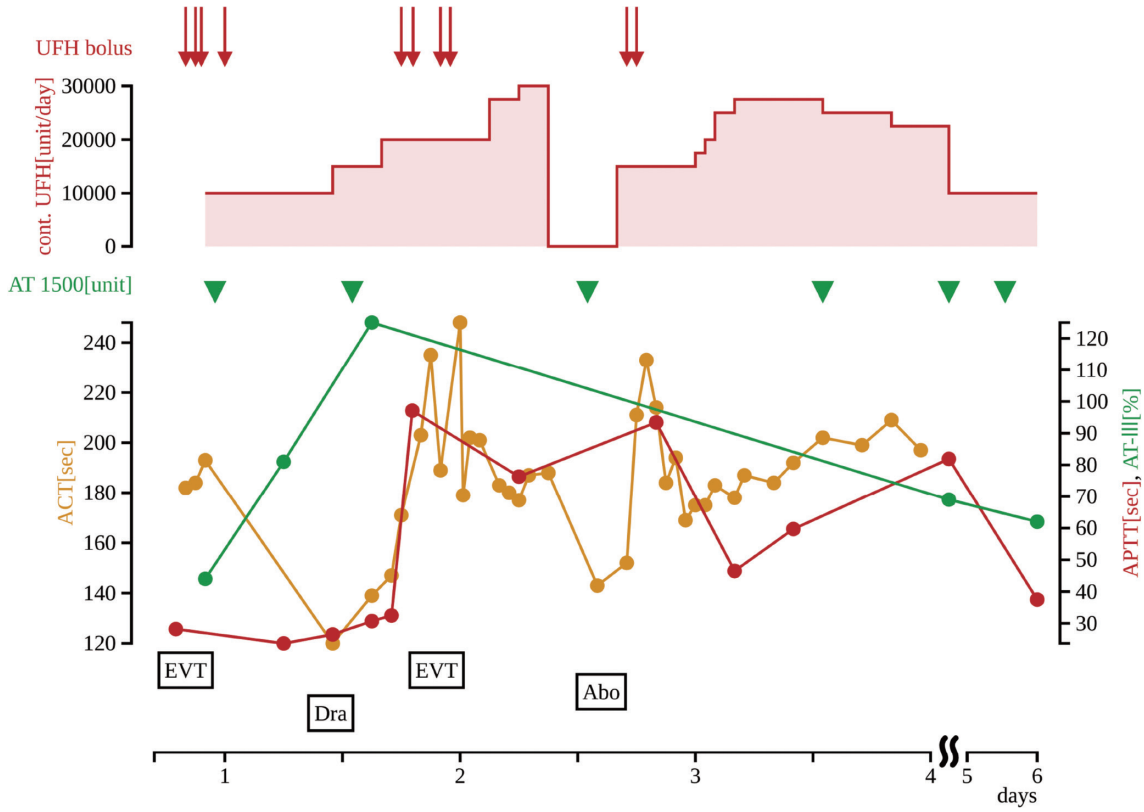

Fig. 3. Clinical course of the patient.
Despite administrating unfractionated heparin (UFH) and antithrombin (AT) concentrate, neither the activated clotting time nor activated partial thromboplastin time was prolonged on the first day of hospitalization. It took approximately 24 hours for the heparin to reach the therapeutic range. UFH was discontinued during the therapeutic abortion.
UFH, unfractionated heparin; cont, continuous unfractionated heparin; AT, antithrombin concentrate; ACT, activated clotting time; APTT, activated partial thromboplastin time; EVT, endovascular treatment; Dra, ventricular drainage; Abo, therapeutic abortion.

anticoagulants (DOACs) and a specific thrombin inhibitor (argatroban) have no established evidence of efficacy in CVT. Thus, heparin is the first-choice anticoagulant for CVT. However, since the effectiveness of heparin is achieved by activating AT, patients with an AT deficiency have heparin resistance (Anderson and Saenko 2002). A combination of heparin and AT concentrate is generally used to manage thrombosis in patients with AT deficiency. Nevertheless, AT concentrate has not been proven to benefit patients with AT deficiency in acute thrombosis (Patnaik and Moll 2008). Only three cases of CVT during pregnancy with AT deficiency have been reported (Özsener et al. 2001; McAuley et al. 2005; Sharpe et al. 2011). Two of the cases were treated with anticoagulation (heparin or warfarin) and AT concentrate, and the other was managed without anticoagulation and only with a cesarean section. All reported cases yielded good outcomes. We recognized heparin resistance and diagnosed AT deficiency at an early stage. We immediately administered AT concentrate, as well as a bolus and continuous UFH under frequent ACT and APTT monitoring. In addition, we performed repeated thrombectomy with an aspiration catheter and direct catheter thrombolysis with urokinase. However, in contrast to the reported cases, the patient was refractory to these treatments. The severity of the CVT contributed to this fatal outcome. Our case had several reported variables associated with poor prognosis in CVT, including severe neurological symptoms, intracerebral hemorrhage, and thrombosis of the deep venous system (Saposnik et al. 2011). In such a severe CVT case, the slight delay in achieving the therapeutic range of heparin possibly led to this fatal outcome; it took approximately 24 hours for the heparin to reach the therapeutic range. Switching to other anticoagulants earlier may be needed. In a report of CVT in a pregnant woman with low AT activity, though AT deficiency was not confirmed, the patient was successfully treated with argatroban (King et al. 2016). This case also had a strong heparin resistance, and switching to argatroban was effective. Recently, DOACs have been shown to have similar efficacy to heparin or vitamin K antagonists in treating venous thromboembolism in patients with thrombophilia (Campello et al. 2020). An early decision to switch to these alternative anticoagulants is required when heparin resistance is persistent.

Endovascular treatment was performed in our case. A randomized control study comparing the effectiveness of

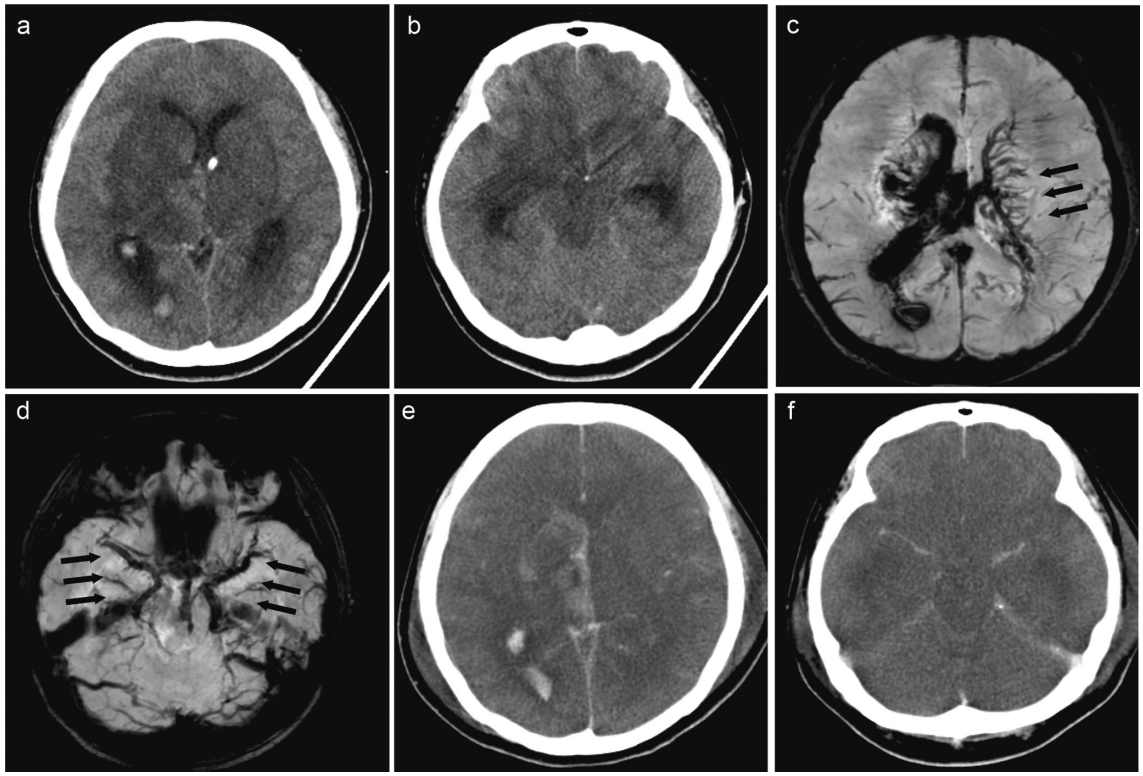

Fig. 4. Computed tomography (CT) and magnetic resonance imaging of the head on the second day, and autopsy imaging. (a, b) CT of the head on the second day of hospitalization shows worsened brain edema and acute hydrocephalus. (c, d) Susceptibility-weighted magnetic resonance imaging on the second day reveals occluded deep cerebral veins with low intensity (arrows). (e, f) CT of the head (autopsy imaging) reveals whole-brain edema.

endovascular treatment with medical treatment failed to show the effectiveness of endovascular treatment (Coutinho et al. 2020); however, the mortality and other adverse events were not statistically higher in the endovascular treatment group. In an observational study, 87.5% of patients had good outcomes, even in a patient with ICH (Guo et al. 2020). In our case, recanalization was achieved in both sessions without adverse events. Therefore, although endovascular treatment could not improve our patient's outcome, it was not at least harmful.

The patient in our case received a COVID-19 vaccination 24 days before developing CVT. Currently, two types of COVID-19 vaccines exist, adenoviral vector vaccines and mRNA vaccines. CVT, specifically VITT, in patients who have received adenoviral vector COVID-19 vaccines has been reported (Sharifian-Dorche et al. 2021; Ahmed et al. 2022). VITT is reported to resemble heparin-induced thrombocytopenia and has a high mortality rate of 39% (Sharifian-Dorche et al. 2021). The time from vaccination to the onset of CVT was 4-42 days (Ahmed et al. 2022). In contrast, CVT after an mRNA vaccine is rare. There have been only five case reports documenting eight cases (Cheng 2021; Dias et al. 2021; Fan et al. 2021; Yamaguchi et al. 2021; Zakaria et al. 2021). Unlike VITT, CVT after an mRNA vaccine responded to heparin and did not present thrombocytopenia. The time from vaccination to the onset of CVT was 1-16 days in the reported cases, which was shorter than in our case. Since there are only eight cases, it seems inappropriate to exclude the relationship between CVT and the vaccine only by the time window. The pathophysiology of this disease has not been clarified, and it is uncertain whether and how an mRNA vaccine contributed to the development of CVT in our case. However, her sister and mother, who also had AT deficiency, reported uncomplicated pregnancies. Neither received the vaccine in their perinatal period. Her mother received the vaccine without adverse events, while her sister did not receive it. The unknown mechanisms of thrombogenicity due to mRNA vaccination possibly contributed to the development of CVT. COVID-19 vaccination may require careful evaluation in patients with prothrombic factors. Further investigations are needed.

Our case highlights the difficulty in the management of severe CVT in a pregnant patient with AT deficiency. Treatment with UFH and AT concentrate may be ineffective in severe CVT cases with AT deficiency. Early recognition of AT deficiency and an immediate switch to other anticoagulants may be required. The mRNA COVID-19 vaccinations may require careful evaluation for patients with prothrombotic risk factors.

Conflict of Interest

The authors declare no conflict of interest.

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