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LETTER TO THE EDITOR

Major bleeding in a patient with warfarin-hypersensitive and factor *IX* propeptide variant, p.Ala37Thr, who was treated with a direct oral anti-Xa inhibitor

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Dear Editor,

A variant of coagulation factor IX (FIX) is usually associated with hemophilia B, which causes severe bleeding, a prolonged activated partial prothrombin time (APTT) and markedly decreased FIX activity with a family history [1]. A variant in the *FIX* propeptide, either p.Ala37Thr or p.Ala37Val, is associated with a bleeding tendency in patients using warfarin [2, 3] and is considered to be very rare. Thus, we read with great interest the recent article by Pezeshkpoor et al. [4], which analyzed 18 patients with this variant in Switzerland. Patients with this variant had no symptoms unless they received warfarin treatment for thrombosis, which suggests that the actual prevalence may be higher than reported. We recently detected this variant in a patient with antiphospholipid antibodies (aPL) and asymptomatic cerebral thrombosis. This patient had a severe bleeding tendency after treatment with both warfarin and direct oral anticoagulant (DOAC).

A 49-year-old man was referred to the neurology department because of asymptomatic cerebral infarction. He has no previous bleeding episodes and no family history of stroke, thrombosis, or bleeding episode. Prolonged APTT (58.4 s) elevated diluted Russell viper venom time ratio (2.68), and anti-β2 glycoprotein I antibody (9.7 U/mL) and anticardiolipin antibody IgG (39 U/mL) titers were observed. He was diagnosed with antiphospholipid antibody syndrome (APS), and thrombosis screening demonstrated asymptomatic cerebral infarction in the right parietal region on brain magnetic resonance imaging. A neurological examination revealed no remarkable findings. Warfarin treatment according to the monitoring of prothrombin time (PT)-international normalized ratio (INR) was started for the secondary prevention of thrombosis. Two months later, he developed spontaneous intramuscular hemorrhage in the bilateral calf muscles, and he had difficulty walking. Although the PT-INR was 1.52, the patient's APTT was markedly prolonged (154 s) (Fig. 1). A coagulation factors analysis revealed markedly low FIX activity (< 0.5%), while the patient's FX activity was 32.8%. After stopping warfarin, the intramuscular hemorrhage was ameliorated, and the coagulation factors, including FIX (83.3%), returned to normal, with the exception of APTT (66.0 s). A gene analysis of FIX revealed a missense mutation p.Ala37Thr. As an alternative anticoagulant treatment, DOAC, ribaroxaban® (Bayer, Leverkusen, Germany) (10 mg/day) was started. Ten days later, the patient noticed ecchymoma in his left lower leg; his APTT (123.1 s) was prolonged, anti-Xa activity (1.31 IU/ml), and his FIX activity (48.8%) was decreased. Ribaroxaban was changed to low dose (5 mg/day) of apixaban® (Pfizer, New York, USA), after which, here, was anti-Xa activity (0.90 IU/ml) and no recurrence of hemorrhage.

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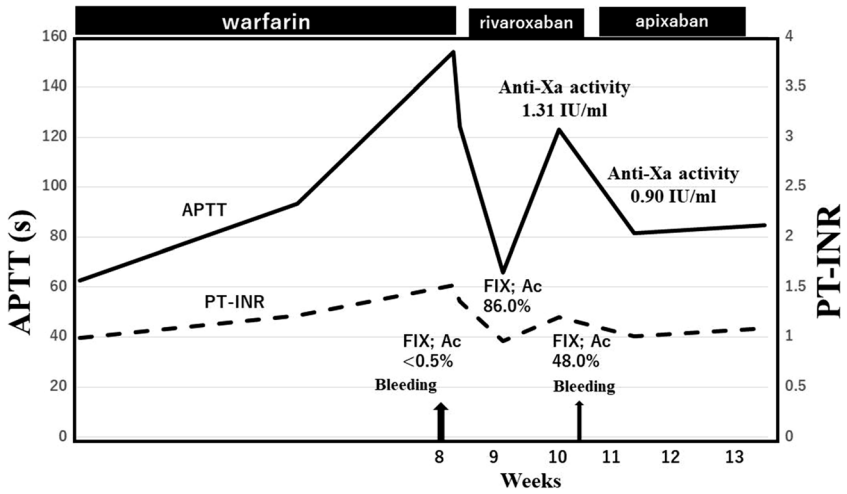

Fig. 1 The clinical course and laboratory data. APTT activated partial thromboplastin time, PT prothrombin time, INR international normalized ratio, FIX Ac FIX activity

The possible causes of bleeding during DOAC treatment in our patient with APS include (1) combination between DOAC and *FIX* propeptide variant, p.Ala37Thr; (2) combination between the DOAC and an aPL; and (3) combination between the DOAC, aPL, and *FIX* propeptide variant, p.Ala37Thr. We herein report a case of bleeding with the separate use of DOAC and warfarin in as APS patient with *FIX* propeptide variant, p.Ala37Thr. Low-dose DOAC treatment may be useful for APS patients with *FIX* propeptide variant, p.Ala37Thr, who need to continue anticoagulant therapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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