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LETTER TO THE EDITOR

Letter in response to Bounaix et al. "Management of anticoagulation and factor XIII replacement in a patient with severe factor XIII deficiency and recurrent venous thromboembolic disease: case report and review of literature"

To the Editor:

Severe factor (F)XIII deficiency is a rare bleeding disorder characterized by spontaneous, severe bleeding necessitating prophylactic FXIII infusions. Thrombotic complications in patients with FXIII deficiency are rare, and experience with therapeutic anticoagulation in patients with such a severe congenital bleeding disorder is scarce. Recently, recommendations on the use of antithrombotic therapy in patients with hemophilia were formulated [1] as cardiovascular disease including thrombotic disorders is an emerging medical issue in patients with a severe congenital bleeding disorder. Recently, Bounaix et al. [2] were the first to describe a patient with severe FXIII deficiency and recurrent venous thrombotic events.

Hereby, we present a similar case concerning a patient with severe FXIII deficiency enduring 2 thrombotic events. He was diagnosed at the age of 6 years with severe FXIII deficiency with subcutaneous bleeds and joint bleeds. This was later found to be due to compound heterozygosity of splice site mutations in intron 5 and intron 3. He was started on cryoprecipitate prophylaxis after a spontaneous intracranial bleed at the age of 15 years. Three years later, he was switched to plasma-derived FXIII prophylaxis. On prophylaxis, there were no bleeding complications. He was on a stable prophylaxis of 1250 IU of FXIII (Cluvot, CSL Behring) every month (15 IU/kg) with a FXIII trough level of 10%.

At the age of 58 years, he presented with a deep vein thrombosis 4 days after his prophylactic FXIII infusion and 6 weeks after a skin infection in his left foot (see Figure). The ultrasound showed a thrombosis of 20 cm in the left femoral vein as well as in the soleal vein and anterior and posterior tibial veins. Screening for provoking factors was performed, showing normal physical examination findings; normal computed tomography scan of his neck, thorax, and abdomen; normal prostate-specific antigen level, and negative result for lupus anticoagulants. He was treated with apixaban 10 mg twice daily for 7 days, thereafter 5 mg twice daily for 3 months, and intensified FXIII prophylaxis of 1250 IU every other week with a trough level of 24% and peak level of 62%.

Two months after stopping the apixaban and returning to FXIII prophylaxis of 1250 IU every month, he presented with pulmonary embolism 2 weeks after a 3-hour flight and 3 days after his prophylactic FXIII infusion. His apixaban was restarted and prophylaxis frequency intensified to 1250 IU every 2 weeks, aiming for a trough level of >20%. Physical examination again showed no abnormalities, neither did his blood counts nor screening for hereditary thrombophilia (absence of FV Leiden and prothrombin mutation, no activated protein C resistance, and normal levels of protein C, protein S, and antithrombin).

A year after his pulmonary embolism, he did not experience any bleeding while on anticoagulation.

This is the second case of recurrent venous thromboembolism in severe FXIII deficiency with only potentially weak provoking factors. There is minimal experience with therapeutic anticoagulation. In our case, a trough FXIII level >20% during therapeutic doses of apixaban seems enough to prevent bleeding complications, similar to the recommended minimum trough levels for oral anticoagulation in hemophilia [1].

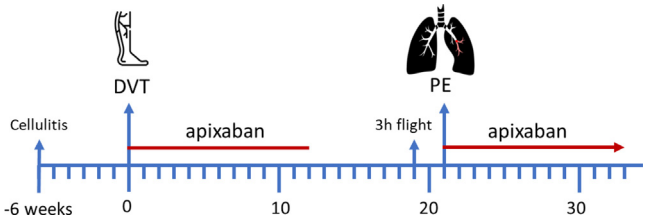

FIGURE Timeline of potential provoking factors and thromboembolic events. DVT, deep vein thrombosis; PE, pulmonary embolism.

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AUTHOR CONTRIBUTIONS

L.F.D.v.V. wrote the manuscript, which was critically reviewed by F.N.C. and R.E.G.S.

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