Recurrent vital thrombotic events in a young man with *FVIII* gene duplication

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To the Editor: The coagulation system is a complex regulatory system in the human body. In this case, the young patient had various vital thrombosis, including cerebral venous sinus thrombosis (CVST), coronary thrombosis, and left ventricular thrombus. However, the patient had neither hypercoagulable-related diseases nor risks nor coagulative or fibrinolytic protein deficiency.[1] Further genetic testing did not show the usual gene mutations relevant to coagulation dysfunction. We report such a patient with a slight elevation in coagulation FVIII activity and a rare *FVIII* gene duplication.

The patient was a 24-year-old man with a history of CVST 3 years prior, and he was treated with warfarin (3 mg/day) for 1 year. Risk factors for atherosclerosis were initially absent, and he had no family history of coronary heart disease or recurrent thrombosis. The patient presented to the emergency room with intermittent chest pain for 11 days and oppressive ongoing chest pain for 11 h. The electrocardiogram showed ST-segment elevation in lead I, aVL, and V1–V6 [Figure 1A].

His blood pressure was 145/78 mmHg, and his heart rate was 118 beats/min. No cardiac murmurs, crackles, or wheezes of lung bases were noted by auscultation.

Emergency coronary angiography revealed that the left anterior descending (LAD) artery was incompletely obstructed with a thrombus that progressed distally [Figure 1C]. After thrombus aspiration therapy the coronary angiography showed LAD reperfusion [Figure 1D]. Optical coherence tomography (OCT) was performed after thrombus aspiration. The artery wall appeared to be normal, and the 3-layered architecture was clearly visible [Figure 1E and 1F] combined with a massive red thrombus [Figure 1G]. His echocardiography showed the decreased motion of the left ventricular apex. There was no mural thrombus or intracardiac shunt. A typical thrombophilia screen for activated protein C resistance, antithrombin III, protein S, anticardiolipin antibody, lupus anticoagulant, and fibrinogen showed that all levels were normal: antithrombin III was 95% (normal range 80%–120%), activated fibrinolysin was 95% (normal range 80%–150%), activated protein C was 91% (normal range 70%–140%), and protein S was 82% (normal range 63.5%–149%). Additionally, a hematological system panel genetic test was performed.

The patient was administered a continuous infusion of platelet IIb/IIIa inhibitor (tirofiban 0.125 $\mu g \cdot kg^{-1} \cdot min^{-1}$) for 24 h followed by low-molecular-weight heparin (Clexane 6000 U every 12 h) for 4 days. His chest pain was relieved and the electrocardiogram showed ST-segment resolution [Figure 1B]. Based on secondary prevention, the patient was treated with dual antiplatelet drugs, an angiotensin-converting enzyme inhibitor (ACEI), a β receptor blocker, and statin; folate was added because of hyperhomocysteinemia. Anticoagulant therapy was not included given that no evidence of hypercoagulability was found.

Four weeks after the MI, echocardiography showed left ventricular mural thrombus without any left ventricular wall motion abnormalities. The patient was then treated with warfarin (3 mg/day) in addition to dual antiplatelet therapy. Before warfarin was applied, his plasma levels of coagulation factor were assessed, with a slight elevation of coagulation FVIII activity to 166% (Normal range 100%–150%) noted; other coagulation factors were in the normal range. The hematological system panel test revealed a duplicate chrX: 153991029-154348425 region (including *FVIII* entire gene, GenBank: NM_000132.4). Two months later, echocardiography showed that the mural thrombus had disappeared. The

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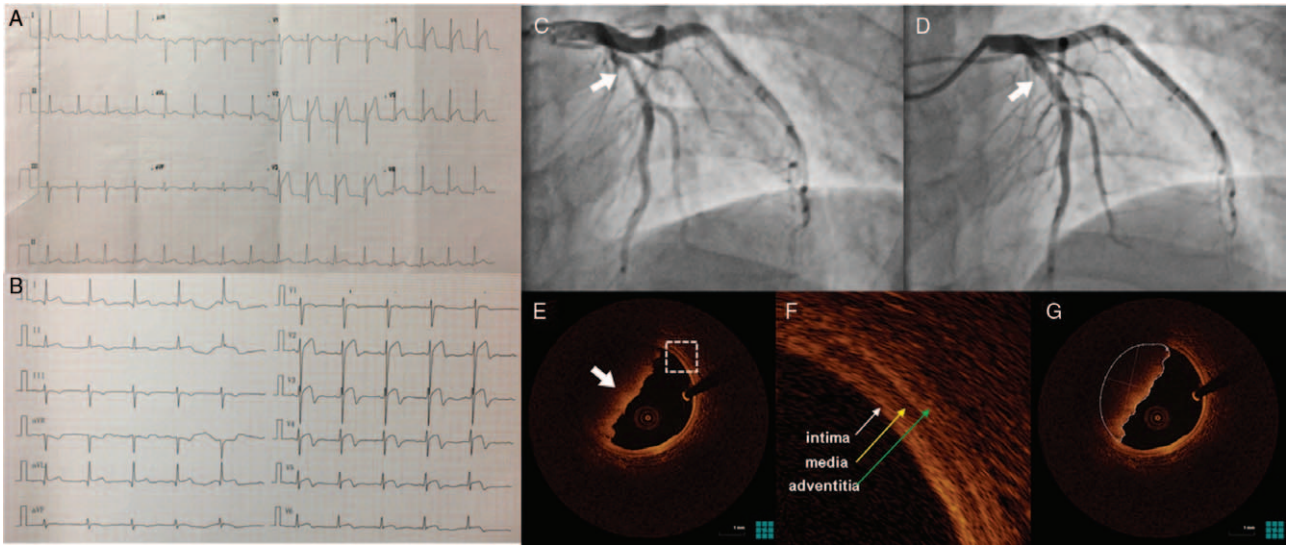

Figure 1: Representative image of the patient. (A) The electrocardiogram of the patient, when he presented to the emergency room with oppressive ongoing chest pain, showed ST-segment elevation in lead I, aVL, and V1–V6. (B) The electrocardiogram of the patient, when his chest pain was relieved, showed ST-segment resolution. (C) Emergency coronary angiography showed that the LAD was incompletely obstructed with a thrombus. (D) Emergency coronary angiography revealed LAD reperfusion after thrombus aspiration therapy. (E) Cross-sectional OCT image of the culprit lesion. The arrowhead indicates the red thrombus, with high backscattering and high attenuation. The square frame indicates the normal artery wall. (F) The 3-layered architecture of the normal artery wall, comprising an intima that has high backscattering or is signal rich (*white arrow*), low backscattering, or signal-poor media (*yellow arrow*), and adventitia that frequently has high backscattering and is heterogeneous (*green arrow*). (G) Cross-sectional OCT image corresponding to the white arrowhead in the cross-sectional OCT image of the culprit lesion, showing that the area of the red thrombus was 5.58 mm^2. LAD: Left anterior descending artery, OCT: Optical coherence tomography.

patient was administered dual antiplatelet and warfarin therapy for 6 months, followed by aspirin and warfarin for 5 months. No recurrent thrombosis occurred.

The patient had been diagnosed with CVST at the age of 21 years. CVST is a potentially devastating, though rare, thrombotic event, with an annual incidence of 3 to 4 cases per million individuals.[2] CVST occurs most often in young women, especially during pregnancy and the puerperium period, or in other acquired and congenital prothrombotic conditions such as infection.[3] The European Stroke Organization guidelines recommend using oral anticoagulants for 3 to 12 months after CVST.

FVIII is a glycoprotein that plays a crucial role in the intrinsic pathway of blood coagulation. Elevations in FVIII levels are thought to be an independent risk factor for venous thrombosis. Elevated FVIII occurs frequently in patients with CVST and is a strong risk factor for this condition.[4] The relative contributions from genetic and inherited factors in the etiology of persistently elevated plasma FVIII levels remain unknown. Nevertheless, inherited factors may be important in at least some patients.[5] It remains unknown what gene mutations lead to FVIII elevation. Regarding the present case, the *FVIII* gene region duplication currently available in the Database of Genomic Variants does not cover the region we identified. Such changes might alter the production, activity, or metabolism of FVIII, affecting hemostasis and coagulation. Nonetheless, further mechanistic research is needed. Recent research found that $JAK2^{V617F}$-positive essential thrombocythemia patients complicated with CVST were more likely to having thrombosis.[6] Therefore, genetic tests may contribute to risk stratification in CVST patients.

This is a rare report of a patient who had a coronary thrombosis combined with CVST. Coagulopathy should be taken seriously, and genetic studies may be helpful.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

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