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Letter to the Editor

Protein S Deficiency with Recurrent Thromboembolism after Splenectomy in a Patient with Hemoglobin H Disease

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To the editor.

Splenectomy is an effective treatment for hemoglobin H (HbH) disease; however, thromboembolic events (TEEs) frequently occur in patients with thalassemia following splenectomy.[1,2] The pathogenic mechanisms may involve the chronic hypercoagulable state observed in patients with thalassemia without a spleen, including thrombocytosis, chronic platelet activation, and perturbation of the red blood cell membrane.[3,4] Reports of recurrent thromboembolism in patients with HbH disease associated with congenital thrombophilic mutations are scarce.[1] Here, we report the case of a patient with HbH disease with a *PROS1* mutation associated with PS deficiency who experienced recurrent venous thromboembolism (VTE) after splenectomy.

A 30-year-old man with non-deletional HbH disease first developed symptoms of anemia at 3 years old, and a $--^{SEA}/\alpha^{CS}\alpha$ genotype was detected in the thalassemia gene. The proband was non-transfusion-dependent but experienced several hemolytic crises, mostly triggered by infections, resulting in three erythrocyte transfusions. He underwent splenectomy at the age of 18 years due to worsening anemia and splenomegaly with abdominal signs. There was no anticoagulation after surgery, and his Hb level was subsequently maintained at 9.4–10.7 g/dL and his platelet count at 493–521 × 10^9/L.

The proband's first thrombotic event occurred at the age of 26 years, involving a popliteal vein and fibular vein thrombus. Despite receiving anticoagulant treatment with heparin, the patient suffered two further thrombotic events. At the third thrombotic event, routine blood tests revealed Hb 9.6 g/dL (reference value 11.5–15.0 g/dL) and a platelet count of 453 × 10^9/L (reference value 125–350 × 10^9/L). Coagulation test results showed a prothrombin time of 13.7 s (reference value 10.8–16.5 s), activated partial thromboplastin time of 31.7 s (reference value 24.0–38.0 s), fibrinogen of 2.4 g/L (reference value 2.0–4.0 g/L), and thrombin time of 19.0 s (reference value 14.0–21.0 s). Additional laboratory studies demonstrated PC activity of 33.0% (reference value 60%–140%), PS activity of 5.2% (reference value 63.5%–149%), and antithrombin III activity of 83.0% (reference value 83%–128%). Genetic analysis was therefore performed. Next-generation sequencing of the proband and his family members was carried out to detect underlying variants associated with PC and PS deficiencies. The proband was shown to be heterozygous for the *PROS1* gene, c.149A>C (p.Lys50Thr), inherited from his mother, which was further confirmed by Sanger sequencing (**Figure 1**). The proband continued to receive long-term anticoagulation therapy with no more TEEs.

TEEs are frequently reported in patients with thalassemia following splenectomy. Taher et al.[5] analyzed 8860 patients with thalassemia and found an overall incidence of VTE of 1.65%, among which 93% of affected patients had a history of splenectomy. In another study of thalassemia intermedia, VTE occurred in 22.5% of patients with splenectomy, compared with only 3.5% of patients without splenectomy.[6] Several risk factors are known to have a synergistic effect on the pathogenesis of TEE in thalassemia; however, studies of recurrent TEEs in thalassemia, particularly in HbH related to congenital thrombophilic mutations, are limited. PC and PS mutations are frequent genetic risk factors involved in VTE in the Chinese population, and the presence of these mutations may aggravate the risk of thrombosis in patients with thalassemia.

PS combines with PC to promote the degradation of coagulation factors Va and VIIIa and assists in activating protein C in mediating the inhibition of thrombin production by platelet-derived particles in plasma.[7] Deficiencies of these proteins thus increase the risk of VTE.[8] There have been several studies on the inherited anomalies of anticoagulation factors, such as PS and PC, in patients with venous thrombosis in the Chinese population.[9-11] In the current family, the proband, his identical twin brother, and their mother all had the *PROS1*: c.149A>C mutation and their PS

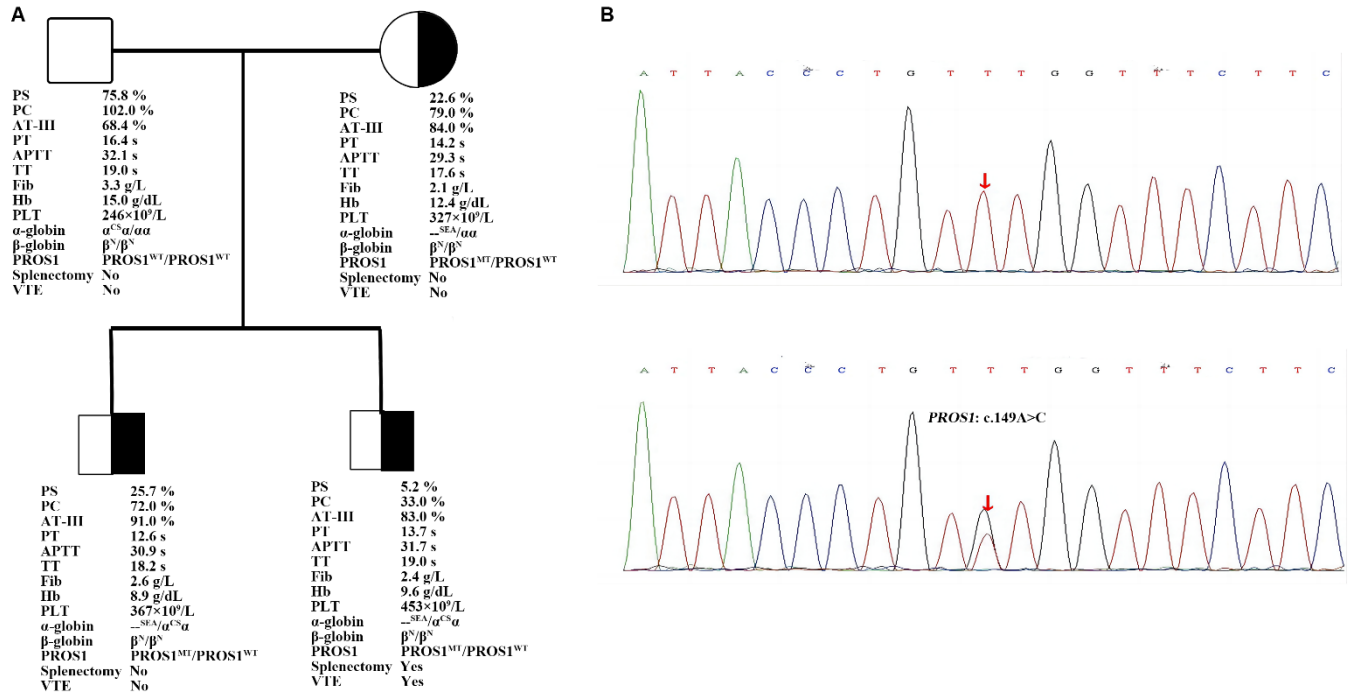

Figure 1. A Chinese family with a heterozygous *PROS1* mutation causing PS deficiency. **A**. Pedigree, hematological parameters, and genotype data for family members. **B**. Sanger sequencing of the *PROS1* gene showed a c.149A>C mutation.

activity was significantly decreased, suggesting that the mutation led to a decrease in PS function. The proband's brother and mother also had PS deficiency but had no history of VTE; notably, the proband had undergone splenectomy, indicating that splenectomy may play a key role in the occurrence of VTE in such patients. In addition, the screening for congenital thrombophilia probably should be made for thalassemia patients with recurrent thromboembolism.[12]

In conclusion, this report highlights the case of a patient with HbH disease with PS deficiency who experienced recurrent thromboembolism after splenectomy and required long-term anticoagulant treatment. These findings suggest that if thrombotic events repeatedly occur in a patient with thalassemia, not only the risk factors associated with a hypercoagulable state, but the possibility of congenital thrombophilia should be considered.

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