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Research Letter

Hereditary angioedema with deep vein thrombosis and pulmonary thromboembolism during pregnancy

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Dear Editor,

The patient was a gravida 4, para 2, 39-year-old Japanese woman who was clinically diagnosed with hereditary angioedema (HAE) at 8 years old. The functional C1-inhibitor (C1-INH) level was low, but C1-INH protein level was not examined. Therefore, the type of HAE appeared to be type I or type II. She had her first childbirth by emergency caesarean section because of aggravation of HAE. Subsequently, she had a miscarriage and artificial abortion because of aggravation of HAE (Fig. 1A). She received tranexamic acid (TXA) (1500 mg/day) for long-term prophylaxis before this pregnancy. An attack of HAE was well controlled. Attack frequency was one to two per week until the second trimester of pregnancy, and then decreased to one per month in the third trimester. The patient reported left leg pain, edema and an increase in calf circumference at 35 weeks and 6 days of gestation. A total of 1000 IU of plasma-derived C1-INH was administered immediately. However, the edema did not improve. Therefore, she visited our hospital 2 days later (Fig. 1B). Blood urea nitrogen levels and the hematocrit were in the normal range. DVT was suspected, although D-dimer levels were not high and decreased from 7.1 to 6.1 µg/dL. Doppler ultrasonography showed DVT from the common femoral vein to the popliteal vein. Peripheral oxygen saturation was 92% without dyspnea. Therefore, pulmonary thromboembolism (PTE) was suspected and diagnosed by contrast-enhanced computed tomography (Fig. 1C and D). Continuous unfractionated heparin was started and TXA was discontinued. An inferior vena cava (IVC) filter was temporarily inserted with C1-INH for acute exacerbation of

PTE. Emergency cesarean section was performed for active labor at 36 2/7 weeks of gestation. Anticoagulation by unfractionated heparin was administered postoperatively and was finally replaced by warfarin. The IVC filter was removed at 2 days postoperatively. The clinical course was without complications.

We searched the literature for associations of HAE with pregnancy and thromboembolism in PubMed. To the best of our knowledge, there are no reports on increased risk factors of thromboembolism with HAE during pregnancy. In our case, although the D-dimer level was not high, we suspected DVT because of persistent edema with C1-INH treatment. Reshef et al. reported that elevated D-dimer levels in attacks of HAE are not associated with an increased thrombotic risk [1]. Therefore, thromboembolism should be considered because D-dimer is not recommended for evaluating venous thromboembolism in pregnancy. In our case, previous pregnancies had uncontrollable attacks. Therefore, TXA was used to prevent attacks. Farkas et al. reported that there is not any evidence for an increased risk of thromboembolism during treatment with C1-INH [2]. However, TXA has a potential risk of thromboembolism [3]. Deficiency of C1-INH leads to excessive production of bradykinin, which is primarily responsible for angioedema of HAE [4]. Subsequently, bradykinin induces tissue permeability, vascular dilation, endothelial vascular smooth muscle, and a shift in intravascular fluid to the interstitial third space of subcutaneous or submucosal tissue [5]. Additionally, pregnancy itself is a state of hypercoagulability. Therefore, these findings suggest that TXA, intravascular fluid depletion caused by an attack of HAE, and hypercoagulability of pregnancy contribute to DVT. However, whether the number of attacks contributes to DVT is unknown.

In conclusion, our findings indicate that HAE with TXA in pregnancy is a possible risk factor of thromboembolism. It is to be

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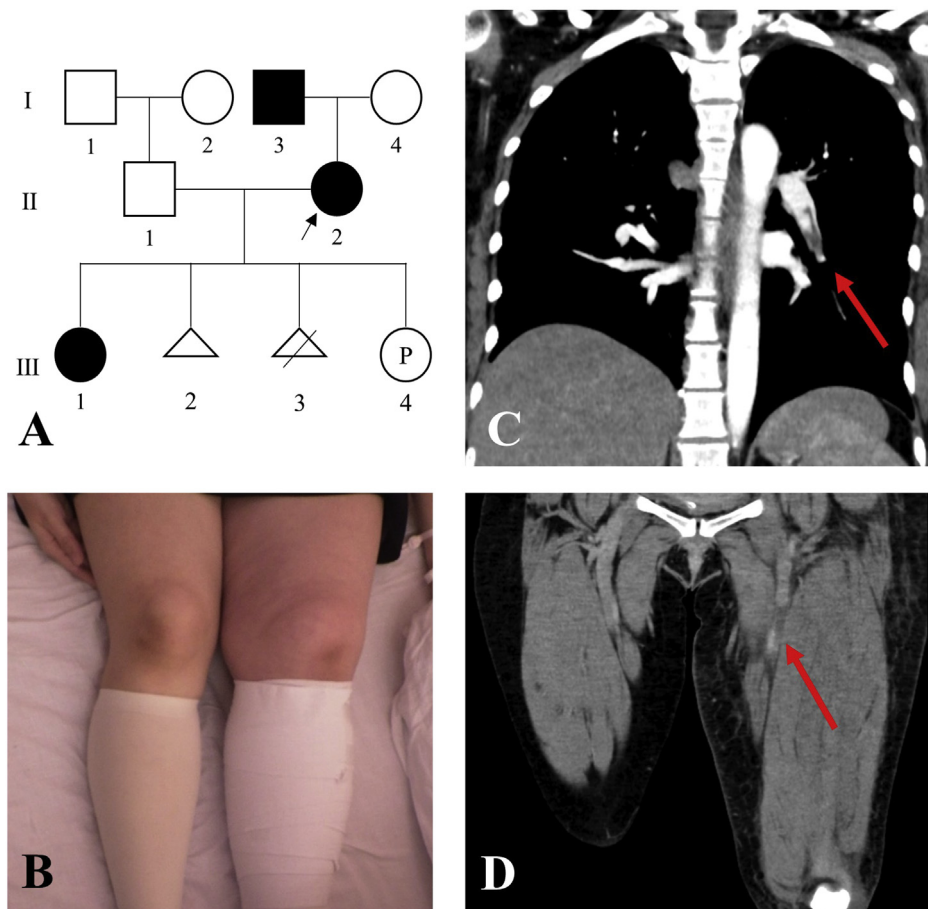


Fig. 1. Pedigree in this family. This patient is II-2 (A). Left leg edema in the patient at 36 weeks and 5 days of gestation (B). Contrast-enhanced computed tomography of the chest (C) and leg (D). Each arrow indicates the part of thrombosis with left pulmonary artery (C) and left common femoral vein (D).

determined if using TXA for HAE in pregnancy is acceptable or only C1-INH should be used.

Conflicts of interest

None.

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