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Case Report

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Acquired Hemophilia Presenting with Upper Extremity Venous Thrombosis

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In contrast to the typical presentation of swelling, pain, a rash, or darkened skin in venous thrombosis of the extremity, the typical appearance of acquired hemophilia is mucocutaneous bleeding. Both diseases may be associated with an elevated D-dimer concentration. Venous thrombosis is uncommon in patients with acquired hemophilia, which has a prevalence of one to four in one million per year. Although the typical appearance of erythema and swelling of the extremity is highly suggestive of venous thrombosis, a prolongation of activated partial thromboplastin time should not be ignored. Here, we describe two patients with acquired hemophilia misdiagnosed as venous thrombosis, highlighting the importance of differential diagnosis through familiarization of their clinical manifestations. The appropriate diagnostic strategy and treatment for acquired hemophilia were also reviewed.

Key words: acquired hemophilia, venous thrombosis, activated partial thromboplastin time

Case Reports

Case 1

A 62-year-old Asian man with a history of gouty arthritis and chronic hepatitis B without cirrhosis was transferred to our emergency department for refractory gastrointestinal bleeding and anemia. He had not previously taken any anticoagulants or antiplatelet agents. About seven days before transfer to our facility, he was admitted to another hospital for melena and a circulating hemoglobin concentration of 4.2 g/dL (normal range, 13.5 – 17.5 g/dL). He declared no history of alcohol abuse or any other recent medication. On admission at the other hospital, gastroscopy showed duodenal ulcer bleeding for which 14 units of packed red blood cells (PRBC) were transfused. Repeated gastroscopy for persistent melena demonstrated uncontrolled duodenal ulcer bleeding, for which he was transferred to our hospital. At our emergency department, he complained of swelling of his right upper extremity two days after receiving blood transfusion via the right cubital vein. Multiple ecchymosis patches were noted on his right elbow and hand. Sonography and computed tomography revealed intramuscular hematoma at the right distal biceps muscle with venous thromboses in the right subclavian, basilic, and brachial veins (Fig. 1).

The activated partial thromboplastin time (aPTT) was 100.2 s (normal range, 23.3 – 34.9 s) and the prothrombin time (PT) was 11.5 s (normal range, 9.5 – 11.7 s) with an international normalized ratio of 1.14. To identify

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the cause of aPTT prolongation, a mixing test was performed by mixing the patient's plasma with normal plasma in a 1:1 ratio. The results showed a partial decrease in aPTT from 93.8 s to 66.9 s, suggesting the presence of a clotting factor inhibitor in his blood. Although his bleeding time and thrombin time were both within normal limits, the clotting time was prolonged to 30 minutes (normal range, 5 – 12 minutes). The level of von Willebrand factor (vWF) was 115% (normal range for Type O blood, 53.7% – 148.5%). Further tests revealed a factor VIII level of less than 1% (normal range, 70% – 150%) and the presence of factor VIII inhibitor at a concentration of 190.14 Bethesda Units (BU)/mL (normal range, < 0.6 BU/mL), suggesting the diagnosis of acquired hemophilia. The patient's aPTT gradually decreased to close to the normal range after steroid treatment with subsequent improvements of his gastrointestinal bleeding and right arm venous thrombosis.

Case 2

The second patient was a 59-year-old woman with a history of dyslipidemia, who denied recent use of anticoagulants or antiplatelet agents. She suffered from left forearm swelling, pain, and ecchymosis for 5 – 6 days without fever, trauma, or open wound. At the emergency department, she received tramadol via intramuscular injection at the left deltoid area for pain control. Computed tomography revealed focal thrombosis in the left basilic vein (Fig. 2). Although aPTT results were still pending, one dose of subcutaneous enoxaparin (60 mg) was given with the tentative diagnosis of left arm venous thrombosis. The initial aPTT was 84.3 s (normal range, 23.3 – 34.9 s), PT was 10.8 s (normal range, 9.5 – 11.7 s), and D-dimer concentration was 1.47 mg/L (normal range, < 0.55 mg/L). A mixing test revealed incomplete correction of aPTT from 111.2 s to 61.4 s. The patient's lupus anticoagulant screening was 37.4 s (normal range, 31 – 44 s), factor VII was 103.8% (normal range, 69% – 160%), and factor IX was 117% (normal range, 70% – 150%). Further tests showed a

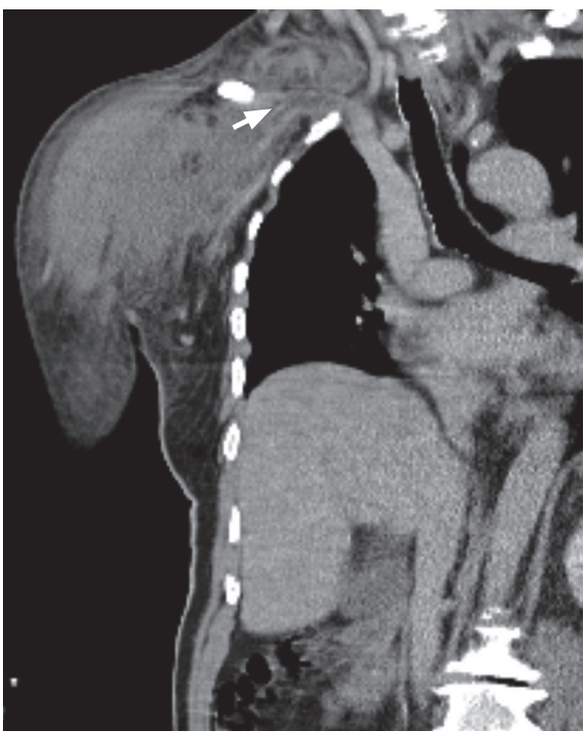

Fig. 1 Thrombosis in right subclavian vein (white arrow).

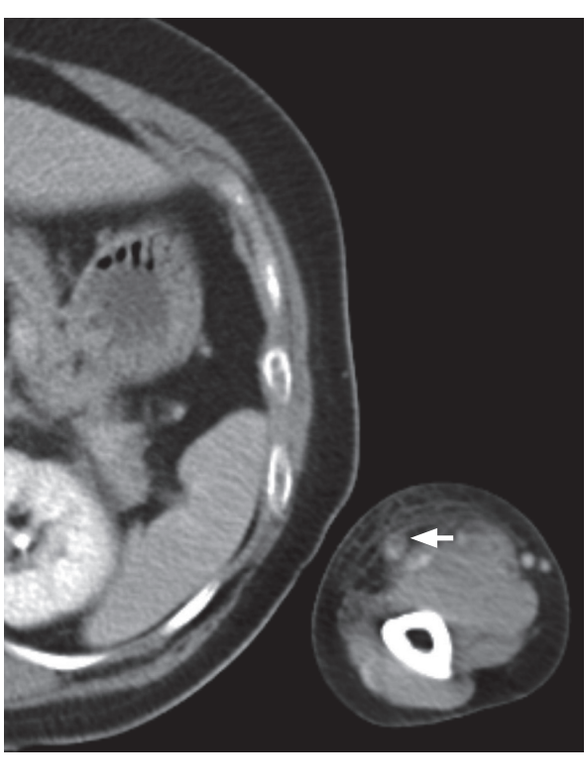

Fig. 2 Thrombosis in left basilic vein (white arrow).

factor VIII level of < 1% (normal range, 70% – 150%) and a factor VIII inhibitor concentration of 41.93 BU/mL (normal range, < 0.6 BU/mL), compatible with the diagnosis of acquired hemophilia. This patient was prescribed with activated prothrombin complex concentrate, cyclophosphamide, and prednisolone. Eventually, her aPTT returned to normal after one month. The left forearm swelling and ecchymosis gradually resolved without complication.

Discussion

Acquired hemophilia, a rare hematologic disease, occurs with a prevalence of one to four in one million people per year with a mortality rate of 7.9% to 22%.[1] The etiology is believed to involve the inhibition of factor VIII in the coagulation cascade by spontaneous autoantibodies. The disease is associated with autoimmune diseases, hematologic and solid organ malignancies, hepatitis B and C, pregnancy (often one to four months post-partum), and medications (e.g., clopidogrel, beta-lactam antibiotics, phenytoin, and sulfa drugs).[2] However, about 50% of patients are idiopathic.[1] About 33% of the 166 cases enrolled in a study by the Hemostasis and Thrombosis Research Society between 2000 and 2011 had blood product exposure. Although the association between transfusion and acquired hemophilia remains unclear, acquired hemophilia has been reported to be diagnosed after the transfusions of PRBC, fresh frozen plasma, platelets, whole blood, coagulation factors, or cryoprecipitate.[3]

The most frequent clinical presentation of acquired hemophilia is subcutaneous hemorrhage which was noted in 27.1% of patients. Mucosal hemorrhage, such as epistaxis and that in the gastrointestinal or genitourinary tract, was reported in 21.1% of patients.[4] Other hemorrhagic complications also include intramuscular hematoma (5.4%), bleeding from surgical/vessel puncture site (1.8%), intracranial hemorrhage (1.8%), and post-partum hemorrhage (3.6%). Unlike congenital hemophilia, which typically presents with hemarthrosis, only 4.2% of patients with acquired hemophilia experienced bleeding into the joints.[3]

Our literature review showed that deep vein thrombosis was rarely reported in cases of acquired hemophilia. In the case series published in 2019, venous thrombosis was noted in only 10 patients diagnosed with acquired hemophilia between 1982 and 2019 with involvement of the lower extremity or inferior vena cava in all cases. The coagulation cascade could be initiated from the intrinsic or extrinsic pathway. When the intrinsic pathway is limited by the inhibitor of factor VIII, the extrinsic pathway may be strengthened via a higher level of tissue factor/factor VII complex.[5] The increased tissue factor level may trigger the formation of venous thrombosis.[6] Both intramuscular hemorrhage and deep vein thrombosis could cause swelling of the extremity.

On encountering patients presenting with acute hemorrhage and a prolonged aPTT but a normal PT, heparin contamination should first be ruled out. Clotting factor deficiency of the intrinsic pathway should be considered if aPTT can be completely corrected by mixing the patient's plasma with normal plasma in a 1:1 ratio, while a persistently abnormal aPTT on mixing test indicates the presence of a clotting factor inhibitor. The next step involves the ruling out of lupus anticoagulants through investigating the activities of factors VIII, XI, X, XI, XII, and the von Willebrand factor. If factor VIII activity is reduced, the inhibitor should be quantified by a specific assay such as the Bethesda assay for the diagnosis of acquired hemophilia.[2]

The goals of managing acquired hemophilia include the control of hemorrhage and the elimination of factor VIII inhibitor. Due to the risk of intramuscular hematoma formation, intramuscular injection, unnecessary surgical interventions, and invasive medical procedures should be avoided. Furthermore, prescribing

anticoagulants for patients diagnosed with acquired hemophilia who present with venous thrombosis may increase the risk of hemorrhage. Appropriate treatments against acquired hemophilia include corticosteroids, immunosuppressants, intravenous immunoglobulin, factor VIII concentrates, and plasmapheresis.

Conclusion

Venous thrombosis may be the first manifestation of acquired hemophilia for which the prescription of an anticoagulant before PT and aPTT tests is strongly contraindicated. A mixing aPTT test is needed if the patient exhibits aPTT prolongation but a normal PT.

Author Contributions

Ying-Che Lo: data collection, literature search, writing articles. Cheuk-Kwan Sun and I-Ting Tsai: reviewed and approved the final articles.

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Informed Consent Statement

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Data Availability Statement

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Conflicts of Interest

The authors declare no conflict of interest.

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