The Development of Acute Systemic Multiple Thrombosis after Achieving Remission during Systemic Glucocorticoid Therapy for Acquired Hemophilia A

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Abstract:
Acquired hemophilia A (AHA) is a hemorrhagic disorder. Whether or not severe thrombotic events can develop without the use of bypassing agents in AHA patients is unclear. An 80-year-old woman with AHA underwented immunosuppressive therapy with prednisolone at 1 mg/kg daily. After achieving remission, she suddenly developed multiple organ failure due to acute systemic thrombosis and died within a few hours of the diagnosis. Patients with AHA, especially those with risk factors for thrombosis, have a considerable risk of developing thrombosis during the recovery phase of factor VIII activity and should be carefully monitored by coagulation testing.

Key words: acquired hemophilia A, thrombosis, glucocorticoid therapy, von Willebrand factor

Introduction
Acquired hemophilia A (AHA) is a rare but life-threatening hemorrhagic disorder that occurs due to the development of autoantibodies against coagulation factor VIII. AHA reportedly has a high mortality rate because of complications such as infection and severe bleeding (1). In AHA patients, thrombotic events can occur as complications of using bypassing agents, such as recombinant activated factor VII (2, 3). However, whether or not severe thrombotic events can develop without the use of bypassing agents is unclear. Furthermore, when thrombotic events are likely to occur and what are the risk factors of thrombotic events in AHA patients not using bypassing agents are also unknown.

We herein report a patient with AHA who did not use bypassing agents but nevertheless died of acute multi-organ thromboembolism shortly after achieving remission with steroid therapy.

Case Report
An 80-year-old woman with hypertension and rheumatoid arthritis that had been well-controlled for 40 years (under treatment with a calcium channel blocker and prednisolone at 5 mg daily by her family physician) was referred to our institution for a hemorrhagic condition. Laboratory testing showed that her hemoglobin level had decreased to 70 g/L, the international normalized ratio of prothrombin time (PT-INR) was 0.93, the activated partial thromboplastin time was prolonged (APTT) to 93.9 seconds, and the fibrinogen level (Fbg) was 254 mg/dL. Coagulation testing revealed that the factor VIII (FVIII) level was extremely suppressed at 1.0%, and the titer of anti-FVIII inhibitor was 21.5 B.U./mL (Fig. 1). Laboratory testing to detect anti-phospholipid antibodies showed that lupus anticoagulant (1.03), anti-cardiolipin/β2-glycoprotein-I complex antibodies (<1.2 U/mL), and anti-cardiolipin antibodies (<8 U/mL) were all negative (Table). Computed tomography revealed that a
Table. Laboratory Testing Data at the First Visit and at the Thrombotic Event.

| Laboratory data                      | At the first visit | At the thrombotic event |
|--------------------------------------|-------------------|-------------------------|
| Leukocyte count (μL)                 | 7,800             | 8,900                   |
| Hemoglobin (g/dL)                    | 7.0               | 10.1                    |
| Platelet count (μL)                  | 30.5x10^4         | 26.9x10^4               |
| Lactate dehydrogenase (U/L)          | 272               | 674                     |
| Aspartate aminotransferase (U/L)     | 25                | 123                     |
| Alanine aminotransferase (U/L)       | 6                 | 62                      |
| γ-Glutamyltranspeptidase (U/L)       | 10                | 22                      |
| Alanine aminotransferase (U/L)       | 221               | 242                     |
| Total bilirubin (mg/dL)              | 1.6               | 0.7                     |
| Blood urea nitrogen (mg/dL)          | 28.9              | 54.7                    |
| Creatinine (mg/dL)                   | 0.87              | 0.87                    |
| Amylase (U/L)                        | 84                | 558                     |
| Creatine kinase (U/L)                | 98                | 1045                    |
| C-reactive protein (mg/dL)           | 0.16              | 10.33                   |
| PT INR                               | 0.93              | 1.08                    |
| APTT (second)                        | 93.9              | 34.2                    |
| Fibrinogen (mg/dL)                   | 346               | 254                     |
| FDP (μg/mL)                          | 9.8               | 31.9                    |
| D-dimer (μg/mL)                      | 8.1               | 15.1                    |
| Antithrombin (%)                     | 124               | 121                     |
| TAT (ng/mL)                          | ND                | 23.4                    |
| PIC (μg/mL)                          | ND                | 2.8                     |
| Protein C (%)                        | ND                | 107                     |
| Protein S (%)                        | ND                | 68.9                    |
| VWF activity (%)                     | 221               | 492                     |
| VWF antigen (%)                      | 300               | 535                     |
| Lupus anticogulant                   | 1.03              | ND                      |
| α-CL/β2GPI (U/mL)                    | <1.2              | ND                      |
| aCL IgG (U/mL)                       | <8                | ND                      |

PT INR: international normalized ratio of prothrombin time, APTT: activated partial thromboplastin time, FDP: fibrin/fibrinogen degradation products, TAT: thrombin-antithrombin complex, PIC: plasmin-antiplasmin complex, VWF: von Willebrand factor, α-CL/β2GPI: anti-cardiolipin/β2-glycoprotein-1 complex antibodies, aCL: anticardiolipin antibodies, ND: no data
abdominal pain with obstinate constipation. The next day, she suddenly developed a high-grade fever accompanied by hypotension. Laboratory tests revealed a platelet count of 269×10^9/L, serum lactate dehydrogenase level of 674 U/L, serum aspartate aminotransferase level of 123 U/L, serum creatinine level of 0.87 mg/dL, serum amylase level of 558 U/L, and serum creatine kinase level of 1,045 U/L. A venous blood gas analysis showed a pH of 7.099, pCO2 of 57.2 mmHg, HCO3^- of 17.3 mmHg, and anion gap 17.3 mEq/L, indicating that severe anion-gap metabolic acidosis concurrent with respiratory acidosis had developed. Abdominal enhanced computed tomography revealed multiple organ infarctions, including the kidney, liver, and spleen. Furthermore, the stomach, small intestine except for duodenum, and colon were not enhanced because of an impaired arterial blood flow (Fig. 2). Coagulation testing revealed a PT-INR of 1.08, APTT of 34.2 seconds, fibrin/fibrinogen degradation products level of 31.9 μg/mL, D-dimer level of 15,100 ng/mL, and fibrinogen level within the reference value range. She was diagnosed with acute systemic multiple thrombosis and progressed to fatal multiple organ failure by systemic hypoperfusion. She ultimately died within few hours of this diagnosis.

The results of several coagulation tests and blood culture tests performed on the last day were reported a few days later. The thrombin-antithrombin complex and plasmin-antiplasmin complex had increased to 23.4 ng/mL and 2.8 μg/mL, respectively, and the FVIII level was elevated to 128.8%. The protein C level, protein S level, and antithrombin level were within the respective reference value ranges. The von Willebrand factor (VWF) activity and antigen were highly elevated to 492% and 535%, respectively (Table). The results of two sets of blood cultures were both negative.

**Discussion**

In the present case, aggressive systemic thrombosis occurred in the remission phase of AHA that was controlled with glucocorticoids and without the use of any bypassing agents, such as recombinant activated factor VII. To our
knowledge, this is the first detailed case report of severe systemic thrombosis in a patient with AHA treated without any bypassing agents. Patients with AHA occasionally develop thrombosis during recombinant activated factor VII therapy (2, 3).

Because the obstinate constipation and left upper abdominal pain preceded a high-grade fever and systemic thrombosis, this patient might have developed ischemic colitis at the onset, which may have advanced to gangrenous ischemic colitis. Laboratory tests at the thrombotic event showed that serum lactate dehydrogenase, amylase, and creatine kinase level were elevated, and severe metabolic acidosis concurrent with respiratory acidosis developed, which might have been caused by central respiratory failure owing to a decreased level of consciousness. Gangrenous ischemic colitis often provokes septic shock, metabolic acidosis, and elevated laboratory markers, such as lactate dehydrogenase, amylase, and creatine kinase (4). Septic shock caused by gangrenous ischemic colitis may therefore have triggered acute systemic thrombosis in this patient, although the results of blood culture tests performed on the last day were negative. However, because the platelet count, fibrinogen test, PT, and APTT values were within the reference range, this patient was not diagnosed with disseminated intravascular coagulation. Furthermore, because the platelet count was not decreased and the serum creatinine level was within the reference range, thrombotic thrombocytopenic purpura was not suspected.

Several potential causes may underlie the eventual development of severe systemic thrombosis in this patient. First, the rapid elevation of the activation of FVIII in remission phase of AHA might have caused acute systemic thrombosis. Indeed, a number of studies have noted that an elevated FVIII level leads to both venous and arterial thrombosis in a dose-dependent manner (5). Second, the patient’s advanced age and comorbidities, such as rheumatoid arthritis and hypertension, might have been related to the systemic thrombosis, as these are noted risk factors. Furthermore, the thyroid tumor may have been malignant and associated with her thrombogenicity. An older age is a well-known risk factor of venous thrombosis (6). The patient’s 40-year medical history of rheumatoid arthritis might have been involved in this thrombotic event. It has been reported that patients with rheumatoid arthritis have a 1.5- to 6-fold increased risk of venous thromboembolism compared to non-RA patients (7). Her rheumatoid arthritis needed continuous therapy with prednisolone at 5 mg daily to control her symptoms. She had also developed hypertension and been treated with a calcium channel blocker. Atherosclerosis often develops as a complication of long-term glucocorticoid therapy due to direct endothelial cell damage (8), and atherosclerosis may be accelerated in the patient of rheumatoid arthritis as a consequence of the inflammatory vasculitis (9). It is suggested that atherosclerosis, which is caused by long-term glucocorticoid therapy, hypertension, and rheumatoid arthritis, associated with the thrombotic event in this patient. The possibility that the thyroid tumor was malignant and associated with her thrombogenicity, was not ruled out by a histological diagnosis, although the thyroid tumor was believed to be benign based on her medical history. Malignancy is well known to be a major risk factor of thrombotic tendency (10). Third, the severe infection caused by gangrenous ischemic colitis may have contributed to the acute systemic thrombosis in this patient, as infection is also a well-known risk factor of thrombosis (10). Finally, the high levels of VWF activity induced by glucocorticoid therapy for AHA might have led to acute systemic thrombosis in this case, whereas the vascular endothelial damage caused by systemic multiple thrombosis might have contributed to the elevation of VWF. FVIII is known to bind to its carrier protein VWF (5, 11), and the half-life of free FVIII decreases in the absence of VWF (5, 12). The therapeutic doses of dexamethasone increased the VWF levels, which may have caused adverse vascular events by promoting VWF-dependent thrombus formation, as previously reported (13).

In conclusion, patients with AHA, especially those with risk factors for thrombosis, such as an advanced age, comorbidities causing atherosclerosis, glucocorticoid therapy, and high levels of VWF activity, are at a considerable risk of developing thrombosis during the recovery phase of FVIII activity and should be carefully monitored by coagulation testing.

The authors state that they have no Conflict of Interest (COI).

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