—Case Reports—

Relapse of Acquired Hemophilia A after COVID-19 Infection

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Acquired hemophilia A (AHA) is a rare disease in which an autoantibody causes bleeding by interacting with and inhibiting the coagulation activity of endogenous factor VIII (FVIII). Most cases of AHA are idiopathic; known causes include autoimmune diseases, malignant tumors, pregnancy, drugs, and viral infections. An 86-year-old man was diagnosed with AHA based on the following results: an activated partial thromboplastin time (aPTT) extension of 130.7 seconds, presence of an inhibitor pattern in a mixing study, an endogenous factor VIII (FVIII) level of <1%, and an FVIII inhibitor titer of >5.1 Bethesda units (BU). The activity of von Willebrand factor (vWF) was diminished (<10%), which was considered a complication of acquired von Willebrand syndrome (AVWS). The patient was started on prednisolone, and the inhibitor level eventually became negative. vWF values also became normal. However, 1 year later, he was hospitalized for treatment of coronavirus disease 2019 (COVID-19). Blood testing showed an aPTT extension of 110.5 seconds, FVIII level of 4%, and FVIII inhibitor titer of 0.8 BU; thus, a relapse of AHA was diagnosed. After administration of corticosteroid and remdesivir, he recovered from COVID-19 and AHA. The inhibitor level became negative on the 9th day of admission. Several studies have implicated COVID-19 infection and vaccination in AHA. We recommend that aPTT be measured when patients with AHA are infected with SARS-CoV2, to confirm AHA relapse.
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Key words: COVID-19, acquired hemophilia A, acquired von Willebrand disease, factor VIII, mixing study

Introduction

Acquired hemophilia A (AHA) is a rare disease (incidence rate: 1.48 per million) in which an autoantibody (inhibitor) causes bleeding by interacting with and inhibiting the coagulation activity of endogenous factor VIII (FVIII). Approximately half of all AHA cases are idiopathic; known causes include autoimmune diseases, malignant tumors, pregnancy, drugs, and viral infections[1–3].

The parameters measured in blood tests include platelet count, prothrombin time and international normalized ratio, and activated partial thromboplastin time (APTT). It is necessary to distinguish AHA from congenital hemophilia A, von Willebrand disease (VWD), and antiphospholipid antibody syndrome. Moreover, family history and von Willebrand factor (VWF) activity must be confirmed and cross-mixing studies performed. Combined AHA and VWD are rarely reported[2,4]. Detection of FVIII inhibitor is essential for diagnosis of AHA.

Mixing studies are widely used for AHA screening. In these studies, different proportions of the plasma of the patient and normal individuals are mixed, and APTT is measured. The resultant graphical pattern distinguishes between the presence of an inhibitor and a coagulation deficiency[5,6]. As an advantage, mixing studies yield same-day results; however, they cannot be used for definitive diagnosis, as drugs taken by the patient (e.g., direct oral

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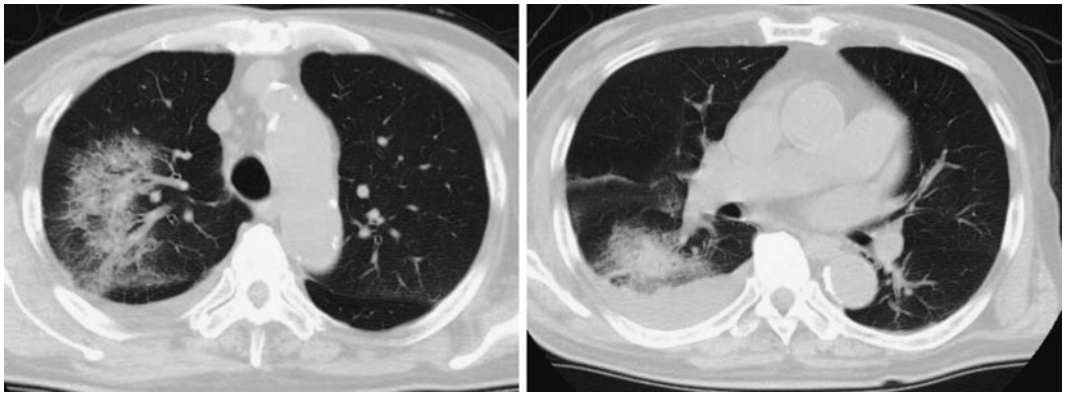

Fig. 1 A computed tomography scan of the 86-year-old patient on admission confirms the presence of pneumonia.

anticoagulants and heparin) and chronic diseases (e.g., anti-phospholipid antibody syndrome) may affect the results[5,6]. To obtain accurate results, it is necessary to confirm patient information, such as a history of medication and disease, at the time of the mixing study.

Since first reported in China in 2019, coronavirus disease 2019 (COVID-19) has spread rapidly throughout the world[7]. Vaccines for SARS-CoV-2, the virus that causes COVID-19, have been developed and administered to countless individuals to control the pandemic. Recent studies have reported rare instances in which AHA relapsed or occurred after infection or vaccination[8,9]. Since COVID-19 is known to cause thrombosis in some cases, a possible relationship may exist between COVID-19 and the coagulation system[10]. However, the mechanism underlying this relationship has yet to be determined.

In this study, we present a case of AHA relapse after SARS-CoV-2 infection and review the relevant literature. To our knowledge, this is the first reported case of its kind in Japan.

Case Presentation

An 86-year-old man had hypertension, atrial fibrillation, hyperuricemia, dyslipidemia, and cerebral infarction sequelae. His body weight was 65 kg. He was taking the following medications: atenolol, warfarin, vonoprazan, febuxostat, amlodipine, rosuvastatin, loxoprofen, rebamipide, and pregabalin. He had no known drug allergies. He was referred to our hospital because of dyspnea and a decreased SpO_2 level (89%). Computed tomography (CT) scan on admission confirmed the previous diagnosis of pneumonia (**Fig. 1**). Blood tests on admission showed a prolonged APTT (130.7 seconds) and decreased hemoglobin level (7.4 g/dL) (**Table 1**). Subcutaneous bleeding was observed in the right inguinal region. Warfarin was discontinued and antibiotics were administered, but the APTT did not improve. Subcutaneous and intramuscular hemorrhage in the left knee and subcutaneous hemorrhage in the bilateral forearms newly appeared, and his hemoglobin level had decreased to 5.7 g/dL. Therefore, four units of red blood cells were transfused. His respiratory status remained unchanged. Because prolonged APTT and low hemoglobin level suggested alveolar hemorrhage rather than pneumonia, his previous physician consulted a hematologist (one of the present authors), who conducted a mixing study. In the mixing study, the immediate reaction exhibited a coagulation-deficient pattern, whereas the delayed reaction showed an inhibitor pattern (**Fig. 2a**). Although the results of a lupus anticoagulant test were normal, FVIII activity was <1%, and the FVIII inhibitor titer was elevated (>5.1 Bethesda units (BU)/mL) (**Table 1**). On the basis of these results, AHA was diagnosed. CT scan and blood tests did not reveal a malignant tumor or collagen disease; therefore, he seemed to have no underlying disorder. vWF activity was low (<10%), but the level of vWF antigen was normal (127%). Since there was no enlargement of the bleeding site at the time of consultation, the patient did not require FVIII inhibitor bypassing activity (FEIBA) or recombinant activated factor VII (rFVIIa). We reduced the dose of prednisolone because of his old age, and he was started on prednisolone 30 mg/day, after which the APTT began to decrease. Five weeks after prednisolone initiation, FVIII inhibitor was not detectable. It did not reappear, and prednisolone administration was terminated 10 months after the diagnosis. During hospitalization, warfarin was replaced with apixaban.

The patient was followed-up at our hospital's outpatient care unit every 2 months. He developed COVID-19

Table 1 Laboratory findings

At diagnosis						At relapse			
WBC	7.40×10^3 /μL	TP	7.20 g/dL	COVID-19 PCR	negative	WBC	1.09×10^4 /μL	TP	6.60 g/dL
(Stab 4.5%, Seg 78.0%, Lympho 39.0%, Mono 6.0%, Baso 0.5%, Promyelo 0.5%, Myelo 1.5%, Lympho 9.0%)		Alb	3.60 g/dL	Factor VIII activity	<1.00 %	(Stab 10.0%, Seg 74.0%, Lympho 10.0%, Mono 6.0%, Lympho 10.0%)		Alb	3.10 g/dL
		BUN	21.20 mg/dL	Factor VIII inhibitor titer	>5.10 BU/mL			BUN	12.10 mg/dL
RBC	2.80×10^6 g/dL	Creat	1.14 mg/dL	Factor IX activity	81.00 %	RBC	3.86×10^6 g/dL	Creat	0.99 mg/dL
Hb	7.40 g/dL	T-bil	1.94 mg/dL	Factor XI activity	59.00 %	Hb	10.30 g/dL	T-bil	0.94 mg/dL
Hct	25.20 %	AST	26.00 U/L	Factor XII activity	35.00 %	Hct	32.50 %	AST	23.00 U/L
MCV	89.00 fL	ALT	19.00 U/L			MCV	84.20 fL	ALT	16.00 U/L
MCH	26.10 pg	LDH	598.00 U/L			MCH	26.70 pg	LDH	262.00 U/L
MCHC	29.40 g/dL	ALP	287.00 U/L			MCHC	31.70 g/dL	ALP	84.00 U/L
Plt	32.70×10^4 /μL	γ-GTP	73.00 U/L			Plt	34.40×10^4 /μL	γ-GTP	59.00 U/L
APTT	130.70 sec	Na	142.90 mEq/L			APTT	110.50 sec	Na	139.70 mEq/L
PT-INR	2.43	K	4.25 mEq/L			PT-INR	1.59	K	3.75 mEq/L
D-dimer	8.30 μg/mL	Cl	110.30 mEq/L			D-dimer	1.50 μg/mL	Cl	105.50 mEq/L
Antinuclear antibody	negative	CRP	8.26 mg/dL			FDP	5.90 μg/mL	CRP	14.77 mg/dL
Lupus anticoagulant	1.10	BS	102.00 mg/dL			Antinuclear antibody	negative	BNP	183.30 pg/mL
Von Willebrand factor activity	<10.00 %	HbA1c	5.70 %			Lupus anticoagulant	1.10	COVID-19 PCR	positive
Von Willebrand factor antigen	127.00 %	BNP	299.00 pg/mL			Anti-cadiolipin IgG antibody	<4.00 U/mL	Factor VIII activity	4.00 %
						Anti-β2-glycoprotein I antibody	<0.70 U/mL	Factor VIII inhibitor titer	0.80 BU/mL
								Von Willebrand factor activity	88.00 %

Abbreviations: Alb, albumin; ALT, alanine aminotransferase; ALP, alkaline phosphatase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; BS, blood sugar; BU, Bethesda units; BUN, blood urea nitrogen; COVID-19, coronavirus disease 2019; Creat, creatinine; CRP, C-reactive protein; FDP, fibrin degradation product; γ-GTP, γ-glutamyl transpeptidase; Hb, hemoglobin; Hct, hematocrit; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; Plt, platelet; PT-INR, prothrombin time-international normalized ratio; RBC, red blood cell; T-bil, total bilirubin; TP, total protein; WBC, white blood cell.

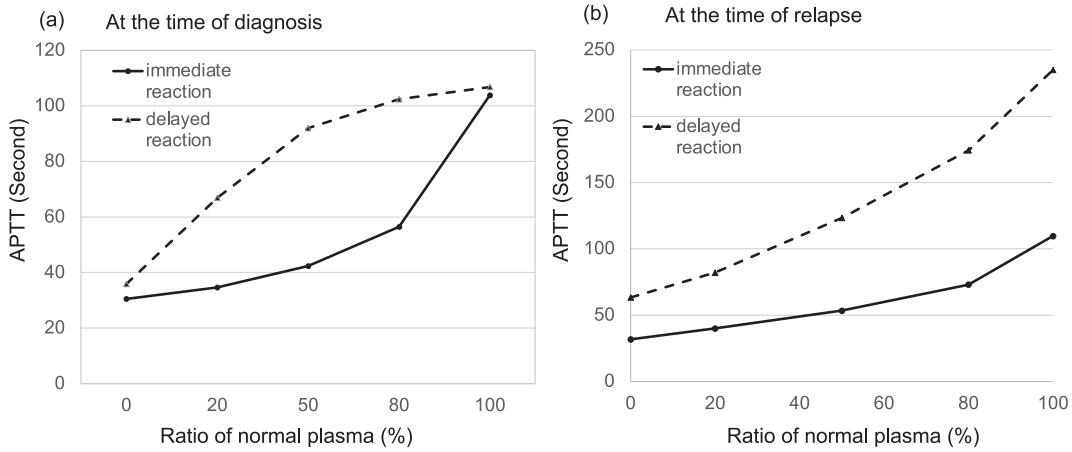

Fig. 2
(a) The result of a mixing test at the time of diagnosis*.
(b) The result of a mixing test at the time of relapse*.
*Immediate reaction: test plasma is mixed with normal plasma and immediately tested.
Delayed reaction: test plasma is mixed with normal plasma and tested after 2 hours incubation at 37°C.
APTT, activated partial thromboplastin time

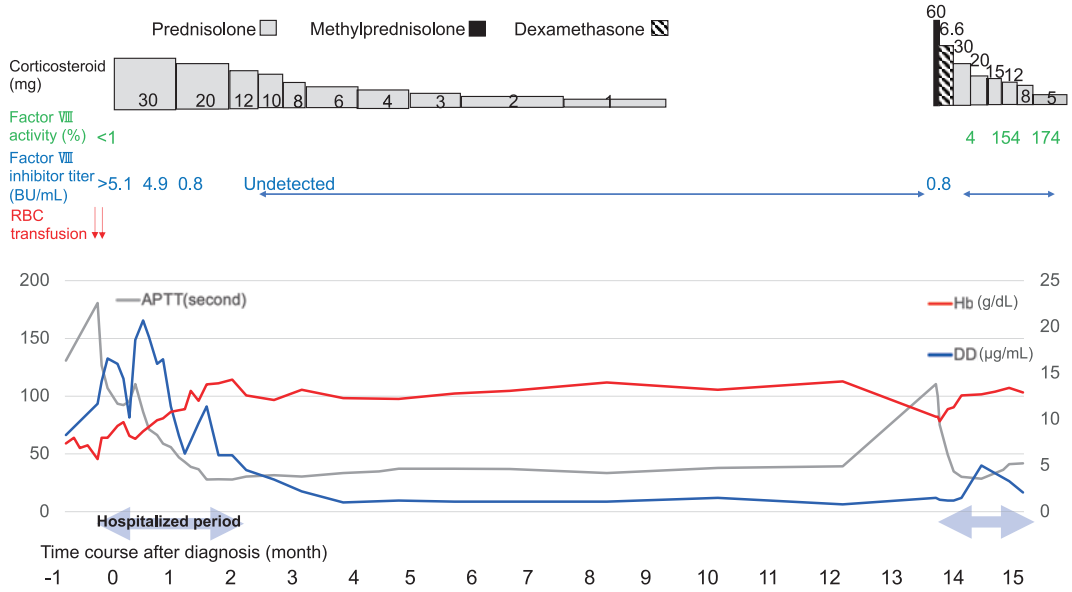

Fig. 3 Clinical course of the 86-year-old patient with acquired hemophilia A.
APTT, activated partial thromboplastin time; DD, D-dimer; Hb, hemaglobin; RBC, red blood cells

1 year after disappearance of FVIII inhibitor and was re-hospitalized. He was inoculated with a COVID-19 vaccine twice. A CT scan showed signs of pneumonia; oxygen was administered, as were methylprednisolone (60 mg/day) and remdesivir (200 mg/day on day 1; 100 mg/day on days 2-5). The next day, methylprednisolone was changed to dexamethasone (6.6 mg/day). The patient had no obvious bleeding, and neither FEIBA nor rFVIII was required. APTT was prolonged (110.5 seconds), suggesting AHA relapse; however, his mixing study did not exhibit an inhibitor pattern (**Fig. 2b**). FVIII activity of 4% and FVIII inhibitor titer of 0.8 BU/mL confirmed relapse of AHA. The results of a lupus anticoagulant test at the time of relapse were normal. After corticosteroid initiation, APTT decreased, and the FVIII inhibitor became undetectable at 9 days after admission. Although the steroid dose was progressively reduced during the treatment course, the FVIII inhibitor titer did not increase. He was discharged 44 days after admission (**Fig. 3**).

Informed consent was obtained from the patient in accordance with the principle of the Declaration of Helsinki. The Institutional Review Board of Fussa Hospital

approved this study (approval number: 2021-42).

Discussion

AHA is predominantly a disease of elderly adults[1,2]. It is associated with tumors, collagen diseases, and other related conditions and often causes serious bleeding in the gastrointestinal tract and lungs[1,2]. Steroids, cyclophosphamide, rituximab, and other medications are used to reduce elevated FVIII inhibitor levels[1,2]. Additionally, FEIBA or rFVIIa is used to stop bleeding[1,2]. A previous study reported that 20% of patients in complete AHA remission developed a relapse at a median of 7.5 months after completion of steroid administration; hence, regular follow-up after the end of treatment period is required[1]. The Japanese guideline recommends follow-up every month until 6 months after the end of treatment, every 2 months from 6 months to 1 year, and every 6 months after 1 year to 2 years. It is possible that anti-FVIII inhibitor autoantibodies of IgA isotype are a potential marker for early relapse, and treatment with rituximab is hypothesized to reduce the relapse rate but is not covered by health insurance in Japan[2]. In the present case, no underlying disease was found. However, at the initial presentation, there was a decrease in VWF activity, which was thought to be a complication of acquired von Willebrand syndrome (AVWS).

The diagnosis of AVWS varies. Some reports diagnosed it as hereditary VWD when vWF activity or the vWF antigen level is <30% in patients with no family history or past history of bleeding, while others diagnose it when vWF multimers are absent[11,12]. Some patients were reported to have decreased VWF activity but normal VWF antigen levels[11,12]. In a study by Cao et al.[4], AVWS occurred in two of six patients with AHA and systemic lupus erythematosus. Indicative of AVWS, vWF activity (although not vWF antigen level) was markedly decreased (<10%) at the time of AHA diagnosis in the present study. vWF multimer analysis was not conducted. AVWS is often alleviated by treating the underlying disorder[11,12]. In our case, vWF activity improved after starting steroid treatment for AHA and did not decrease after treatment completion.

AHA yields an inhibitor pattern in mixing studies. This pattern may be secondary to a coagulation-deficient pattern (with a 2-hour gap between the appearance of the patterns in 37°C incubations)[5,6]. DOACs can affect the results of mixing studies and thus should be discontinued before performing the studies[5,6,13]. In the present case, an immediate coagulation-deficient pattern and a delayed inhibitor pattern were observed in the mixing study performed at the time of the initial AHA diagnosis. At the time of AHA relapse, neither an immediate nor delayed inhibitor pattern was observed, perhaps because of the low FVIII inhibitor titer (0.8 BU/mL) at the time of relapse. The patient was taking apixaban at the time of recurrence; however, it is unlikely that apixaban is related to the coagulation factor deficiency pattern in this case, since oral DOACs generally induce an inhibitor pattern.

Occurrence and recurrence of AHAs, as well as idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, and AVWS, have been reported rarely after COVID-19 infection or vaccination[8,9,14–16], which suggests that COVID-19 may have an effect on the immune system. Wang et al.[17] reported that in 194 COVID-19 patients, autoantibodies to cytokines, chemokines, and cell surface proteins were increased, as compared to levels in uninfected patients. Activation of the lectin pathway is involved in thrombus formation, and it has been reported that COVID-19 infection or vaccination may produce IgG antibodies against factor VIII and vWF complexes and that Spike protein may activate complement via the lectin pathway[13,18,19]. Because the present patient developed AHA immediately after the onset of COVID-19 symptoms, COVID-19 may have been involved in AHA relapse. Therefore, to confirm AHA relapse, we recommend measuring APTT when patients previously diagnosed with AHA are infected with SARS-CoV2.

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