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A Case of Acquired Factor XIII Deficiency with Systemic Lupus Erythematosus Diagnosed after Repeated Intracerebral Hemorrhages

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Abstract

We present a case of autoimmune-acquired factor XIII deficiency associated with systemic lupus erythematosus, which was diagnosed as a cause of repeated intracerebral hemorrhage. An intracerebral hemorrhage occurred in a 24-year-old female patient. Craniotomy was performed to remove the hematoma, but rebleeding occurred at the same site on days 2 and 11, respectively. Detailed blood tests revealed that factor XIII activity decreased. Although autoimmune-acquired factor XIII deficiency is a very rare disease, it can sometimes be fatal when intracerebral hemorrhage occurs. If there is repeated intracerebral hemorrhage, factor XIII activity should be confirmed.

Keywords: factor XIII deficiency, intracerebral hemorrhage, systemic lupus erythematosus, rebleeding, stroke

Introduction

In addition to diagnostic imaging, general bleeding and coagulation tests, including bleeding time, coagulation time, platelet count, prothrombin time, activated partial thromboplastin time, and brain tissue biopsy, are commonly performed to determine the cause of repeated subcortical hemorrhages. Cerebral amyloid angiopathy (CAA) or hemorrhagic predisposition is occasionally diagnosed, but many are unknown. An autoimmune-acquired factor XIII (FXIII) deficiency (AiF13D) is a particularly rare disease. Only approximately 100 cases have been reported globally.[1)] The occurrence of intracerebral hemorrhage (ICH) or abdominal hemorrhage related to AiF13D can sometimes be fatal.[2)] The mechanism for the development of autoantibodies to FXIII remains unclear but is believed to be due to a breakdown of the immune mechanism caused by underlying background disease or age-related immune deterioration.[3)] In previous reports, approximately half of the cases were idiopathic with no apparent underlying disease.[3)] In this report, we present a case of AiF13D with systemic lupus erythematosus (SLE) diagnosed after repeated intracerebral hemorrhages, with a literature review.

Case Report

A 24-year-old female patient had no disease history, medication history, or family health history. She presented to our hospital with a headache and nausea. Upon admission, she had a Glasgow Coma Scale of 14, blood pressure of 160/90 mmHg, and no apparent paralysis. Basic hemostasis tests, coagulation factors, and platelet aggregation tests were all normal (Table 1). Head computed tomography (CT) scan revealed subcortical hemorrhage with an estimated hematoma volume of 45 mL in the right temporal lobe (Fig. 1). Contrast-enhanced CT scan showed no obvious vascular abnormality, and since the patient's level of consciousness rapidly decreased after the CT scan, a craniotomy was performed to remove the hematoma. Pathological brain tissue examination showed no vascular abnormalities, such as CAA, arteriovenous malformation, and malignant tumor. However, on days 2 and 11, the rebleeding occurred at the same site, and a craniotomy was carried out to remove the hematoma, respectively (Figs. 2 and 3). In each surgery, hemostasis was adequately confirmed. A close examination of the patient's bleeding susceptibility was performed to scrutinize the cause of recurring bleed-

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Table 1 Common blood solid inspection

	Patient	Reference ranges
Coagulation-active factor VII (%)	124	75-140
Coagulation-active factor VIII (%)	82	60-150
Von willebrand factor activity (%)	169	60-170
Protein C activity (%)	121	64-146
Protein S Activity (%)	47	56-126
Lupus anticoagulant (SCT ratio)	0.72	<1.16
Bleeding time (min)	2.30	2-5
Platelet count ($\times 10^4/\mu L$)	14.2	15-35
Platelet aggregation capacity (COLL 1) (%)	54	60-90
Platelet aggregation capacity (ADP1) (%)	67	60-90
Prothrombin time (PT) (s)	12.5	11.0-14.0
Prothrombin time-international normalized ratio (PT-INR) (s)	0.93	–
Activated partial thromboplastin time (APTT) (s)	34.4	28-40

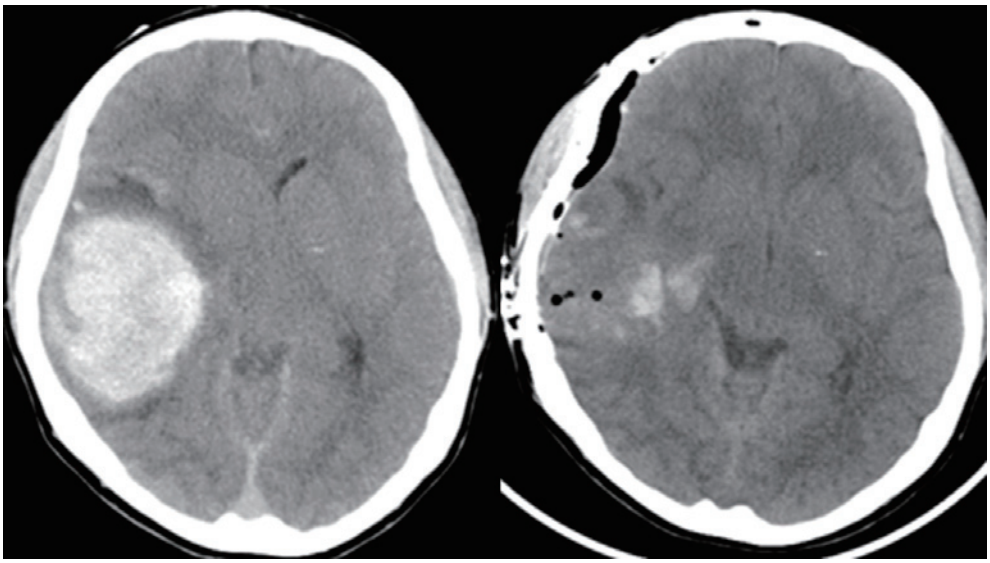

Fig. 1 Head CT scan on admission.
Head CT scan at the time of initial treatment. The left side is a preoperative image. The right side is a postoperative image.

ing. On day 16, it revealed a marked decrease (<3%) in FXIII activity.

In this case, FXIII-enriched formulation was administered twice at 16 IU/kg. Detailed evaluation of the FXIII activity transition after administration of FXIII-enriched formulation showed a rapidly decreased FXIII activity (30.0% recovery at 30 min). Finally, it showed 5% FXIII activity without significant FXIII activity improvement.

We diagnosed the patient with autoimmune FXIII deficiency based on these results and the cross-mixing test with normal plasma. Blood tests were performed, considering the complication of another autoimmune disease, which revealed elevated antinuclear antibodies and anti-DNA antibodies and hypocomplementemia (Table 2). Urine protein and renal dysfunction were also observed, and a diagnosis of SLE was made. Repeated FXIII agent and immunosuppressive drug administration were started on days 21 and 39 of hospitalization. The patient was transferred to the hospital at mRS 3 with no rebleeding.

Discussion

Coagulation factor FXIII is a transglutaminase binding fibrin monomer that is essential for clot stabilization and fibrinolysis and proteolysis resistance that subsequently provides hemostasis and wound healing.[1)] FXIII deficiency causes hemorrhaging and slow wound healing. In this report, following the Guidance on Diagnostic Criteria for Autoimmune Hemorrhaphilia FXIII/13, the diagnosis of AiF 13D was made based on normal bleeding time, decreased

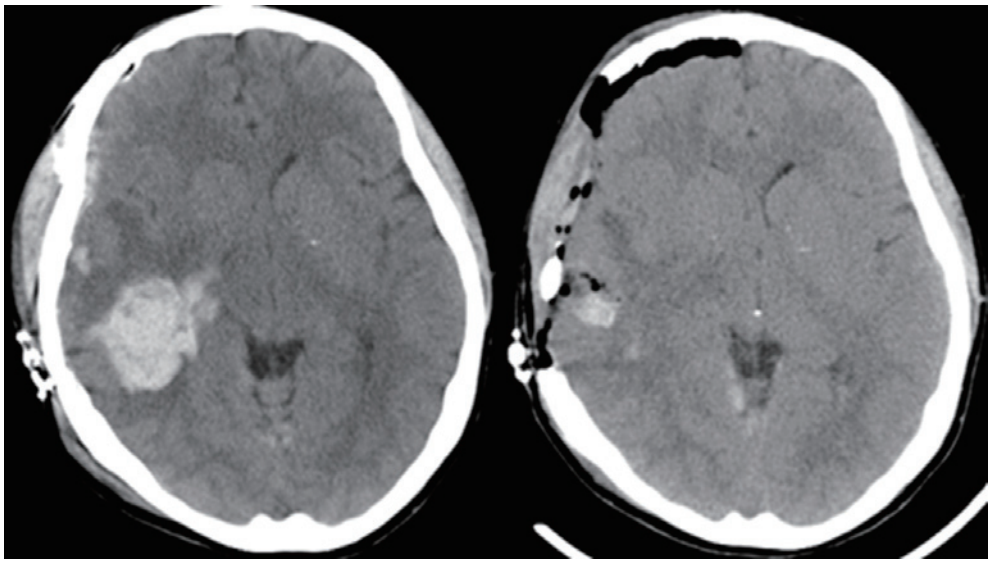

Fig. 2 Head CT scan at rebleeding on day 2.
Head CT scan on the second day of admission. The left side is a preoperative image. The right side is a postoperative image. Besides craniotomy for removing hematoma, decompression surgery was performed.

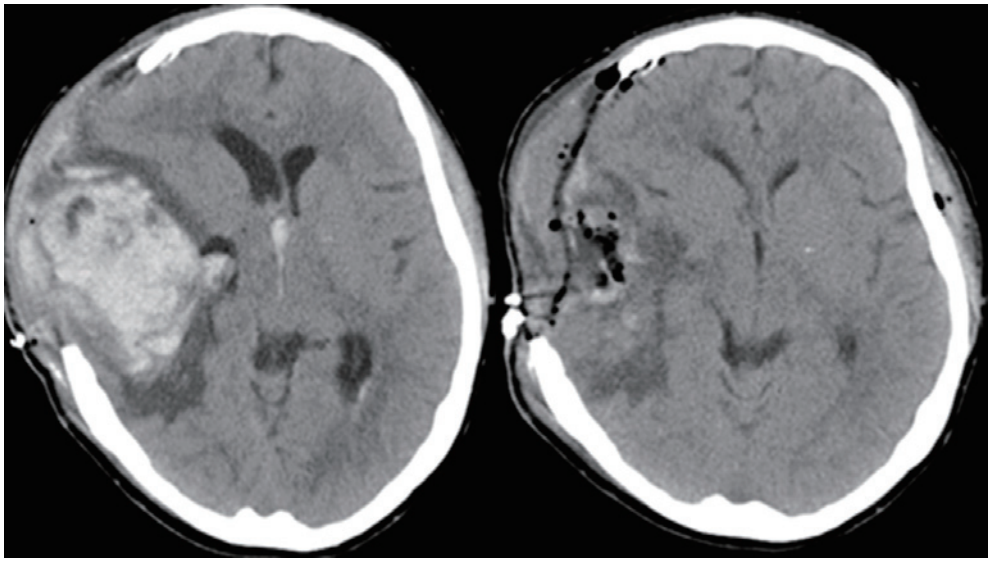

Fig. 3 Head CT scan at rebleeding on day 11.
Head CT scan on the 11th day of admission. The left side is a preoperative image. The right side is a postoperative image.

FXIII quantification test, cross-mixture test results with normal plasma, and rapid decrease in recovery rate after FXIII agent administration.[3] On admission, D-dimer was within the normal range. This finding indicated a lack of fibrin cross-linked by the activated FXIII. Very few studies report on acquired FXIII deficiency complicated by ICH. A Pubmed search for "Factor XIII deficiency" and "intracerebral hemorrhage" excluded those with no case reports and those with congenital origin. There were only two reported cases. The first case is an acquired FXIII deficiency with CAA, in which the patient developed acute subdural hematoma (ASDH) the day after developing ICH (subcortical hemorrhage).[4] The second case is an acquired FXIII deficiency associated with SLE and the onset of ASDH.[5] Therefore, this report is the first to present a case of acquired FXIII deficiency with SLE with repeatedly developed ICH. AiF13D often rebleeds half to several days after hemostasis, although rebleeding 4-7 days after hemostasis was reported.[6] Moreover, the relative risk of bleeding after neurosurgery increases 3.9-fold when FXIII activity is <80% and 6.4-fold when <60%.[7] In terms of treatment, immunosuppressive therapy should be started promptly in all patients. Particularly, corticosteroids (prednisolone 0.5-1 mg/kg/day) should be the first-line therapy. In the presence of

Table 2 Blood test

	Patient	Reference ranges
IgG (mg/dL)	1830	861-1747
IgA (mg/dL)	607	93-393
IgM (mg/dL)	37	50-269
CH50 (U/mL)	13.4	30-45
C3 (mg/dL)	39.8	73-138
C4 (mg/dL)	6.2	11-31
Antinuclear antibody (IU/mL)	80	<40
Anti-DNA antibody (IU/mL)	>200	<6.0
Anti-SS-A/Ro antibody E (U/mL)	1.2	<10.0
IC (C1q) (μg/dL)	10.7	<3.0
Haptoglobin (mg/dL)	206	50-220
Anti-CLβ2GP1 (U/mL)	<1.2	<3.5
Anticardiolipin antibody (U/mL)	10	<10.0
Anti-Sm antibody (U/mL)	15.0	<10.0

bleeding symptoms, FXIII administration should be used for the syndrome.[8] In this case, the patient had sufficient hemorrhagic potential as an SLE complication. FXIII administration alone did not produce a sustained increase in FXIII activity and did not reduce the risk of bleeding; thus, corticosteroid therapy (prednisolone at 1 mg/kg) was administered. FXIII should be evaluated preoperatively in patients with autoimmune diseases, such as SLE; if FXIII is decreased, FXIII replacement, steroids, or immunosuppressive agents should be taken into account.

Conclusion

When the cause of subcortical hemorrhage cannot be identified via imaging and general coagulation tests and AiF13D may be one of the causative diseases, a detailed search for coagulation factors is required.

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Informed Consent

Informed consent was obtained from the patient involved in the study.

Conflicts of Interest Disclosure

All authors declare that they have no conflicts of interest associated with this manuscript. The manuscript has not been published previously and is not under consideration for publication elsewhere.

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