Clin. Lab. 2026;72:XXX-XXX

CASE REPORT

Spontaneous Postpartum Hematomas Revealing Acquired Hemophilia A with Extreme Inhibitor Interference: a Case Report and Literature Review

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ABSTRACT

Background: **Acquired hemophilia A (AHA) is a rare autoimmune bleeding disorder caused by autoantibodies against factor VIII. Extremely high-titer inhibitors may cause laboratory interference patterns mimicking combined factor deficiencies.**
Methods: **We report a 28-year-old woman with extensive postpartum hematomas. Investigations included coagulation screening, factor assays, serial dilution studies (undiluted to 1:16), and anti-factor VIII antibody quantification using the Nijmegen method. Factor VIII activity was measured by both one-stage clot-based and chromogenic assays. Immunological workup excluded associated autoimmune conditions. Treatment consisted of first-line immunosuppression with rituximab and prednisone followed by emicizumab (for refractory disease).**
Results: **Initial testing showed isolated aPTT prolongation (ratio 3.82) with apparent deficiency of factors VIII, IX, XI, XII (all 0%). Serial dilutions revealed differential recovery with factors IX, XI, XII progressively normalized while factor VIII remained at 0%. Anti-factor VIII antibodies exceeded 256 BU/mL. At one-year follow-up, factor VIII activity reached 54% and inhibitor titer 2.1 BU/mL.**
Conclusions: **Extremely high-titer anti-factor VIII antibodies can cause spurious multi-factor deficiencies through assay interference rather than true multiple factor inhibition. Serial dilution studies are essential for accurate diagnosis. This interference phenomenon must be recognized in order to avoid misdiagnosis and ensure appropriate treatment of severe AHA.**
(Clin. Lab. 2026;72:xx-xx. DOI: 10.7754/Clin.Lab.2025.251045)

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Case Report accepted December 8, 2025

KEYWORDS

postpartum hemorrhage, acquired hemophilia A, factor VIII inhibitor, serial dilution assay, assay interference

CASE PRESENTATION

A 27-year-old woman presented to our laboratory six months postpartum for evaluation requested by her internist due to extensive hematomas on the upper and lower extremities (Figure 1). Her medical history included an uncomplicated first vaginal delivery. During her second vaginal delivery, she experienced immediate postpartum hemorrhage with a hemoglobin level of 4 g/dL, managed conservatively with uterine aspiration and blood transfusions. Three months following this de-

livery, she began developing spontaneous ecchymoses. She was breastfeeding at the time of presentation and was not taking any medications. There was no personal or family history of autoimmune diseases or bleeding disorders.

Her complete blood count at presentation was unremarkable, with hemoglobin 12.1 g/dL, white blood cell count 8.4 x 10^3/µL, and platelet count 329 x 10^3/µL. Hemostasis testing revealed significant isolated prolongation of aPTT (108/28.3 seconds; ratio: 3.82) with normal prothrombin time (PT) and fibrinogen levels.

The Rosner index was calculated at 68.7%, strongly suggesting the presence of an inhibitor.

Initial coagulation factor assays demonstrated factor VIII, IX, XI, and XII levels at 0% (normal range 50 - 150%), with normal levels of factor V (FV: 95%) and factor XIII (FXIII: 92%). Von Willebrand factor (vWF) functional activity was within normal limits at 106%. Mixing studies were performed by combining equal volumes of patient plasma and normal pooled plasma and are presented in Table 1. Platelet aggregation studies were unremarkable for the following agonists: ADP, collagen, arachidonic acid, and ristocetin.

Immunological workup (antinuclear antibodies, anti-double-stranded DNA antibodies, anti-cardiolipin antibodies, anti-beta-2-glycoprotein I antibodies, and lupus anticoagulant) was negative, excluding associated autoimmune conditions.

Follow-up testing was performed one month later. The complete blood count remained unremarkable. Hemostasis evaluation revealed further prolongation of aPTT (113.8/28.3 seconds; ratio 4.02). Serial dilution studies were extended to better characterize the interference pattern (Table 2).

FVIII activity was also measured using a chromogenic assay on undiluted plasma, revealing 0% activity, confirming true FVIII deficiency and ruling out technical artifacts specific to clot-based methodology.

Anti-FVIII antibody screening was positive with an inhibition rate of 99%. Anti-FVIII antibody titer exceeded 256 BU/mL (Nijmegen method), representing an extremely high titer associated with severe acquired hemophilia A.

These results indicated the presence of anti-FVIII antibodies with inhibitory activity that, at extremely high concentrations, also interfered with the assays of factors IX, XI, and XII, a pattern not previously described in the literature.

Treatment and follow-up

Given the diagnosis of acquired hemophilia A with extremely high-titer inhibitor, a multidisciplinary approach was initiated. The patient did not have active bleeding at diagnosis, thus bypassing agents were not required for acute hemostatic management.

First-line immunosuppressive treatment was initiated following international guidelines, consisting of rituximab (375 mg/m² intravenously weekly for 4 consecutive weeks) and corticosteroids (prednisone 60 mg daily orally with planned gradual taper).

Follow-up hemostasis testing at 6 and 8 weeks showed no improvement in FVIII levels or reduction in inhibitor titers, indicating inadequate response to first-line therapy.

Given the refractory response to standard, emicizumab therapy was initiated with a loading dose of 3 mg/kg subcutaneously weekly for 4 weeks followed by maintenance dose of 1.5 mg/kg subcutaneously every week. Emicizumab, a bispecific monoclonal antibody that mimics the cofactor function of activated FVIII by bridging activated factor IX and factor X, provided hemostatic coverage while ongoing immunosuppression worked to eradicate the inhibitor.

Inhibitor monitoring during treatment

Serial monitoring of anti-FVIII antibodies demonstrated progressive decline in both inhibitor titer and inhibition rate (Table 3). FVIII activity measurements were performed using chromogenic assay with bovine reagents, which are not affected by emicizumab interference.

Factor assays after three months of treatment revealed normalization of factors IX, XI, and XII activity, but persistently low factor VIII activity (Table 4). Notably, the aPTT remained prolonged but improved, and could not be used for monitoring due to emicizumab interference with phospholipid-dependent coagulation assays. Clinically, the patient was asymptomatic with complete resolution of hematomas and absence of other bleeding manifestations.

Long-term outcome

At one-year follow-up, the patient demonstrated excellent clinical and laboratory response. Clinically, she reported no new bleeding episodes.

Laboratory findings:

aPTT ratio: 1.45 (marked improvement from initial 3.82), FVIIIc activity (chromogenic, bovine): 54%, anti-FVIII antibody titer: 2.1 BU/mL, inhibition rate: 15%. She was currently off all treatment with emicizumab discontinued after 10 months and the immunosuppression tapered.

DISCUSSION

The unique interference pattern: A novel observation

This case represents, to our knowledge, the first documented instance of anti-FVIII antibodies at extremely high titers (> 256 BU/mL) causing measurable interference with factor IX, XI, and XII activity assays by clot-based methodology. While isolated factor VIII deficiency is the hallmark of acquired hemophilia A, our patient initially presented with apparent complete deficiency of all intrinsic pathway factors (VIII, IX, XI, and XII at 0%), raising concern for a combined factor deficiency or consumptive coagulopathy, neither of which was

Table 1. Initial factor activity assay results (February).

Factors	Normal range	Undiluted	1:4 Dilution	1:8 Dilution
FVIII (%)	50 - 150	0	0	0
FIX (%)	50 - 150	0	1.1	3.2
FXI (%)	50 - 150	0	0.2	2
FXII (%)	50 - 150	0	0	0.1

Table 2. Factor activity assay results with extended dilutions (March).

Factors	Normal range	Undiluted	1:2 Dilution	1:4 Dilution	1:8 Dilution	1:16 Dilution
FVIII (%)	50 - 150	0	0	0	0	0
FIX (%)	50 - 150	0	0	0	1.3	2.7
FXI (%)	50 - 150	0	0	0.1	2.3	3
FXII (%)	50 - 150	0	0	1.2	3.5	4
FXIII (%)	70 - 140	92.3	-	-	-	-
vWF (%)	50 - 150	106.1	-	-	-	-

Table 3. Monitoring of anti-FVIII during treatment.

Date	FVIII Chromogenic activity (%)	Inhibition rate (%)	Anti-FVIII titer (BU/mL)
March 26	< 0.1	100	> 256
April 22	< 0.1	100	> 256
May 16	0.1	99	78
May 30	0.1	99.8	44
June 13	0.1	99.8	29.44
June 20	0.1	99.79	32.64
July 1	0.1	95.75	24
July 8	1	94.73	24.4
August 2	0.1	93.12	13.92

Table 4. Hemostasis testing results after three months of second-line treatment (August).

Parameter	Result	Normal range
PT	95%	70 - 120%
INR	1	0.8 - 1.2
aPTT *	not interpretable	-
FVIIIc Activity (one-stage)	0.1%	50 - 150%
FVIII Activity (chromogenic, bovine)	0.1%	50 - 150%
FIXc Activity	98.7%	50 - 150%
FXIc Activity	91.5%	50 - 150%
FXIIc Activity	75.5%	50 - 150%
Anti-FVIII Antibody Titer	13.92 BU/mL	< 0.6
Inhibition Rate	93.12%	0%

*** aPTT not interpretable due to emicizumab interference.**

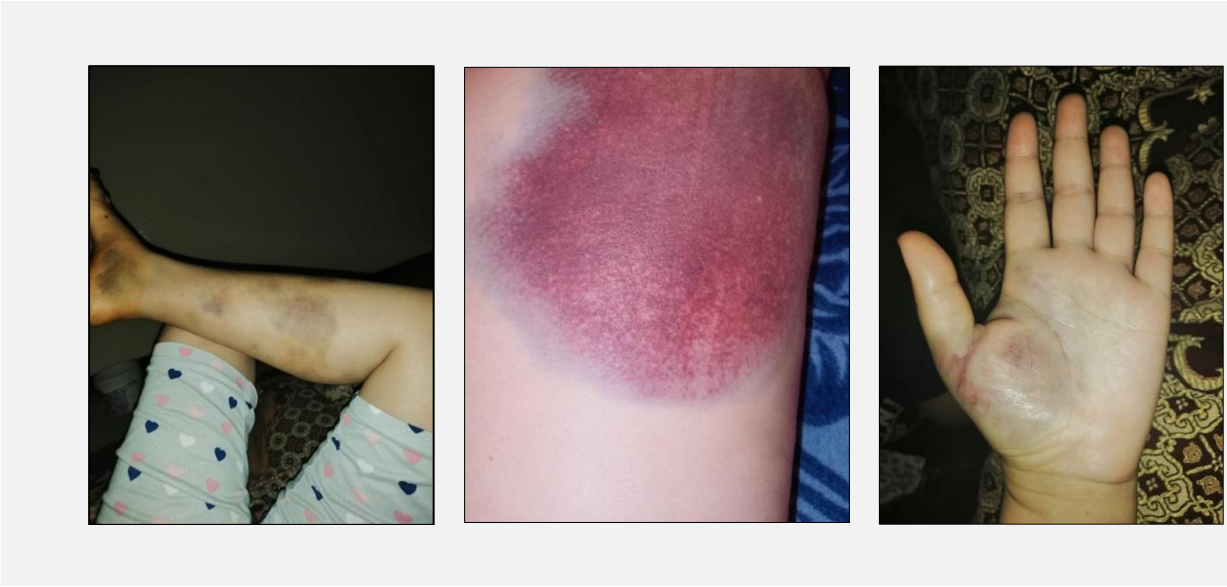

Figure 1. Hematomas of the upper and lower extremities at presentation.

Hemostasis testing was performed on ACL TOP750-Werfen analyzer. Factor assays were performed using one-stage clot-based methodology.

supported by the clinical presentation or other laboratory parameters.

The key diagnostic insight came from serial dilution studies, which revealed a striking differential pattern: while factor VIII activity remained undetectable across all dilutions, factors IX, XI, and XII demonstrated progressive recovery beginning at 1:8 dilution. This dose-dependent interference pattern, combined with the subsequent selective normalization of FIX, FXI, and FXII activities following immunosuppressive therapy, conclusively demonstrated that the apparent multi-factor deficiency was an artifact of assay interference rather than true multiple factor inhibition.

Potential mechanisms of interference

Several mechanisms may explain this unprecedented interference pattern:

High antibody concentration effect

Anti-FVIII antibodies at concentrations exceeding 256 BU/mL may physically interfere with the clot-based assay system. Since all intrinsic pathway factor assays use aPTT-derived methodology with factor-deficient plasmas, extremely high concentrations of immunoglobulins could cause non-specific prolongation of clotting times that is misinterpreted as factor deficiency.

Assay-specific technical interference

The one-stage clot-based assays measure the time to fibrin formation, which depends on the entire coagulation cascade. An extremely potent FVIII inhibitor might alter the kinetics of the coagulation cascade in ways that disproportionately affect the apparent activity of upstream factors (IX, XI, XII) when measured in factor-deficient plasma systems.

Plasma matrix effects

The presence of massive amounts of anti-FVIII IgG may alter the plasma matrix sufficiently to affect the interaction between test plasma and factor-deficient substrate plasmas in ways that become negligible upon dilution.

The resolution of this interference following immunosuppression, with normalization of FIX, FXI, and FXII while FVIII remained inhibited, provides strong evidence that the phenomenon was concentration-dependent and specific to the presence of extremely high-titer anti-FVIII antibodies.

Comparison to known interference patterns

Lupus anticoagulants are well-documented to prolong aPTT and can cause spuriously low measurements of intrinsic pathway factors. However, our patient had negative lupus anticoagulant testing, and the interference pattern differed significantly: lupus anticoagulants typically cause proportional prolongation across all phospholipid-dependent assays and do not show the dose-dependent resolution seen with dilution in our case. Furthermore, lupus anticoagulants interfere with chromogenic assays to a much lesser extent, whereas our patient showed 0% FVIII activity by both clot-based and chromogenic methods, confirming true FVIII inhibition.

Diagnostic challenges and clinical implications

This case underscores several critical diagnostic principles.

Serial dilution studies are essential
When confronted with unexpectedly low levels of multiple coagulation factors in the context of isolated aPTT prolongation, serial dilution studies can distinguish true multi-factor deficiencies from assay interference. The differential recovery pattern in our patient (persistent FVIII deficiency vs. recovery of FIX, FXI, FXII) was diagnostic.

Multiple assay methodologies improve accuracy
Confirmation of FVIII deficiency using both clot-based and chromogenic methodologies (with the latter using bovine reagents less susceptible to certain interferences) strengthened diagnostic confidence. Chromogenic assays are particularly valuable in settings where assay interference is suspected.

Clinical-laboratory correlation is paramount
The patient's clinical picture, spontaneous hematomas without laboratory features of DIC, thrombocytopenia, or multi-organ dysfunction, was inconsistent with a true combined factor deficiency, prompting further investigation.

Misdiagnosis risks
Without recognition of this interference pattern, clinicians might incorrectly diagnose combined factor deficiency, leading to inappropriate treatments (such as fresh frozen plasma administration) or failure to recognize and treat the underlying acquired hemophilia A.

Postpartum acquired hemophilia A: context and comparison
Postpartum acquired hemophilia A is a rare variant of this already uncommon condition, accounting for only 1 - 5% of all AHA cases. Several features of our patient's presentation warrant discussion.

Timing and pregnancy history
Most postpartum AHA cases occur after the first pregnancy, with symptom onset typically within the first 3 months postpartum. Our patient developed the condition after her second pregnancy. The immediate postpartum hemorrhage following her second delivery may have been the initial manifestation of developing inhibitor formation, though inhibitor testing was not performed at that time.

Clinical severity
The inhibitor titer in our patient (> 256 BU/mL) represents an extremely high titer. While inhibitor titers do not always correlate with bleeding severity, titers > 5 BU/mL are considered high-responding and associated with more challenging management. Our patient's extremely high titer, combined with extensive ecchymoses, positioned her in a high-risk category. Notably, she did not experience life-threatening hemorrhage (intracranial, gastrointestinal, or retroperitoneal), which occurs in up to 30% of AHA cases and carries significant mortality risk.

Delayed diagnosis
The 6-month interval between delivery and laboratory diagnosis (3 months of symptoms before seeking care) represents a concerning delay that is unfortunately common in postpartum AHA. Many patients and clinicians attribute postpartum symptoms to normal physiologic changes or complications of delivery, leading to diagnostic delays. Early recognition is critical, as mortality rates of 5 - 10% are largely attributable to delayed diagnosis and catastrophic bleeding.

Prognosis
Postpartum AHA generally carries a more favorable prognosis compared to AHA in other settings, with higher rates of spontaneous remission and better response to immunosuppression. However, our patient's extremely high inhibitor titer and initial lack of response to standard immunosuppression suggested a more severe phenotype. The ultimate achievement of complete remission at one year, with FVIII recovery to 54% and inhibitor titer decline to 2.1 BU/mL, is consistent with the generally good prognosis of postpartum AHA but required aggressive multimodal therapy.

Emicizumab in acquired hemophilia A: An emerging strategy
The use of emicizumab in our patient represents an important therapeutic innovation in AHA management. emicizumab is a humanized bispecific monoclonal antibody that bridges activated factor IX and factor X, mimicking the cofactor function of activated factor VIII, thereby bypassing the need for functional FVIII.
Traditional management of AHA involves two complementary strategies: 1) control of acute bleeding with bypassing agents (recombinant activated factor VII or activated prothrombin complex concentrate) or recombinant porcine FVIII, and 2) eradication of the inhibitor with immunosuppressive therapy. However, patients with refractory inhibitors or those awaiting response to immunosuppression may require weeks to months of protection against bleeding. Emicizumab offers several advantages in this context. Indeed, it can be given as outpatient with weekly or biweekly dosing, improving compliance as well as patient quality of life. It also provides homeostasis management while immunosuppression works to eradicate the inhibitor.
Emerging data from case series suggest that emicizumab is effective in AHA, with most patients achieving adequate hemostatic control and many reaching remission without major bleeding events.
Emicizumab interferes with all phospholipid-dependent coagulation assays, including aPTT and one-stage FVIII assays, complicating laboratory monitoring. We employed chromogenic FVIII assays with bovine reagents, which are unaffected by emicizumab, to monitor inhibitor eradication and FVIII recovery. This approach allowed accurate assessment of when remission was

achieved and treatment could be safely discontinued.

Laboratory methodology considerations
This case highlights important technical aspects of coagulation testing.

One-stage vs. chromogenic FVIII assays
The one-stage clot-based assay, while widely available and most commonly used, measures the time to fibrin formation in factor-deficient plasma supplemented with the patient's sample. It is susceptible to various interferences including lupus anticoagulants, heparin, and, as our case demonstrates, extremely high antibody concentrations. The chromogenic assay measures FVIII activity in a two-stage reaction independent of fibrin formation, offering greater specificity and resistance to certain interferences. Both assays confirmed 0% FVIII activity in our patient, validating the true deficiency, but chromogenic assays were essential for monitoring during Emicizumab therapy.

Bovine vs. human reagents
The use of bovine-derived reagents in chromogenic assays is particularly important in two scenarios: 1) patients with lupus anticoagulants, where bovine phospholipids are less affected, and 2) patients receiving emicizumab, where bovine factor X is not recognized by the bispecific antibody. Our laboratory's use of bovine chromogenic reagents proved essential for accurate FVIII monitoring throughout treatment.

CONCLUSION

Acquired hemophilia A is a rare but potentially life-threatening bleeding disorder requiring prompt recognition and aggressive management. This case illustrates a previously unreported phenomenon in which anti-FVIII antibodies at extremely high titers (> 256 BU/mL) caused spurious deficiencies of multiple intrinsic pathway factors (IX, XI, XII) through assay interference, potentially leading to diagnostic confusion. The differential recovery pattern with serial dilution studies, combined with selective normalization following immunosuppression, established that this was an artifact of antibody concentration rather than true multi-factor inhibition.
Key lessons from this case include: 1) the importance of serial dilution studies when confronted with unexpected multi-factor deficiencies; 2) the value of employing multiple assay methodologies (clot-based and chromogenic) to confirm factor deficiencies and overcome interferences; 3) the need for clinical-laboratory correlation to avoid misdiagnosis; and 4) the emerging role of emicizumab as a valuable therapeutic option in AHA, providing hemostatic prophylaxis while immunosuppression eradicates the inhibitor.
This case expands our understanding of laboratory challenges in diagnosing and monitoring acquired hemophilia A and underscores the necessity of specialized expertise in coagulation disorders for optimal patient management. The excellent long-term outcome - complete clinical remission with FVIII recovery to 54% at one year - demonstrates that even severe, high-titer postpartum AHA can be successfully managed with contemporary multimodal therapy including immunosuppression and emicizumab.

Declaration of Generative AI in Scientific Writing:
No generative AI tools were used in the preparation of this manuscript.

Declaration of Interest:
The authors declare no conflicts of interest.

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