Delayed Diagnosis in a 61-Year-Old Hispanic Male with Ecchymoses, Soft Tissue Bleeding, and Edema

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CASE DESCRIPTION

A 61-year-old Hispanic male presented to the emergency department (ED) with ecchymoses and edema of his left forearm and elbow after mild trauma from bumping into a table during the previous evening. Past medical history revealed hypertension, severe gout on colchicine, and negative family and medical history of bleeding or thrombosis. His history was negative for anticoagulants and other medications. Toxicology screens were negative. The patient's hemoglobin (Hb) was 14.3 g/dL (reference interval: 12.0–16.0 g/dL), platelet count (PLT) of 234 k/µL (reference interval: 150–450 k/µL), prothrombin time (PT) of 13.0 s (reference interval: 11.8–14.8 g/dL), and a marked prolonged activated partial thromboplastin time (aPTT) of 70.5 s (reference interval: 23.3–38.6 s). The patient was otherwise stable and referred to outpatient hematology to work-up a potential coagulation disorder. However, he was unable to secure hematology follow-up.

One month later, the patient presented to the ED a second time with worsening ecchymoses and swelling, now involving bilateral extremities and abdomen. He received his influenza vaccine the previous week, shortly before his ecchymoses began; however, it is uncertain whether the injection exacerbated his bruising. The patient's Hb dropped from 14.3 g/dL to 10.2 g/dL, aPTT remained prolonged (73.3 s), PLT (297 k/µL), and PT (13.7 s). After hospital admission, mixing studies demonstrated immediate inhibition, partially correcting aPTT, as well as a subsequent time-dependent inhibition 1-hour postincubation (>10 s difference). While a lupus aPTT screen and StaClot lupus anticoagulant (LA) were both positive, Dilute Russell Venom Viper Time (DRVVT) screen ratio, thrombin-time, fibrinogen, serum protein electrophoresis, and platelet aggregation were normal. Table 1 summarizes the coagulation results at hospital admission.

The patient's hematoma worsened with Hb dropping to 6.6 g/dL 1 day post-admission. He received 1 unit of RBCs and 1 unit of plasma. Acquired hemophilia A (AHA) was suspected based on bleeding severity and time-dependent inhibitor prolongation of aPTT. The patient was subsequently administered an empiric therapy of steroids, cyclophosphamide, and 4 doses of rituximab. Antibiotic therapy was initiated to address immunosuppression associated with these therapeutic agents. Additionally, recombinant activated Factor VII (rFVIIa) was administered every 2 hours initially, then reduced to once every 6 hours.

The send-out Nijmegen–Bethesda assay confirmed the presence of a Factor VIII (FVIII) antibody titer at 310.1 BU/mL (reference interval: <0.6 U/mL). FVIII activity was undetectable at <1% (reference interval: 60%–150%). Two weeks after admission, the patient received porcine FVIII (pFVIII), with a loading dose of 200 U/kg, maintenance doses of 100 U/kg, and tapering doses of 50 U/kg by day 3. The patient's bleeding improved with full hemostasis, decreased swelling, and improved ambulation after 3 weeks of therapy. His FVIII activity improved to 36%, as well as normalization of the aPTT by day 26. He was discharged on day 27 and continued to receive care at a tertiary hemophilia clinic. While recurrent, intermittent

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episodes may be common due to persistent antibodies, to our knowledge, the patient did not have additional subsequent hospitalizations. This may be a loss to follow-up.

QUESTIONS TO CONSIDER
• How should a prolonged aPTT be clinically approached?
• What are the clinical implications of a positive LA screen in the context of a suspected FVIII inhibitor?
• What are the types of FVIII antibody?
• What are clinical considerations in managing AHA?

Table 1. Patient reference ranges and laboratory coagulation studies upon admission (i.e., at second ED visit).

Test	Patient	Reference range
Hemoglobin (g/dL)	10.2 (L)	12.0–16.0
PLT (k/μL)	297	150–450
aPTT (s)	73.3 (H)	23.3–38.6
aPTT 1:1 mix, immediate (s)	53.8 (H)	23.3–38.6
aPTT 1:1 mix incubated (s)	67.5 (H)	23.3–38.6
PT (s)	13.7	11.8–14.8
PTT (LA sensitive) (s)	115.7 (H)	34.7–47.9
PTT (LA sensitive) 1:1 mix (s)	72.8 (H)	34.7–47.9
DRVVT Screen (ratio)	1.08	0.80–1.20
StaClot® LA (with hexagonal phospholipid neutralization)	Positive (>8 s correction)	Negative (<8 s correction)

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the August 2023 issue of *Clinical Chemistry*. To view the case and comments online, go to https://academic.oup.com/clinchem/issue/69/8 and follow the link to the Clinical Case Study and Commentaries.

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