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CASE REPORT

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Laboratory work-up/diagnostics of acquired factor XI inhibitor

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Summary

Acquired coagulation factor deficiencies are caused by inhibitory autoantibodies which are usually directed against clotting factor VIII (FVIII), causing acquired hemophilia A (AHA). Clotting factor inhibitors usually cause abnormalities in screening coagulation tests (activated partial thromboplastin time [aPTT] and/or prothrombin time [PT]). Other coagulation factor inhibitors are much rarer, particularly inhibitors to factor XI (FXI).

We present the case of an 82-year-old woman referred to a hematological center for isolated aPTT prolongation in pre-surgery screening tests. No bleeding symptoms were reported either at admission or in the patient's medical history. One stage coagulation factor assays revealed lower factor VIII, IX, XI, XII levels. The Nijmegen modification of the Bethesda assay showed the presence of an inhibitor to factor XI (22.1 BU/mL). No autoantibodies to coagulation factors VIII, IX and XII were found: inhibitor titers were all below 0.6 BU/mL. Acquired hemophilia C was diagnosed (the presence of autoantibodies to clotting factor XI).

Key words: isolated aPTT prolongation, acquired hemophilia, acquired factor deficiences, hemophilia C, clotting factor XI

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Introduction

Acquired coagulation factor deficiencies are associated with the presence of autoantibodies that affect the function and/or increase the clearance of proteins active at different stages of the coagulation cascade. They are mostly directed against factor VIII (FVIII) and are responsible for acquired hemophilia A (AHA). They may be observed in patients with cancer or autoimmune diseases as well as in pregnant women. Inhibitors to coagulation factors (with the exception of von Willebrand and factor XIII) usually manifest as abnormalities in screening coagulation tests (activated partial thromboplastin time (aPTT) and/or prothrombin time (PT)) [1].

Acquired hemophilia A is a rare bleeding disorder that may occur in patients with no history of bleeding. About half the cases are idiopathic, but AHA can also be secondary to autoimmune, dermatological or oncological diseases. About 10% of non-idiopathic cases is related to neoplastic diseases (may precede diagnosis as an extremely rare paraneoplastic syndrome) [2]. Inhibitors against other coagulation factors, including factor XI (FXI), are reported less frequently, mostly in patients with autoimmune diseases such as systemic lupus erythematosus [3], rheumatoid arthritis [4], Crohn's disease [5], membranoproliferative glomerulonephritis [6] and associated with malignant neoplasms [7, 8]. Acquired factor XI deficiency has also been described in a SARS-

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Table 1. Laboratory results

Test	I visit Result	II visit Result	Reference range
PT (s)	11.0	11.3	9.8–12.1
PT (INR)	1.00	1.10	0.85–1.15
aPTT FSL (s)	40.80	40.30	25.0–33.5
aPTT FS (s)	38.60	38.80	23.0–31.0
TT (s)	18.3	19.00	14.0–21.0
Fibrinogen (Clauss's method, g/l)	2.9	2.8	1.8–3.5
Factor VIII (%)	26.6	33.50	50–150
Factor IX (%)	9.9	13.40	50–150
Factor XI (%)	11.4	12.6	50–150
Factor XII (%)	34.30	34.7	50–150
Factor VIII, chromogenic method (%)	155.80	160.8	50–150
Factor IX, chromogenic method (%)	102.7	120.7	50–150
Factor VIII inhibitor [UB/mL]		< 0.6	
Factor IX inhibitor [UB/mL]		< 0.6	
Factor XI inhibitor [UB/mL]		22.1	
Factor XII inhibitor [UB/mL]		< 0.6	
Lupus anticoagulant	Negative	Negative	Negative
IgG anticardiolipin antibodies (GPL)	3.00		0.0–15.0
IgM anticardiolipin antibodies (MPL)	6.36		0.0–12.0
Anti-beta-2-glycoprotein 1 antibodies, IgG (SGU)	1.06		0.0–20.0
Anti-beta-2-glycoprotein 1 antibodies, IgM (SGU)	1.90		0.0–20.0

PT — prothrombin time; aPTT — activated partial thromboplastin time (aPTT); TT — thrombin time

-COV-2 infected patient [9]. The risk of bleeding events in patients with FXI deficiency is relatively low, and the correlation between factor activity and clinical symptoms is rather weak. In most cases, severe bleeding episodes are related to trauma or surgery [10]. AHA laboratory diagnostics requires access to a specialized laboratory. Typically a 2–3 fold increase in aPTT is observed. In most cases Factor VIII activity falls below 15%. Mixing tests demonstrate no aPTT correction after 1–2 hour incubation of patient's plasma with equal volume normal plasma. For AHA diagnosis to be confirmed it is necessary to measure FVIII activity and perform the Nijmegen modification of the Bethesda assay to detect the FVIII neutralizing antibodies (BU/mL) [2].

Case report

An 82-year-old woman referred to a specialist for abnormal aPTT results (49 sec and 68 sec, normal range: 25.0–33.5 sec) detected at qualification for elective cataract surgery. Prothrombin time (PT), fibrinogen concentration, thrombin time (TT) and blood counts were within normal range. Her history of bleeding was negative; no bleeding complications were reported after gynecological surgery, both knees arthroplasty or tooth extraction. The patient had previously been diagnosed with hypertension, diabetes and depression. Two reagents of different sensitivity to lupus anticoagulant (LA) were used to measure aPTT: Actin FSL (LA sensitive) and Actin FS (LA insensitive). The results were abnormal for both reagents (40.8 sec and 38.6 sec, respectively). Factor VIII, IX, XI and XII activity in one stage coagulation factor assays (aPTT modification with Actin FS) decreased to 26.6%, 9.9%, 11.4% and 34.3%, respectively (Table 1). Factor VIII and IX activity in chromogenic tests was within normal range: 155.8% and 102.7%, respectively. The presence of lupus anticoagulant, anti-cardiolipin antibodies and anti-β2-glycoprotein I antibodies in IgG and IgM was excluded. In a follow-up study 2 weeks later the results were similar: aPTT was prolonged with both reagents; factor VIII, IX, XI and XII activity

assessed with the one-step method decreased to 33.5%, 13.4%, 12.6% and 34.7%, respectively; factor VIII and IX activity in chromogenic method was normal: 160.8% and 120.7%, respectively. In the Nijmegen modification of the Bethesda assay, factor XI inhibitor was estimated at 22.1 BU/mL. No autoantibodies to factors VIII, IX and XII were detected; the inhibitor titer for all factors was below 0.6 BU/ml. Acquired hemophilia C (the presence of autoantibodies to factor XI) was diagnosed. All tests were performed with reagents from Siemens (Erlangen, Germany) and BCS XP analyzer (Siemens, Erlangen, Germany). Anti-cardiolipin and anti-β2-glycoprotein I antibodies in IgG and IgM class were assessed using Quanta Lite ACA IgG/IgM and Quanta Lite aβ2GPI IgG/IgM immunoenzymatic kits (Inova Diagnostics, San Diego, USA).

The administered prednisone dose was reduced to 0.5 mg/kg, because of age and comorbidities. After 8 weeks, FXI activity increased to 25% and FVIII, FIX and FXII activity was normal. Prednisone was poorly tolerated; the patient complained of weakness, dizziness, and exacerbation of depression and diabetes (insulin therapy was required). No bleeding events were reported during the observation period, so the dose was reduced and then the steroid therapy was discontinued. The patient was informed about the possibility of bleeding and received a written instruction for immediate administration of recombinant active factor VII if bleeding occurs. During 15 months of follow-up no bleeding complications were observed. Factor XI activity gradually decreased to 11%. The FXI inhibitor titer is now 15 BU/mL.

Discussion

Isolated aPTT prolongation may be related to the presence of unfractionated heparin, lupus anticoagulant and congenital or acquired deficiencies of coagulation factors VIII, IX, XI, XII. To differentiate between isolated deficiency of one of the coagulation factors and the presence of inhibitors, a correction (mixing) test with normal plasma is required. No aPTT correction is also observed in the presence of lupus anticoagulant, therefore, to confirm the diagnosis of AHA, it is necessary to measure the activity of the coagulation factor and perform the Bethesda test for the presence of neutralizing antibodies. Sometimes the inhibitor of one coagulation factor interferes with the activity of other factors through decreasing their activity (false-positive results). The same may also occur in the presence of lupus anticoagulant. To eliminate the effect of inhibitor or LA on the readings of coagulation factors activity in one stage assays, the measurements can be made in a diluted test sample. It is also possible to use LA-insensitive reagent or chromogenic assays (available for factor VIII and IX) for measuring aPTT. Clinical data on acquired FXI disorder is rather scarce and the course of the disease is difficult to predict [11]. Our observations fit in with reports on asymptomatic, accidentally diagnosed cases [11, 12]. In the described case, the patient was not subjected to any invasive procedures and suffered no trauma during the observation period; the clinical course of her disease cannot therefore be fully presented.

Author contribution statements

TI — author of design, methods, research, data analysis, manuscript preparation; JZ — clinical evaluation of the patient, data analysis, contribution to manuscript approval; TS — final manuscript approval.

Conflict of interest: none declared.

References

1. Zdziarska J, Musiał J. Acquired hemophilia A: an underdiagnosed, severe bleeding disorder. Pol Arch Med Wewn. 2014; 124(4): 200–206, doi: 10.20452/pamw.2192, indexed in Pubmed: 24658664.
2. Tiede A, Collins P, Knoebl P, et al. International recommendations on the diagnosis and treatment of acquired hemophilia A. Haematologica. 2020; 105(7): 1791–1801, doi: 10.3324/haematol.2019.230771, indexed in Pubmed: 32381574.
3. Bortoli R, Monticielo OA, Chakr RM, et al. Acquired factor XI inhibitor in systemic lupus erythematosus-case report and literature review. Semin Arthritis Rheum. 2009; 39(1): 61–65, doi: 10.1016/j.semarthrit.2008.03.005, indexed in Pubmed: 18519152.
4. Reece E. Spontaneous factor XI inhibitors. Arch Intern Med. 1984; 144(3): 525, doi: 10.1001/archinte.1984.00350150119031.
5. Kyriakou DS, Alexandrakis MG, Passam FH, et al. Acquired inhibitors to coagulation factors in patients with gastrointestinal diseases. Eur J Gastroenterol Hepatol. 2002; 14(12): 1383–1387, doi: 10.1097/00042737-200212000-00016, indexed in Pubmed: 12468962.
6. McManus MP, Frantz C, Gailani D. Acquired factor XI deficiency in a child with membranoproliferative glomerulonephritis. Pediatr Blood Cancer. 2012; 59(1): 173–175, doi: 10.1002/pbc.23287, indexed in Pubmed: 21850674.
7. Goodrick MJ, Prentice AG, Copplestone JA, et al. Acquired factor XI inhibitor in chronic lymphocytic leukaemia. J Clin Pathol. 1992; 45(4): 352–353, doi: 10.1136/jcp.45.4.352, indexed in Pubmed: 1577975.
8. Jethava Y, Alamelu J, Rangarajan S, et al. Acquired agranulocytosis and factor XI deficiency in association with thymoma. J Clin Oncol. 2011; 29(20): e604–e606, doi: 10.1200/JCO.2010.34.3707, indexed in Pubmed: 21537052.
9. Andreani G, Uscello L, Montaruli B, et al. Acquired factor XI deficiency during SARS-CoV-2 infection: not only thrombosis. TH Open. 2020; 4(3): e233–e235, doi: 10.1055/s-0040-1714696, indexed in Pubmed: 32939441.

10. Wheeler AP, Gailani D. Why factor XI deficiency is a clinical concern. Expert Rev Hematol. 2016; 9(7): 629–637, doi: 10.1080/17474086.2016.1191944, indexed in Pubmed: 27216469.
11. W Collins P, Chalmers E, Hart D, et al. United Kingdom Haemophilia Centre Doctors' Organization. Diagnosis and management of acquired coagulation inhibitors: a guideline from UKHCDO. Br J Haematol. 2013; 162(6): 758–773, doi: 10.1111/bjh.12463, indexed in Pubmed: 23889317.
12. Cugno M, Gualtierotti R, Tedeschi A, et al. Autoantibodies to coagulation factors: from pathophysiology to diagnosis and therapy. Autoimmun Rev. 2014; 13(1): 40–48, doi: 10.1016/j.autrev.2013.08.001, indexed in Pubmed: 23954454.