Acquired haemophilia A imitating uterine tumour in a patient with *de novo* diagnosis of hepatitis C

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Dear Editor,

We would like to present a case report of a patient diagnosed with acquired haemophilia A (AHA) in the perioperative period.

AHA is an extremely rare disorder, with annual incidence of 1.5 cases per million people [1, 2]. This clinical entity is caused by autoantibodies directed against coagulation factor VIII, leading to decreased serum activity of thereof [3], and is characterized by spontaneous, trauma-induced bleeding, or that caused by an invasive procedure [4]. Approximately 50% of cases are idiopathic in origin, affecting both sexes, with a median age at diagnosis of 74 years [5, 6].

CASE HISTORY/EXAMINATION

A forty-nine-year-old female was scheduled for laparotomy due to a uterine tumour of an unknown origin and this structure was shown in a computed tomography (CT) of the abdominal cavity. Her medical history (including history, of trauma) was insignificant. She denied having any drug history while reporting an allergy to metamizole. During during the procedure (30th Oct) no uterine tumour was detected, instead a large organised haematoma adjacent to the posterior uterine wall and a left ovary cyst were found, the haematoma was evacuated while the left ovary cyst was resected. Directly after the procedure, the patient was successfully extubated and transferred to the Department of Gynaecology and Obstetrics. Six hours later the patient became hypotonic, increased drainage of blood from the peritoneal cavity was observed and an exploratory re-laparotomy was performed (31st Oct). However, no obvious source of bleeding was found. Following the second surgical intervention, the patient was transferred to the Intensive Care Unit (ICU). On admission to the ICU the patient was sedated, intubated, mechanically ventilated and, as the patient was haemodynamically stable, no vasopressors were required. There was minimal amount of blood in the drains implanted into peritoneal cavity while the surgical dressing was clean. Sedation was terminated and the patient was extubated following a local protocol.

DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS AND TREATMENT

As the primary surgery revealed a large organised haematoma and no uterine tumour, we concluded that there may have been some sort of coagulopathy present prior

Table 1. Standard laboratory tests of coagulation on admission to the ICU

Parameter	Result	Reference value
Platelets	198	130–400 G L⁻¹
Fibrinogen	365	200–393 mg dL⁻¹
aPTT	56.3	25.4–36.9 s
INR	1.16	0.8–1.2
PT	13.1	9.4–12.5 s
Prothrombin Activity	80	80–120 %
D-dimers	669	< 500 ng mL⁻¹

aPTT: activated partial thromboplastin time; INR: international normalised ratio; PT: prothrombin time

to the primary surgery. The fact that there was no obvious source of bleeding revealed during the exploratory re-laparotomy only increased our suspicion of an unspecified coagulopathy. Following two surgical procedures with significant blood loss, haemodilution and consumption coagulopathy might have been aggravating factors. The standard laboratory tests of coagulation on admission to the ICU are presented in Table 1. The results revealed insignificant changes in prothrombin time (PT) and D-dimers, whereas the activated partial thromboplastin time (aPTT) was 1.52 times the upper range limit. Isolated prolongation of aPTT refuted a diagnosis of haemodilution and consumption coagulopathy. The differential diagnosis included deficiency of coagulation factor VIII, IX, XI, XII, high-molecular weight kininogen, prekalikrein or the presence of an inhibitor. Due to excessive bleeding, another explorative laparotomy was performed (1st Nov) and, at this point, haemostatic packing was used. A haematology consultation was requested. As there was no correction of aPTT following fresh frozen plasma (FFP) transfusion, we suspected the presence of an inhibitor. The presence of lupus anticoagulant affecting multiple intrinsic coagulation factors was refuted, as it is associated with thrombosis. By working through the laboratory diagnostic algorithm (Fig. 1), the presence of an inhibitor to factor VIII was suspected. Despite there being no information on coagulopathy in the patient's notes before surgical interventions, during in-depth history taking in the ICU, the patient reported signs of coagulopathy (ecchymoses on arms, excessive menstrual bleeding) during during the period of three months before hospitalisation in the ICU. The patient's relatives submitted additional documentation that revealed two deranged historical results of aPTT test (98 s, 102 s), with PT and fibrinogen concentration within normal values and a negative test result for lupus anticoagulant. To confirm the diagnosis, we performed a correction mixture test that revealed the presence of an inhibitor (aPTT following mixture with normal plasma was 97.4 s). The activity of factor VIII was as low as 1.2%/1.2 IU dL⁻¹ (reference value: 50–150%/50–150 IU dL⁻¹). The serum concentration

of inhibitor was 5.6 U mL^{-1} (Bethesda method) [7]. Upon confirmation of AHA we started disease-specific treatment according to the haematology consultation. Immunosuppressive therapy with methylprednisolon (Solu-Medrol, Pfizer Europe, Kent, Great Britain) in the dose of 1 mg kg^{-1} once daily was introduced. In order to prepare the patient for removal of haemostatic packing (3rd Nov), 0.1 mg kg^{-1} of recombinant activated factor VII (rFVIIa, Novoseven, Novo Nordisk, Bagsværd, Denmark) along with 1 g of tranexamic acid (Exacyl, Sanofi-Aventis, Paris, France) was given following the induction of anaesthesia, rFVIIa was repeated after 4 h, followed by activated prothrombin complex concentrate (aPCC, FEIBA NF, Baxter, Poland) in the maximum dose of 100 U kg^{-1} twice daily. As there was no cessation of bleeding in the postoperative period (bleeding at the site of central line insertion, bleeding at the site of removed peritoneal drains), we continued the patient on the maximum dose of aPCC. As the patient tested positive for the anti-hepatitis C virus antibody (anti-HCV), we ordered a confirmatory test [real time-PCR (Polymerase Chain Reaction)], that confirmed the presence of HCV-RNA (Ribonucleic Acid). There were signs of paralytic ileus following surgery which was managed medically with metoclopramide. Despite maximum dosing of aPCC, subsequent imaging showed new haematoma located anteriorly to the left kidney which was decided to be managed conservatively due to extremely high risk of bleeding complications. The newly-developed haematoma was a potential source of infection and, with no options to remove it, we decided to start the patient on a pathogen-targeted (Staphylococcus haemolyticus, Methicillin-Resistant Coagulase-Negative Staphylococcus, MRCNS) antibiotic (Vancomycin Kabi, Fresenius Kabi, Poland) and continued
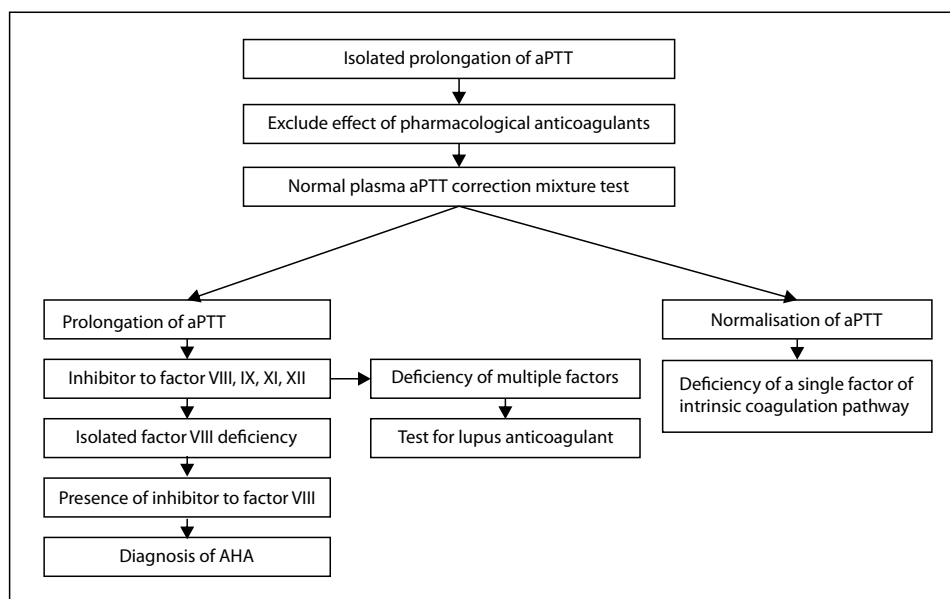

Figure 1. Proposed laboratory diagnostic algorithm for acquired haemophilia A

Table 2. Standard laboratory tests of coagulation during hospitalisation in the ICU

Parameter	03.11.	04.11	05.11	06.11	07.11	08.11	09.11	10.11	11.11	12.11	13.11	14.11	15.11	16.11
Platelets [G L^{-1}]	68	44	32	125	147	246	331	489	580	589	656	581	475	484
Fibrinogen [mg dL^{-1}]	464	371	196	163	130	176	192	171	175	133	145	117	105	138
aPTT [s]	78.6	96.4	89	76.6	92	91	104	57.4	57.8	40.5	47.8	40.1	43.5	39.2
INR	0.89	0.96	0.95	0.96	1.10	1.01	1.14	1.14	1.10	1.20	1.22	1.05	1.17	1.06
PT [s]	10.0	10.0	10.7	10.9	12.4	11.4	12.9	12.9	12.4	12.8	14.0	11.9	13.2	12.0
Prothrombin Activity [%]	122	122	109	106	87	99	82	82	87	83	74	92	79	91
D-dimers [ng mL^{-1}]	3864	2460	11439	7162	19444	29846	17658	17417	12169	13453	11801	7638	4479	5956

aPTT: activated partial thromboplastin time; INR: international normalised ratio; PT: prothrombin time; reference values as in Table 1

this treatment for 10 days. Antibiotic sensitivity testing of the MRCNS showed Minimum Inhibitory Concentration (MIC) over Break-Point (BP) for vancomycin of 1.5. As soon as clinical signs of bleeding stopped, the dose of aPCC was reduced to 50 U kg^{-1} twice daily, followed by 50 U kg^{-1} once daily. There was a trend for shorter aPTT with treatment (Table 2). The patient occasionally required transfusion of platelets (trigger: < 50 G L^{-1}) and fibrinogen (trigger: < 150 mg dL^{-1}). As the patient was at high risk for venous thromboembolic (VTE) complications (postoperative period, immobilisation, treatment with coagulation factors), we decided to perform daily ultrasound screening for deep vein thrombosis. Mechanical prophylaxis of VTE in the form of compression stockings was introduced at admission to the ICU.

OUTCOME AND FOLLOW-UP

As soon as clinical signs of bleeding subsided and there was no progression in the size of the haematoma, the patient was encouraged to start rehabilitation activities out of bed. Due to deranged peristalsis the patient was continued on parenteral nutrition until discharge. After 16 days of hospitalisation in the ICU the patient was transferred to the Department of Haematology and Bone Marrow Transplantation of the Medical University of Silesia in Katowice for further treatment. According to documentation from the aforementioned department, the patient received a single dose of aPCC, factor VIII activity increased to 59.9%, there was no inhibitor detected, intravenous methylprednisolone was switched to oral prednisone (Encorton, Polfa S.A., Poland). After 8 days of hospitalisation in the Department of Haematology the patient was discharged home.

DISCUSSION

Although acquired haemophilia A is an extremely rare disorder, hospital doctors should be cognisant of its characteristic features and sustain a high degree of suspicion when a patient without individual or family history of coagulopathy presents with an isolated prolongation of aPTT [2]. Diagnosis of AHA in the perioperative period complicates the perioperative course of patients and constitutes a direct threat to life due to bleeding. Our patient was primarily scheduled for non-elective laparotomy for a uterine tumour that was suspected to be causing bleeding into peritoneal cavity as a drop in haemoglobin concentration was observed. However, the tumour seen on the CT scan was, in fact, a large peritoneal haematoma caused primarily by AHA. In patients with undiagnosed AHA, this clinical scenario is common, with laparotomy due to an abdominal cavity tumour being performed only to discover that the tumour is actually a retroperitoneal haematoma. Treatment of AHA is directed at management of bleeding and elimination of the inhibitor. In the above-presented case we used both rFVIIa and aPCC to control bleeding and maximal recommended doses were administered for 10 days. To eliminate the inhibitor we used methylprednisolone. Although it is more common to use oral prednisone, due to paralytic ileus we were not able to use this route of administration, prolonged paralytic ileus was most likely a consequence of a retroperitoneal haematoma. Our patient achieved full remission, defined as an increase in factor VIII activity to above 50%.

CONCLUSIONS

When faced with abnormal results of coagulation tests in the perioperative period it is imperative to find its causes and all elective procedures should be postponed. Haematology consultation should be requested if there is diagnostic uncertainty. In the presence of isolated prolongation of aPTT in a patient without history of inherited coagulopathy, one should suspect acquired haemophilia A. In patients with de novo diagnosis of acquired haemophilia A all invasive procedures are contraindicated.

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