Compartment syndrome of the forearm with life-threatening bleeding after fasciotomy as the presenting sign of postpartum acquired hemophilia A: a case report

Marie Van Laer[a], Andrea Penaloza[a], Willem Stockman[c], Philippe Meert[a], Catherine Lambert[b] and Cédric Hermans[b]

Acquired hemophilia A (AHA) is a rare bleeding disorder caused by the development of autoantibodies against clotting factor VIII. Although the cause of this disorder remains obscure, it is often linked to malignancies, drug administration, autoimmune diseases and pregnancy. In pregnancy-associated AHA, hemorrhagic symptoms usually present 1–4 months peripartum, however they may occur up to 1-year postpartum. Compartment syndrome of the forearm is also very uncommon complication of AHA but can have devastating consequences. We report a rare case of a compartment syndrome of the forearm in a 30-year-old woman 2.5 months postpartum as the presentation of pregnancy-associated AHA. *Blood Coagul Fibrinolysis* 30:120–126 Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

Blood Coagulation and Fibrinolysis 2019, **30**:120–126

Keywords: acquired hemophilia A, bleeding disorder, compartment syndrome, hemorrhagic shock, peripartum acquired hemophilia A, pregnancy

[a]Division of Emergency Medicine, [b]Division of Hematology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels and [c]Division of Critical Care Medicine, AZ Delta Hospital, Roeselare, Belgium

Correspondence to Cédric Hermans, MD, PhD, FRCP (Lon, Edin), Division of Adult Haematology, St-Luc University Hospital, Avenue Hippocrate 10, 1200 Brussels, Belgium
Tel: +32 2 64 17 85/+32 2 764 17 40; fax: +32 2 764 89 59;
e-mail: cedric.hermans@uclouvain.be, hermans.cedric@gmail.com

Received 4 July 2018 **Revised** 1 February 2019
Accepted 1 February 2019

Introduction

Acquired hemophilia A (AHA) is a rare bleeding disorder caused by the development of autoantibodies against clotting factor VIII (FVIII). The incidence is 1.3–1.5 persons per million each year and increases with age until 70–80 years [1–8]. AHA is probably under-reported. In contrast to congenital hemophilia, where hemarthroses are the most common bleeding symptom, the hemorrhages in AHA more commonly involve the skin, mucous membranes and muscles [5]. Although the cause of this disorder remains obscure, it is often linked to malignancies, drug administration, autoimmune diseases and rarely, pregnancy [9–12,14].

Pregnancy-associated AHA (P-AHA) hemorrhagic symptoms mostly present 1–4 months peripartum, however they may occur up to 1-year postpartum [15,16]. The most common presentations are bleeding in the skin or muscles, hematuria, hematemesis or melena and prolonged postpartum or postoperative bleeding [5]. These complications may be life or limb threatening but can oftentimes be prevented by early diagnosis and appropriate therapy [15,24]. In P-AHA, FVIII inhibitor may be transferred via the placenta to the fetus causing bleeding disorders, such as intracranial bleeding, in the newborn [17,18,61].

AHA should be suspected when a patient with no previous history of bleeding presents with bleeding and an unexplained prolonged activated partial thromboplastin time (aPTT) [20,21]. The diagnosis is confirmed when low plasma FVIII activity is present together with a FVIII inhibitor, as shown on the Bethesda assay [16,19]. Negative testing for lupus anticoagulant is important because it is the most common cause of isolated prolonged aPTT, it can act as a (fast reacting) inhibitor in aPTT mixing studies and even sometimes results in an artificially low FVIII activity (in one-stage clotting tests and in chromogenic substrate assays) [22]. Clinically lupus anticoagulant causes more a thrombophilic state. Therefore, lupus anticoagulant should be considered as a priority differential diagnosis, particularly in patients who do not bleed [22]. But one should know that patients with AHA may have concomitant lupus anticoagulant [63–65].

It may also cause false-positive results in the Bethesda Assay (inhibitor detection and quantification), but less common with the Nijmegen modification due to the use of immunodepleted plasma [22]. Lupus anticoagulant can be excluded in most patients by specific tests as the diluted Russel viper venom time based assays [62] that use snake venom to activate factor X and induce clotting in the presence of phospholipids and calcium [22]. On the contrary, no tests are available that can fully discriminate between the two types of immunoglobulins [66]. Most phospholipid-depending coagulation tests are sensitive both to lupus anticoagulant and to inhibitors to FVIII [67–70], and therefore the results strongly depend on the type of test used [71].

Case report

A 30-year-old woman was seen in our emergency department (ED) because of progressive muscle pain and firmness

DOI:10.1097/MBC.0000000000000799

of the right forearm. Two days before admission she developed muscle pain in her right forearm after playing the piano. That day, and again the day of admission, she visited an osteopath who relaxed the muscles of her forearm by manipulation. However, gradually she noticed more pain and tingling in the 4th and 5th finger of the right hand, and visited the ED. One week before admission, she had developed a muscular pain in her left calf for which she also received a manipulation with the appearance of a descending hematoma around the ankle, now in resolution. Two and a half months before admission, she gave birth to a healthy baby. She reported no other medical history, no regular medications, and no allergies.

She was in good health and in no acute distress with normal vital signs. Her physical exam was unremarkable except for a moderate hematoma on the right forearm in its distal third and a nonpainful hematoma around the left ankle with a soft, nontender left calf. The whole forearm was firm and very tender with good capillary refill in the fingers. Radial and ulnar pulses were present. Active flexion and extension of the fingers was possible but very painful, as was passive extension. She had diminished sensation in the ulnar dermatome. The blood results of electrolytes, bicarbonate, renal-function, glucose and albumin were normal. The creatine kinase was 287 U/l, the white-cell count was 10 710/μl and the platelet count ($418 \times 1000/\mu l$) was normal.

She subsequently described paresthesia in fingers 1–3. Compartment pressure measurements in the superficial volar and dorsal compartments (Stryker Surgical, Kalamazoo, MI, USA) both revealed a pressure of 100 mmHg. A compartment syndrome was diagnosed. She was transferred to the operating theatre for fasciotomies.

Postoperatively, the patient described recurring paresthesia and paresis in the fingers. The fasciotomies were revised and extended. Because of oozing, a rotational thromboelastogram was performed and the tests [FIBTEM: maximum clot firmness of 18 mm (normal 9–25 mm) and EXTEM: clotting time of 53 s (normal 38–79 s), clot formation time of 55 s (normal 34–159 s), maximum clot firmness of 69 mm (normal 50–72 mm) and maximum lysis of 2% (normal <15%)] were normal. The INTEM-test (information on the intrinsic coagulation pathway) was not performed. Since, during surgery, dilution coagulopathy can usually be detected by EXTEM, INTEM is not routinely performed in our institution in a healthy young person. The multiplate whole blood aggregometry tests (Roche Multiplate analyser; Roche® Diagnostics International Ltd, Rotkreuz, Switzerland) were normal except for the ASPI test who was 204 (normal range 505–1086), suggesting the intake of aspirin or other nonsteroidal anti-inflammatory drugs, which she confirmed. No routine coagulation-tests [aPTT, prothrombin time (PT)] were unfortunately sent to the lab at that moment.

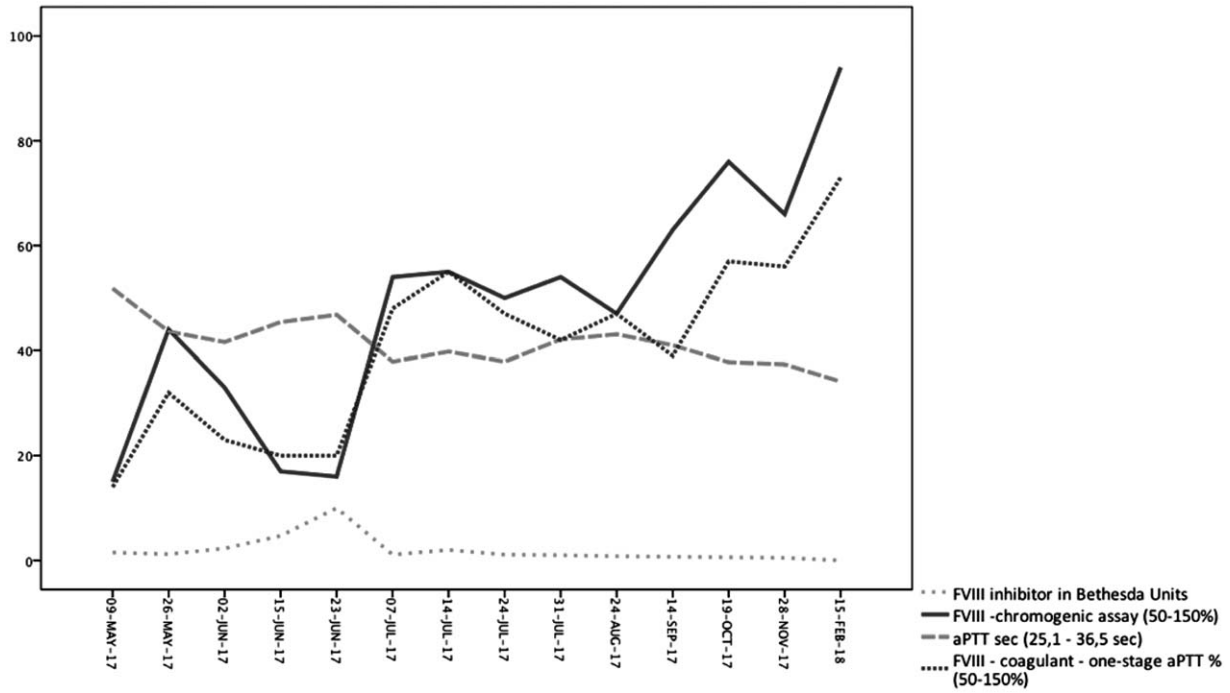
On the 3rd day, the wounds were still oozing, she was hypotensive and the hemoglobin level dropped to 5.9 g/dl. Routine coagulation tests were ordered and 1 g of tranexamic acid was given intravenously with red cell transfusion and fresh frozen plasma. The PT, international normalized ratio and thrombin time were normal. The activated partial thromboplastin time (aPTT; 25.1–36.5 s) was prolonged to 51.8 s. Fibrinogen level (normal range 150–450 mg/dl) was high normal 466 mg/dl. An urgent hematology consult was asked.

An in-depth anamnesis now revealed a mandibular osteotomy and wisdom teeth extraction without bleeding problems some years ago. She had a normal first pregnancy, with delivery under uncomplicated epidural analgesia and a vacuum-assisted vaginal delivery with uterine revision for retained placenta 2.5 months ago. An aPTT was normal 3 weeks before delivery. She now reveals that 4 days before current admission, she had woken up with a blood clot in her mouth.

Coagulation factors and inhibitors testing revealed a deficit in the activity of FVIII (14% one-stage aPTT and 15% on chromogenic assay) and factor XII (30%) and the presence of a FVIII inhibitor [142 Bethesda Units (BU)/ml]. Based on these results and the exclusion of lupus and other systemic diseases a diagnosis of P-AHA was established. The rationale for using both one-stage clotting assay (measures the extent a plasma sample corrects the coagulation time of FVIII deficient plasma in an aPTT based assay) and chromogenic assay (where patient plasma is added to a reaction mixture consisting of thrombin or prothrombin, factors IXa, X, calcium and phospholipid and were then factor Xa production is assumed to be proportional to the amount of functional FVIII present in the sample) for measuring FVIII activity is because chromogenic FVIII assay does not show interference with lupus anticoagulant and because there may be a discrepancy between both results. Sometimes FVIII activity may appear to be higher in a one-stage clotting assay. But the bleeding phenotype of this patient is more closely related to the lower FVIII activity.

She was treated with methylprednisolone 60 mg once a day, recombinant factor VII activated (rFVIIa) 5 mg (90 μg/kg/injection) every 3 h intravenous and tranexamic acid 1 g three times daily intravenous until stabilized, and afterwards as needed in terms of surgical acts and bleeding. She underwent multiple surgeries of her forearm for approaching the wound margins and eventually skin grafting. She left the hospital after a total hospitalization time of 17 days, with a treatment of steroids and oral tranexamic acid. One month after diagnosis, a concomitant treatment with rituximab (four doses in total) was started since FVIII activity was still decreasing (Fig. 1). In addition, the FVIII inhibitor peaked 1.5 months after diagnosis at 162 BU/ml (Fig. 2). At 3 months, because of favorable evolution (FVIII levels of 42% by

Fig. 1



Time–course of laboratory assays from diagnosis to cure.

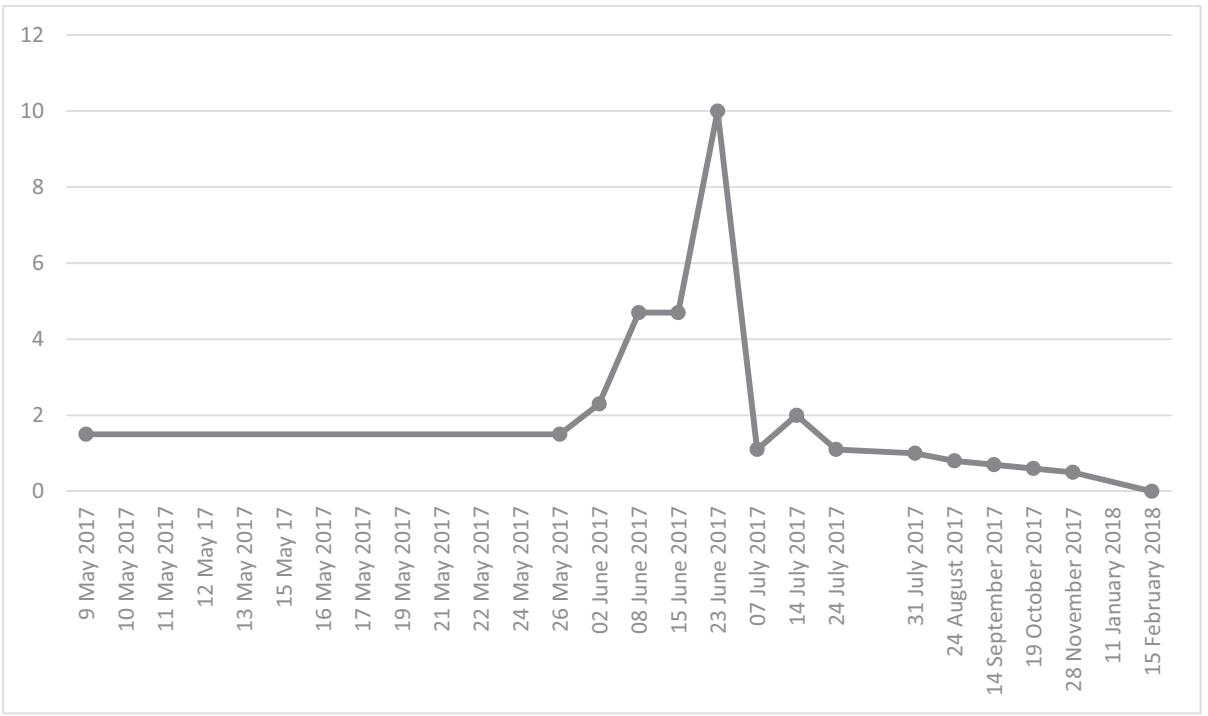
one-stage assay and 54% by chromogenic assay – FVIII inhibitor of 164 BU/ml), treatment with steroids was tapered and stopped and replaced by cyclophosphamide. 2.5 months later, she was neutropenic, without fever or infection for which the treatment was interrupted for 2 weeks. A month after restarting cyclophosphamide, she felt unwell and had hair loss. Because of these complications and normalizing lab data, FVIII level was normalized 5 months after diagnosis (57% by one-stage assay and 76% by chromogenic assay), therapy was finally stopped 6.5 months after diagnosis. She remained in follow-up with monthly monitoring of the FVIII activity (by one-stage and by chromogenic assay), a FVIII-inhibitor screening (by Nijmegen modification of the Bethesda assay) and a hemogram until undetectable FVIII inhibitor 9 months after diagnosis. At that time FVIII level raised to 73% by one-stage assay and 94% by chromogenic assay. She still has some functional disability of her right forearm, but could restart her job.

Discussion

P-AHA typically presents in women with no family or personal history of abnormal bleeding [9,25–27], mostly primagravidas [24]. Delay in diagnosis and initiation of appropriate treatment may increase morbidity and mortality, therefore awareness of this rare bleeding disorder is important [24]. Typical presentation consists of abnormal bleeding in association with a prolonged aPTT, findings which should prompt investigation for (P-)AHA [20,21]. The European Acquired Haemophilia registry (EACH2 registry), that published data of 501 patients from 117 centers in 13 European countries, has shown that delay in the initiation of the appropriate investigation and in the recognition of the significance of a prolonged aPTT occur in a significant proportion of P-AHA patients [24]. In our case, a test to reveal the function of the intrinsic pathway of the coagulation cascade (INTEM or aPTT) was only performed on the 3rd day of hospitalization. In the EACH2 registry, the diagnosis was triggered by abnormal bleeding in all of the cases, most commonly in the skin, mucous membranes and muscles [5]. Intracranial hemorrhages may also occur [28,29]. In our case, there was a presentation with skin hematomas and compartment syndrome first attributed to manipulation by an osteopath, which delayed diagnosis. Among the EACH2 P-AHA cohort, the first reported bleeding episode began at a median of 2.5 months postpartum [24], exactly as in our patient. In very few cases bleeding already started during or even before delivery [24].

The reason why P-AHA usually presents postpartum is not known. A plausible hypothesis is that the mother is exposed to fetal FVIII during delivery [30]. P-AHA might have a complete different pathogenesis than AHA. Investigators found that, in P-AHA, antibodies are often of the IgG1 and IgG3 subclass whereas in non-P-AHA patients

Fig. 2



Time course of factor VIII inhibitor titer (Nijmegen–Bethesda technique) [Bethesda Units (BU)].

more often of the IgG4 subclass. Hence, a Th1-driven response in the generation of autoantibodies in P-AHA compared with Th2 in the non-P-AHA presentations [31]. However, in the EACH2 registry in some women (17%), P-AHA was already present prior to delivery, suggested by the formation of antibodies prior to delivery [24]. Since in our patient, an aPTT was normal 3 weeks before delivery and no bleeding problems were reported at delivery, it is unlikely P-AHA was already present antepartum.

Although no patient died in the P-AHA cohort, probably due to younger age and fewer comorbidities, the mortality rate from bleeding in the entire AHA EACH2 cohort was 3% and the overall mortality 20% [24].

Relapse occurs and therefore monitoring of the levels (monthly the aPTT and FVIII levels during the first 6 months, then every 2–3 months up to 12 months and every 6 months during the 2nd year and beyond, if possible) [20] and close follow-up are advised. It is advised to follow FVIII activity by both one-stage and chromogenic assay, as they may differ. In addition, the clinical FVIII activity correlates most with the lowest value. In literature, more often chromogenic FVIII activity assays gave lower values. But in our patient, there was a lot of variation. In the beginning, the one-stage assay showed the lowest values. At the moment of the peak of the FVIII inhibitor value, 1.5 month after diagnosis, chromogenic assay showed the lowest FVIII activity values. When the FVIII inhibitor titers again went down, one-stage FVIII activity assay gave the lowest values until eradication of the inhibitor.

Although relapse during subsequent pregnancies is uncommon [27], data concerning future pregnancies of women with P-AHA are limited and conflicting. It is reasonable that women with a history of (P-)AHA be followed by a hematologist and screened for aPTT prolongation in the peripartum period [35].

The mainstay of treatment for (P-)AHA is to avoid and stop bleeding, administration of hemostatic agents if needed, eradication of the inhibitor with immunosuppressive therapy (IST) and treatment of underlying diseases if present [23]. Invasive procedures should be avoided and if urgently needed, hemostatic therapy is required before and after the procedures [23]. There are two main options for hemostatic agents in patients with AHA: FVIII replacement therapy and the use of bypassing agents [2,13–15]. Two FVIII concentrates are available: human FVIII (hFVIII) and porcine FVIII (pFVIII). Among some patients AHA antibodies may be nonneutralizing, and continuous administration of FVIII concentrates may be beneficial as replacement therapy [35]. Porcine FVIII can achieve measurable FVIII levels and hemostasis, even if the human inhibitor is high [23,33]. Both have some cons: hFVIII is not effective in the

presence of high titer (>236 BU) inhibitors [36] and one can develop antiporcine FVIII antibodies during therapy [23]. The novel extended half-life FVIII concentrates such as B-domain deleted recombinant porcine factor VIII (rpFVIII) (OBI-1) are promising [32]. OBI-1 is an investigational, B-domain deleted, recombinant porcine FVIII with low cross-reactivity to antihuman FVIII antibodies. It was found to be safe and effective in treating bleeding episodes in 28 patients with AHA, but is not yet tested in P-AHA [33]. Most (P-)AHA patients with high titer inhibitors, will, however, require use of bypassing agents such as activated prothrombin complex concentrate (aPCC) and rFVIIa. They were shown to be superior to FVIII [24,38].

Other hemostatic agents include desmopressin and tranexamic acid (TCA). Desmopressin could release FVIII and Von Willebrand factor from endothelial cells, but this effect is unpredictable and may only suitable for minor bleeding with low inhibitor titers (<247 BU) [36–41]. TCA in combination with either aPCC or rFVIIa normalizes clot stability [44,45]. TCA can also be used topically for oral or skin bleeding [23].

Response to hemostatic therapy should be evaluated clinically [23]. The aPTT will normalize when replacement results in FVIII levels more than 30–50% but is not a predictor of supra-therapeutic levels and not a good marker to guide treatment [23]. Hemostatic agents should not be given in a patient with rising factor levels and no active or increased risk for bleeding. Among P-AHA patients safety of bypass therapy is of major concern, as the peripartum is a hypercoagulable state. The physiologic pregnancy-associated state induces increased thrombin generation, yielding an up to 60-fold increase in the relative risk of venous thromboembolism during the postpartum period [42,43]. Thromboembolism prophylaxis should therefore be considered in nonbleeding hospitalized patients were FVIII activity levels exceeds 50 IU/dl [23].

The second part of the treatment is inhibitor eradication by IST. Most low titer inhibitors tend to disappear spontaneously, whereas patients with high titer inhibitors may be difficult to treat [9,25,35]. In the majority of cases, the potency and the titer of the FVIII inhibitor in P-AHA are rather low [26,43]. The antibodies often display nonlinear FVIII inactivation, causing incomplete FVIII neutralization despite presence of high levels of active inhibitors [47]. The optimal therapeutic strategy to eradicate the inhibitor is unknown, but mostly steroids (prednisone) alone or in combination with cytotoxic agents (mostly cyclophosphamide) are used [34,48]. Current data suggest that the combination of both is more likely to result in a stable autoantibody eradication than steroids alone, but final outcome is not improved, possibly reflecting increased toxicity of the regimens involving cyclophosphamide [49]. In the overall EACH2 cohort of AHA, mortality and morbidity due to complications of IST is high [5]. Despite this, all women in the P-AHA subgroup of the EACH2 registry received IST, probably to reduce the length of time during which the women were at risk of severe hemorrhage [24]. In addition, one should keep in mind that cyclophosphamide is not safe during pregnancy or lactation. Rituximab is increasingly used and seems to be particularly attractive as it is well tolerated [50]. A review including 13 P-AHA patients treated with rituximab, when used as first-line or rescue therapy, obtained a stable complete response in all patients [51]. However, rituximab may cross the placenta and may cause lymphopenia at birth, as reported in neonates exposed to rituximab *in utero* [52].

A novel therapeutic agent, emicizumab, a bispecific antibody that possesses FVIII mimetic activity, has shown promise in the treatment of patients with hemophilia A, including patients with inhibitors [53]. It has not yet been used in P-AHA by our knowledge. High-dose intravenous immunoglobulins alone or in combination with steroids are no longer recommended [20].

Compartment syndrome of the forearm is rare but has been described in some series [54]. It is usually associated with trauma although other causes, such as crush injury, penetrating injury, burns occur. Typical symptoms are pallor, pain disproportional to clinical signs, pain with passive stretch, paresthesia and in late stages paralysis and pulselessness [55]. To preserve muscle and nerve function, the diagnosis should be made in an early stage [56]. Compartment syndrome can be suspected from the clinical history and signs and symptoms and can be confirmed by measuring compartment pressures. A pressure difference of 30 mmHg or less between DBP and compartment pressure is considered compatible with the syndrome [57–59]. However, pressure measurements are not necessary for the diagnosis and the above-mentioned cut-offs should be used cautiously. Treatment consists of urgent fasciotomies of the involved compartments by an experienced surgeon [60].

Conclusion

P-AHA is often underdiagnosed and misdiagnosed. A history of recent bleeding [46] or bruising (or a compartment syndrome as in our patient) associated with no or only moderate trauma, should alert the clinician. A prolonged aPTT further rises suspicion. Awareness of this pregnancy-associated disorder needs to be improved so that appropriate management can be initiated as soon as possible. FVIII activity should be monitored by both one-stage and chromogenic assay, as their values may differ in the course of the disease and earlier studies assume that the bleeding phenotype is more closely related to the lower FVIII-activity levels.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Green D, Lechner K. A survey of 215 nonhemophilic patients with inhibitors to factor VIII. *Thromb Haemost* 1981; **45**:200–203.
2 Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, Villar A. Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. *Br J Haematol* 2003; **121**:21–35.
3 Collins PW, Hirsch S, Baglin TP, Dolan G, Hanley J, Makris M, *et al.* Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. *Blood* 2007; **109**:1870–1877.
4 Tay L, Duncan E, Singhal D, Al-Qunfoidi R, Coghlan D, Jaksic W, *et al.* Twelve years of experience of acquired hemophilia A: trials and tribulations in South Australia. *Semin Thromb Hemost* 2009; **35**:769–777.
5 Knoebl P, Marco P, Baudo F, Collins P, Huth-Kühne A, Nemes L, *et al.* Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). *J Thromb Haemost* 2012; **10**:622–631.
6 Borg JY, Guillet B, Le Cam-Duchez V, Goudemand J, Levesque H. Outcome of acquired haemophilia in France: the prospective SACHA (Surveillance des Auto antiCorps au cours de l'Hemophilie Acquise) registry. *Haemophilia* 2013; **19**:564–570.
7 Huang SY, Tsay W, Lin SY, Hsu SC, Hung MH, Shen MC. A study of 65 patients with acquired hemophilia A in Taiwan. *J Formos Med Assoc* 2015; **114**:321–327.
8 Tiede A, Klamroth R, Scharf RE, Trappe RU, Holstein K, Huth-Kühne A, *et al.* Prognostic factors for remission of and survival in acquired hemophilia A (AHA): results from the GTH-AH 01/2010 study. *Blood* 2015; **125**: 1091–1097.
9 Michiels JJ. Acquired hemophilia A in women postpartum: clinical manifestations, diagnosis, and treatment. *Clin Appl Thromb Hemost* 2000; **6**:82–86.
10 Gheisari R, Bomke B, Hoffmann T, Scharf RE. Clinical features and outcome of acquired haemophilia A: interim analysis of the Dusseldorf study. *Hamostaseologie* 2010; **30**:156–161.
11 Franchini M, Zaffanello M, Lippi G. Acquired hemophilia in pediatrics: a systematic review. *Pediatr Blood Cancer* 2010; **55**:606–611.
12 Oldenburg J, Zeitler H, Pavlova A. Genetic markers in acquired haemophilia. *Haemophilia* 2010; **16 (Suppl 3)**:41–45.
13 Collins PW. Management of acquired hemophilia A. *J Thromb Haemost* 2011; **9 (Suppl 1)**:226–235.
14 Franchini M, Lippi G. Acquired factor VIII inhibitors. *Blood* 2008; **112**:250–255.
15 Collins PW, Percy CL. Advances in the understanding of acquired hemophilia A: implications for clinical practice. *Br J Haematol* 2009; **148**:183–194.
16 Kasper CK, Aledort L, Aronson D, Counts R, Edson JR, van Eys J, *et al.* Proceedings: a more uniform measurement of factor VIII inhibitors. *Thromb Diath Haemorrh* 1975; **34**:612.
17 Kotani Y, Shiota M, Umemoto M, Koike E, Tsuritani M, Hoshiai H. Case of acquired hemophilia with factor VIII inhibitor in a mother and newborn. *J Obstet Gynaecol Res* 2011; **37**:1102–1105.
18 Lulla RR, Allen GA, Zakarija A, Green D. Transplacental transfer of postpartum inhibitors to factor VIII. *Haemophilia* 2010; **16**:14–17.
19 Verbruggen B, Novakova I, Wessels H, Boezeman J, van den Berg M, Mauser-Bunschoten E. The Nijmegen modification of the Bethesda assay for factor VIII:C inhibitors: improved specificity and reliability. *Thromb Haemost* 1995; **73**:247–251.
20 Huth-Kuhne A, Baudo F, Collins P, Ingerslev J, Kessler CM, Levesque H, *et al.* International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. *Haematologica* 2009; **94**:566–575.
21 Collins P, Baudo F, Huth-Kuhne A, Ingerslev J, Kessler CM, Mingot Castellano ME, *et al.* Consensus recommendations for the diagnosis and treatment of acquired hemophilia A. *BMC Res Notes* 2010; **3**:161.
22 Tiede A, Werwitzke S, Scharf RE. Laboratory diagnosis of acquired hemophilia A: limitations, consequences, and challenges. *Semin Thromb Hemost* 2014; **40**:803–811.
23 Kruse-Jarres R, Kempton CL, Baudo F, Collins PW, Knoebl P, Leissinger CA, *et al.* Acquired hemophilia A: updated review of evidence and treatment guidance. *Am J Hematol* 2017; **92**:695–705.
24 Tengborn L, Baudo F, Huth-Kuhne A, Knoebl P, Lévesque H, Marco P, *et al.* Pregnancy-associated acquired haemophilia A: results from the European Acquired Haemophilia (EACH2) registry. *BJOG* 2012; **119**:1529–1537.
25 Hauser I, Schneider B, Lechner K. Postpartum factor VIII inhibitors. A review of the literature with special reference to the value of steroid and immunosuppressive treatment. *Thromb Haemost* 1995; **73**:1–5.
26 Solymoss S. Postpartum acquired factor VIII inhibitors: results of a survey. *Am J Hematol* 1998; **59**:1–4.
27 Baudo F, de Cataldo F. Acquired factor VIII inhibitors in pregnancy: data from the Italian Haemophilia Register relevant to clinical practice. *BJOG* 2003; **110**:311–314.
28 Micic D, Williams EC, Medow JE. Cerebellar hemorrhage as a first presentation of acquired hemophilia A. *Neurocrit Care* 2011; **15**:170–174.
29 Bonnaud I, Saudeau D, de Toffol B, Autret A. Recurrence of spontaneous subdural haematoma revealing acquired haemophilia. *Eur Neurol* 2003; **49**:253–254.
30 Franchini M. Haemostasis and pregnancy. *Thromb Haemost* 2006; **95**:401–413.
31 Lapalud P, Ali T, Cayzac C, Mathieu-dupas E, Levesque H, Pfeiffer C, *et al.* The IgG autoimmune response in postpartum acquired hemophilia A targets mainly the A1a1 domain of FVIII. *J Thromb Haemost* 2012; **10**:1814–1822.
32 Tiede A. Half-life extended factor VIII for the treatment of hemophilia A. *J Thromb Haemost* 2015; **13 (Suppl 1)**:S176–S179.
33 Kruse-Jarres R, St-Louis J, Greist A, Shapiro A, Smith H, Chowdary P, *et al.* Efficacy and safety of OBI-1, an antihaemophilic factor VIII (recombinant), porcine sequence, in subjects with acquired haemophilia A. *Haemophilia* 2015; **21**:162–170.
34 Pardos-Gea J, Altisent C, Parra R, Vilardell-Tarre's M, Ordi-Ros J. Acquired hemophilia A. First line treatment with calcineurin inhibitors and steroid pulses: a 10-year follow-up study. *Haemophilia* 2012; **18**:789–793.
35 Barg AA, Livnat T, Kenet G. An extra X does not prevent acquired hemophilia – pregnancy-associated acquired hemophilia A. *Thromb Res* 2017; **151 (Suppl 1)**:S82–S85.
36 Nemes L, Pitlik E. New protocol for immune tolerance induction in acquired hemophilia. *Haematologica* 2000; **85**:64–68.
37 Collins PW. Treatment of acquired hemophilia A. *J Thromb Haemost* 2007; **5**:893–900.
38 Baudo F, Collins P, Huth-Kühne A, Lévesque H, Marco P, Nemes L, *et al.* Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry. *Blood* 2012; **120**:39–46.
39 Batty P, Moore GW, Platton S, Maloney JC, Palmer B, Bowles L, *et al.* Diagnostic accuracy study of a factor VIII ELISA for detection of factor VIII antibodies in congenital and acquired haemophilia A. *Thromb Haemost* 2015; **114**:804–811.
40 Collins PW, Chalmers E, Hart DP, Liesner R, Rangarajan S, Talks K, *et al.* Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (4th edition). UK Haemophilia Centre Doctors Organization. *Br J Haematol* 2013; **160**:153–170.
41 Franchini M, Lippi G. The use of desmopressin in acquired haemophilia A: a systematic review. *Blood Transfus* 2011; **9**:377–382.
42 Marik PE, Plante LA. Venous thromboembolic disease and pregnancy. *N Engl J Med* 2008; **359**:2025–2033.
43 Pomp ER, Lenselink AM, Rosendaal FR, Doggen CJ. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. *J Thromb Haemost* 2008; **4**:632–637.
44 Hvas AM, Sorensen HT, Norengaard L, Christiansen K, Ingerslev J, Sorensen B. Tranexamic acid combined with recombinant factor VIII increases clot resistance to accelerated fibrinolysis in severe hemophilia A. *J Thromb Haemost* 2007; **5**:2408–2414.
45 Tran HT, Sorensen B, Rea CJ, Bjørnsen S, Ueland T, Pripp AH, *et al.* Tranexamic acid as adjunct therapy to bypassing agents in haemophilia A patients with inhibitors. *Haemophilia* 2014; **20**:369–375.
46 Franchini M. Postpartum acquired factor VIII inhibitors. *Am J Hematol* 2006; **81**:768–773.
47 Sakurai Y, Yakeda T. Acquired hemophilia A: frequently overlooked autoimmune hemorrhagic disorder. *J Immunol Res* 2014;320674.
48 Sborov DW, Rodgers GM. How I manage patients with acquired hemophilia A. *Br J Haematol* 2013; **161**:157–165.
49 Franchini M, Mannucci PM. Acquired haemophilia: a 2013 update. *Thromb Haemost* 2013; **110**:1114–1120.
50 Franchini M, Veneri D, Lippi G, Stenner R. The efficacy of rituximab in the treatment of inhibitor-associated hemostatic disorders. *Thromb Haemost* 2006; **96**:119–125.
51 Bonfanti C, Crestani S, Frattini F, Sissa C, Franchini M. Role of rituximab in the treatment of postpartum acquired haemophilia A: a systematic review of the literature. *Blood Transfus* 2015; **13**:396–400.
52 Hyrich KL, Verstappen SM. Biologic therapies and pregnancy: the story so far. *Rheumatology (Oxford)* 2014; **53**:1377–1385.
53 Shima M, Hanabusa H, Taki M, Matsushita T, Sato T, Fukutake K, *et al.* Factor VIII-mimetic function of humanized bispecific antibody in hemophilia A. *N Engl J Med* 2016; **374**:2044–2053.
54 Peters CL, Scott SM. Compartment syndrome in the forearm following fractures of the radial head or neck in children. *J Bone Joint Surg Am* 1995; **77**:1070.

55 Elliott KG, Johnstone AJ. Diagnosing acute compartment syndrome. *J Bone Joint Surg Br* 2003; **85**:625.

56 Tiwari A, Myint F, Hamilton G. Compartment syndrome. *Eur J Vasc Endovasc Surg* 2002; **24**:469.

57 Reneman RS, Slaaf DW, Lindbom L, Tangelder GJ, Arfors KE. Muscle blood flow disturbances produced by simultaneously elevated venous and total muscle tissue pressure. *Microvasc Res* 1980; **20**:307.

58 Wiederhielm CA, Weston BV. Microvascular, lymphatic, and tissue pressures in the unanesthetized mammal. *Am J Physiol* 1973; **225**:992.

59 Dahn I, Lassen NA, Westling H. Blood flow in human muscles during external pressure or venous stasis. *Clin Sci* 1967; **32**:467.

60 Sheridan GW, Matsen FA 3rd. Fasciotomy in the treatment of the acute compartment syndrome. *J Bone Joint Surg Am* 1976; **58**:112.

61 Ries M, Wolfel D, Maier-Brandt B. Severe intracranial hemorrhage in a newborn infant with transplacental transfer of an acquired factor VII:C inhibitor. *J Pediatr* 1995; **127**:649–650.

62 Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, De Groot PG. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. *J Thromb Haemost* 2009; **7**:1737.

63 Blanco AN, Cardozo MA, Candela M, Santarelli MT, Pérez Bianco R, Lazzari MA. Antifactor VIII inhibitors and lupus anticoagulants in haemophilia A patients. *Thromb Haemost* 1997; **77**:656–659.

64 Seethala S, Collins NP Jr, Comerci G Jr. An unusual etiology for elevation of activated partial thromboplastin time (aPTT) in SLE: acquired hemophilia and lupus anticoagulant. *Case Rep Hematol* 2013; **2013**:521785.

65 Taher A, Abiad R, Uthman I. Coexistence of lupus anticoagulant and acquired haemophilia in a patient with monoclonal gammopathy of unknown significance. *Lupus* 2003; **12**:854–856.

66 Verbruggen B, van Heerde WL, Laros-van Gorkom BA. Improvements in factor VIII inhibitor detection: from Bethesda to Nijmegen. *Semin Thromb Hemost* 2009; **35**:752–759.

67 Verbruggen B. Diagnosis and quantification of factor VIII inhibitors. *Haemophilia* 2010; **16**:20–24.

68 Chantarangkul V, Tripodi A, Arbini A, Mannucci PM. Silica clotting time (SCT) as a screening and confirmatory test for detection of the lupus anticoagulants. *Thromb Res* 1992; **67**:355–365.

69 Triplett DA, Barna LK, Unger GA. A hexagonal (II) phase phospholipid neutralization assay for lupus anticoagulant identification. *Thromb Haemost* 1993; **70**:787–793.

70 Exner T. Diagnostic methodologies for circulating anticoagulants. *Thromb Haemost* 1995; **74**:338–344.

71 Tripodi A, Mancuso ME, Chantarangkul V, Clerici M, Bader R, Meroni PL, *et al.* Lupus anticoagulants and their relationship with the inhibitors against coagulation factor VIII: considerations on the differentiation between the 2 circulating anticoagulants. *Clin Chem* 2005; **51**:1883–1885.