Acquired haemophilia A: a rare cause of postpartum haemorrhage

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A rare cause of postpartum haemorrhage (PPH) is acquired haemophilia A (AHA), a condition that arises from the production of auto-antibodies to Factor VIII. AHA is a rare condition with an incidence of 1–2/million people/year, with a biphasic distribution. The first peak is seen in younger people, predominantly women, and is associated with pregnancy and autoimmune disease. The second peak occurs in older adults (median age 64–78 years) with malignancy and autoimmune disorders, although 50% is idiopathic. AHA is associated with pregnancy, with a demonstrated incidence of 1/350,000 births in UK women.

AHA is diagnosed with an isolated prolonged aPTT in a woman with no history of bleeding problems, which does not correct with the addition of normal human plasma in 1:1 ratio. The reason it does not correct is because of the presence of an inhibitor (antibody), which also inactivates the factor VIII in the normal plasma. A measurement of coagulation factor levels and inhibitor levels is then undertaken and reported in Bethesda units (BU).

The presence of an isolated prolonged aPTT in a peri-partum woman who has no personal or family history of bleeding disorder should be considered AHA until proven otherwise.

Significant delay in diagnosis of AHA has been frequently observed, thought to be due to lack of clinician awareness, which may result in increased morbidity and mortality.

Case report

A 36-year-old multiparous woman (G7 P4) with four previous vaginal deliveries and no previous history of abnormal bleeding presented to North Shore Hospital with secondary postpartum haemorrhage (PPH) on Day 14 postpartum (PP). Her pregnancy was uneventful and the infant in good health. Ultrasound (USS) demonstrated retained products of conception (RPOC), subsequently evacuation of uterus was undertaken and bleeding settled. The patient was discharged.

She represented eight days later with a further massive PPH (EBL 1.8L); a further USS was undertaken and suggestive of arteriovenous malformation (AVM). Subsequent examination under anaesthetic and balloon tamponade was performed prior to transfer to a tertiary hospital where interventional radiology performed empirical arterial embolisation of bilateral distal uterine arteries; of note no AVM was identified. Multiple blood products were administered. Prior to discharge an abnormal aPTT of 60 sec was noted; this corrected with addition of normal plasma. Review was undertaken by general medicine and the elevated aPTT was thought to be secondary to multiple transfusions. The third admission for abnormal bleeding occurred on Day 30 PP resulting in a total abdominal hysterectomy and HDU admission. Haematology was consulted regarding the abnormal aPTT, which did not correct with the addition of normal plasma; factor and inhibitor levels were undertaken and the diagnosis of AHA was made on Day 32 PP, 16 days following the first presentation with abnormal bleeding and 10 days following the first abnormal aPTT. Lupus anticoagulant was negative. At the time of diagnosis aPTT 78s, Factor VIII assay 2%, Factor VIII inhibitor 8 BU (Table 1).

The patient received both haemostatic and immunosuppressive treatment under the care of haematology. Activated Factor VII (FVIIa) was administered for three days.
which was not effective; treatment was then changed to Factor Eight Bypassing Agent (FEIBA). Immunosuppressive treatment was with Prednisone and cyclophosphamide, with a dose of Ritixumab to which she developed an urticarial skin reaction. A trial of intragram was of no benefit. Slow improvement in aPTT and decrease in inhibitor levels occurred. One further episode of bleeding resulted in increased doses of FEIBA, in conjunction with tranexamic acid. Table 2 describes haematologic response to treatment.

The patient was discharged on Day 46 PP, Day 16 following the diagnosis of AHA, and remained on immunosuppressive therapy for eight weeks. Follow up over 14 months revealed no evidence of relapse.

**Table 1:** Summary of blood tests.

<table>
<thead>
<tr>
<th>Days postpartum</th>
<th>Hb</th>
<th>aPTT</th>
<th>Corrected with 1:1 plasma</th>
<th>Haematology</th>
<th>Blood products</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 (admission 1)</td>
<td>117</td>
<td>NA</td>
<td></td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>22 (admission 2)</td>
<td>82</td>
<td>73</td>
<td>Yes</td>
<td></td>
<td>5 units RRC, 4 units FFP</td>
</tr>
<tr>
<td>23</td>
<td>80</td>
<td>62</td>
<td>Yes</td>
<td>Lab comment: Recommend factor studies</td>
<td></td>
</tr>
<tr>
<td>30 (admission 3)</td>
<td>98</td>
<td>61</td>
<td>Partial</td>
<td>Lab comment: factor studies and LAC</td>
<td></td>
</tr>
<tr>
<td>32 Diagnosis AHA</td>
<td>90</td>
<td>78</td>
<td>Partial</td>
<td>Factor VIII 2% Factor VIII inhibitor 8BU Factor IX, XII normal vWF normal LAC normal ACL normal</td>
<td>3 units RRC, 4 units FFP, 1 unit FVIIa, Total RRC: 14 units</td>
</tr>
</tbody>
</table>

Table 1—activated partial thromboplastin time, LAC—Lupus anticoagulant, ACL—anticardiolipin, FVIIa—recombinant activated Factor 7, RRC—red resuspended cells, FFP—fresh frozen plasma.

<table>
<thead>
<tr>
<th>Days postpartum</th>
<th>aPTT</th>
<th>Factor VIII level (%)</th>
<th>Inhibitor level (BU)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>78</td>
<td>2</td>
<td>8</td>
<td>FVIIa</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prednisone/cyclophosphamide</td>
</tr>
<tr>
<td>37</td>
<td>64</td>
<td>3</td>
<td>14</td>
<td>FVIIa</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total FVIIa given-19 units. Prednisone/cyclophosphamide</td>
</tr>
<tr>
<td>40</td>
<td>69</td>
<td></td>
<td></td>
<td>FEIBA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prednisone/cyclophosphamide</td>
</tr>
<tr>
<td>45</td>
<td>54</td>
<td>4</td>
<td>4</td>
<td>FEIBA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prednisone/cyclophosphamide</td>
</tr>
<tr>
<td>51</td>
<td>49</td>
<td>26</td>
<td>0.8</td>
<td>FEIBA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FVIIa stopped. Total administered 40,000IU. Prednisone/cyclophosphamide</td>
</tr>
</tbody>
</table>

Table 2—activated partial thromboplastin time, FVIIa—activated Factor 7.
Figure 1: Algorithm for the diagnosis of patients with suspected acquired haemophilia.

- **Postpartum Haemorrhage**
  - Check - Tone
  - - Tissue
  - - Trauma

- **Ongoing PPH or massive volume**

- **Coagulation Screen**

- **Isolated prolonged aPTT**
  - Normal PT, platelets, fibrinogen

- **Mixing Test 1:1 with normal plasma**
  - Partial or no aPTT correction
  - Exclude heparin
  - Suspect inhibitor of coagulation
  - Consult with Haematology to guide testing
    - Factor levels
    - Lupus anticoagulant
    - Inhibitor testing
    - F VIII activity level low
    - + F VIII inhibitor
  - **Acquired Haemophilia A**

  - aPTT correction to normal
  - Suspect single factor deficiency
  - Consult with Haematology
  - Measure FVIII, IX, XI, XII, vWF
  - Single factor deficiency

aPTT: activated partial thromboplastin time; FVIII: factor VIII; FIX: factor IX; FXI: factor XI; FXII: factor XII; VWF: von Willebrand factor.
Discussion

AHA in peri-partum women can present with primary or secondary PPH, post surgical, traumatic, muscular or subcutaneous bleeding. Unlike congenital haemophilia, AHA rarely presents with haemarthroses.1–4 This bleeding may not respond to usual treatment measures and can be life-threatening, until the cause is established and appropriate treatment provided.1–5 AHA is diagnosed following an isolated prolonged aPTT, which does not correct with the addition of normal human plasma. If there is a factor deficiency aPTT will correct with the addition of normal plasma, however if no correction occurs then this can be due to the presence of an inhibitor (antibody), which also inactivates the Factor VIII in the normal plasma.1–5 A measurement of coagulation factor levels and inhibitor levels is then undertaken and reported in Bethesda units (BU) (Figure 1). Coagulation studies should be performed in the case of massive PPH, especially when there is no evidence of uterine atony, trauma or tissue retention.7 In this case, at first presentation, RPOC was treated and the bleeding settled. At second presentation there was thought to be an AVM, however at interventional radiology no AVM was identified. Empirical embolisation was performed with effect. An abnormal aPTT was identified on this admission; it corrected with a mixing test but factor studies were recommended on laboratory comment and not performed. Ideally haematology consult should have occurred at this point. Follow-up of the abnormal aPTT post-discharge to ensure correction would also have facilitated earlier recognition of the deteriorating situation.

Treatment involves two components; the first is the avoidance of invasive procedures along with haemostatic treatment which is achieved by bypassing Factor VIII in the coagulation pathway. The first line options are activated Factor VII (FVIIa) or Factor Eight Bypassing Agent (FEIBA). These treatments have demonstrated similar efficacy, approximately 90%,1,3 however neither agent works for all women. It is recommended that the alternative agent be used if the primary choice is unsuccessful.1–4

The second component of treatment is immunosuppressive therapy (IST).1–5 Due to the risks of AHA it is recommended that all adults with AHA receive IST. First-line IST includes steroids or steroids and cyclophosphamide.1–5 Steroids and cyclophosphamide are more likely to result in stable and complete remission (70%) than steroids alone (48%). Rituximab has been used as a treatment for AHA with success when initial therapies fail.2–5,8

The bleeding risk remains until remission is achieved, which can take weeks to months. In the EACH2 cohort of pregnancy-related AHA the mean time to inhibitor negative was 26 days, Factor VIII >70IU/dl was 47 days and duration of IST was 96 days. The risks of IST include infection, steroid-induced diabetes and neutropenia.1 Pregnancy-related AHA is rare so there is limited and conflicting data about the risk of recurrence in a subsequent pregnancy, haematology referral and close monitoring are recommended.4

Conclusion

In summary, pregnancy-related AHA is a rare condition that can cause significant bleeding morbidity. A woman with no personal or family history of bleeding disorders and an isolated prolonged aPTT should be considered to have AHA until proven otherwise.1 Retrospectively, in this case, the ordering of factor studies when recommended on haematology comment with subsequent follow-up of abnormal aPTT on discharge from hospital may have led to earlier diagnosis. The absence of an AVM at interventional radiology was another potential clue, as without AVM there was no clear cause for haemorrhage. Consultation with haematology at the time of abnormal aPTT is likely to have led to an earlier diagnosis and potentially decreased morbidity. Awareness of this condition is important to enable provision of prompt diagnosis and appropriate management.

The take home message:
An abnormal aPTT in the setting of acute postpartum haemorrhage is pathologic and warrants immediate haematological specialist consult.
Competing interests:
Nil.

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