CASE REPORT

Acquired haemophilia A: an unusual postoperative complication

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Accepted 25 October 2016

SUMMARY

An African-American man aged 65 years with multiple malignancies in remission was admitted for small bowel obstruction. He was treated with laparotomy following failure of conservative management. Postoperatively, he developed intra-abdominal bleed, which persisted, despite surgical haematoma evacuation. Further haematological workup revealed isolated prolongation of activated partial thromboplastin time (aPTT) with reduced factor VIII (FVIII) activity and raised FVIII inhibitor titre. Assuming acquired haemophilia A (AHA), FVIII inhibitor bypassing activity and corticosteroids were started with subsequent resolution of the bleeding from the surgical site. The patient remained free of bleeding episodes at 3-month follow-up and the aPTT normalised. This case report highlights the association of surgery with AHA and summarises the treatments with underlying mechanisms.

BACKGROUND

Acquired haemophilia A (AHA) is a rare and potentially fatal haemorrhagic disorder that is often missed in diagnosis, particularly in surgical patients. This may be due to lack of experience among non-specialists and overlap with other coagulopathies. Early recognition at the initial rise in activated partial thromboplastin time (aPTT) is critical to avoid significant postoperative bleeding, which is distressing for the patients and clinicians alike. However, successful treatment is possible with novel factor VIII (FVIII) inhibitor eradication strategies that are reinforced by our case.

CASE PRESENTATION

An African-American man aged 65 years presented to the emergency department with diffuse abdominal pain, nausea and vomiting. He had a known history of hypertension, chronic obstructive pulmonary disease and multiple malignancies (renal cell carcinoma, Hodgkin lymphoma, adenocarcinoma of the colon). His cancers were in remission following surgery and radiation as per annual positron emission tomography scans. He also had a recent repair for iatrogenic colonic perforation. On physical examination, he had diffuse abdominal tenderness with hypoactive bowel sounds. Non-contrast CT scan of the abdomen and pelvis revealed dilated proximal small bowel with thin collapsed bowel in the right lower quadrant suggestive of small bowel obstruction (SBO).

Conservative management with bowel rest was started initially, but the patient failed to show clinical improvement. Subsequently, explorative

laparotomy was performed to lyse intra-abdominal adhesions. He received meropenem and vancomycin as preoperative antibiotics, while midazolam, propofol and fentanyl were used for general anaesthesia. On postoperative day (POD) 1, he developed abdominal distension with hypotension and tachycardia, which persisted despite intravenous crystalloid hydration. A repeat CT scan of the abdomen showed dense-free fluid in dependent portions of the true pelvis, small bowel lumen and pericolic gutters suspicious for ongoing intra-abdominal bleed. At this time, haematocrit (Hct) was 22% (reference range 40–51) with prothrombin time (PT) 10.8 s (reference range 9.5–11.3), aPTT 43 s (reference range 24–33), platelets 118 000/ μ L (140 000–400 000/ μ L), International normalised ratio 1.02 (reference range 0.92–1.08) and fibrinogen 357 mg/dL (91–115 mg/dL). His liver function tests (LFTs) were within normal limits. The patient received packed red blood cells followed by explorative laparotomy for haematoma evacuation. No active site of bleeding was identified.

The patient's abdominal symptoms and signs resolved, and he reported passing flatus. However, on POD 6, he started oozing blood from the surgical laparotomy site that continued despite repeated haemostasis and attempts to control it with sutures and pressure dressings. Hct dropped to 18.7% with platelets 217 000/ μ L, PT 11.1 s and aPTT 73 s that failed to correct on mixing study. His LFTs continued to remain within normal limits. This led us to suspect a coagulation anomaly and the on-call haematologist was consulted. Detailed coagulation workup showed reduced FVIII activity of 6% (50–150 normal) with an FVIII inhibitor titre of 5.5 Bethesda unit s (BU) (reference range <0.8) and normal platelet function, normal Von Willebrand Factor (vWF) levels (vWF ristocetin 137% and vWF antigen 263%) and Russell's viper venom test 50 s (normal <44). These findings suggested a diagnosis of AHA.

TREATMENT

The patient was started on FVIII inhibitor bypassing activity at 75 units/kg and prednisone 80 mg/day for treatment of AHA. This led to the resolution of bleeding from surgical site and the patient was discharged subsequently after a short uneventful period of monitoring.

OUTCOME AND FOLLOW-UP

The patient remained clinically stable at 3-month follow-up with no further episodes of bleeding.

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To cite: Arora S, Goyal G, Sarmad R, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-217198

Meanwhile, FVIII inhibitor disappeared and aPTT recovered to normal level (38 s).

DISCUSSION

AHA is an under-recognised (1–4 cases per million) but potentially life-threatening (mortality 8–22%) haemorrhagic disorder.¹ Potential causes of AHA include chronic inflammatory disorders, systemic autoimmune disease, malignancy, pregnancy, medications or surgery.² Medications known to cause drug-induced AHA include penicillins, sulfamides, phenytoin and immunomodulatory agents such as interferon.² The pathogenesis can be likely explained as being an auto-immune response to antigens that resemble FVIII.^{1 2} In the case under discussion, the history of multiple cancers possibly predisposed to AHA, with significant contribution from abdominal surgery.

In AHA, the affected patients usually do not have a prior or family history of spontaneous bleeding.³ The bleeding occurrences in AHA are spontaneous or secondary to minor injury or procedures. Commonly involved bleeding sites include skin, muscles or mucosal surfaces of nasal, gastrointestinal and genitourinary tracts; while haemarthrosis, a hallmark of congenital FVIII deficiency, is rarely seen in AHA.¹

AHA is a diagnosis of exclusion. The accurate diagnosis of this condition suffers various pitfalls, especially in postoperative conditions due to lack of awareness among non-specialists, as well as overlap with other coagulopathies (like disseminated intravascular coagulation, thrombocytopenia).⁴ The diagnosis is suggested by isolated prolongation of aPTT, which fails to correct on mixing study and detection of the FVIII inhibitor.³ In our case, it was confirmed after onset of postoperative bleeding; although an initial rise in aPTT should have prompted haematological screening. Alternative causes of isolated prolonged PTT, including heparin effect and lupus anticoagulant (autoantibody that manifests as thromboembolic complications), must be ruled out based on history and negative lupus anti-coagulant activity.

Only 19 cases of surgery-associated AHA have been reported until date,⁵ including the present case; and AHA after surgery for SBO has never been discussed. Haematological screening must ideally be initiated at the point of the initial rise in the aPTT, and waiting until overt postoperative bleeding is often life-threatening.

Treatment goals include immediate haemostasis followed by FVIII inhibitor eradication. Inhibitor titres are often used to guide therapy. Low inhibitor titres (<5 BU/mL) respond to desmopressin (releases von Willebrand factor, carrier protein for FVIII) and/or recombinant FVIII replacement.⁶ Patients with high inhibitor titres (>5 BU/mL) or severe bleeding (regardless of inhibitor titre) require activated prothrombin complex concentrate or recombinant activated FVII as bypassing agent.⁶ However, the bypassing agents can rarely lead to thrombotic complications including deep vein thrombosis, myocardial infarction and cerebral infarction.

Corticosteroids and/or cytotoxic agents like cyclophosphamide, azathioprine, 6-mercaptopurine and mycophenolate have

been used for inhibitor eradication with remission rates of 60–80%.^{7 8} Anti-CD20 lymphocyte receptor inhibitor (rituximab), alone or in combination with steroids, is reserved only for resistant cases,^{9 10} and in particular surgery-associated AHA.¹¹ Remission in response to inhibitor eradication therapy takes about 4–20 weeks, with clinical signs and symptoms typically clearing ahead of the decline in inhibitor titre.⁶ In cases of drug-induced AHA, the anti-FVIII antibodies or FVIII inhibitor usually resolve following cessation of the offending drug and no specific inhibitor eradication therapy is required.

Learning points

- ▶ Acquired haemophilia A (AHA) is a diagnosis of exclusion, requiring high index of clinical suspicion.
- ▶ AHA should be considered in any patient with unexplained postoperative bleeding with a prolonged activated partial thromboplastin time, as reoperation is dangerous without prior awareness of this condition.
- ▶ Novel factor VIII inhibitor eradication strategies help achieve remission in AHA.

Contributors SA, GG and RS wrote the manuscript draft. KJW reviewed and provided input. Final draft was reviewed by all authors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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