CASE REPORT

Acquired haemophilia A: the importance of early recognition in cases of spontaneous bleeding in the elderly

Neeral Patel,¹ Zoe Wyrko,¹ Syeda Naqvi,² Adam P Croft³

¹Department of Geriatric Medicine, Queen Elizabeth Hospital, Birmingham, UK

²Sandwell General Hospital, West Bromwich, UK

³Department of Rheumatology, University of Birmingham, Birmingham, UK

Correspondence to

Dr Adam P Croft,
a.p.croft@bham.ac.uk

Accepted 2 November 2014

SUMMARY

We describe the case of a 79-year-old man who presented 'off legs' with acute right leg pain. He was initially treated for suspected cellulitis but subsequently found to have spontaneous soft tissue bleeding into the right thigh. He was eventually diagnosed with idiopathic acquired haemophilia A and treated with activated prothrombin complex concentrates to control acute bleeding followed by immunosuppressant therapy. Acquired haemophilia A is a potentially life-threatening and under-recognised bleeding disorder that results from the immune-mediated development of autoantibodies directed against coagulation factor VIII. The disease is more common in elderly individuals where early recognition and treatment is compounded by the presence of other comorbid conditions, including other potential causes of bleeding. These confounding factors and lack of awareness among non-specialists accounts for the delay in diagnosis that is common in this disease and contributes to the persistently high mortality in this age group.

BACKGROUND

Acquired haemophilia A (AHA) is a rare bleeding disorder with a poor prognosis if the condition is not recognised and effective treatment started early.¹ While the overall incidence is approximately one case per million per year, it is more common in the elderly where it is under-reported and under-recognised.² Mortality from bleeding complications is higher in the older person and more frequent within the first few weeks of the diagnosis. Diagnostic delay is one factor that significantly contributes to the higher mortality rate in this group of patients.³ The failure to recognise this condition leads to delays in the initiation of highly effective treatment.⁴ However, the use of this therapy including immunosuppressive therapy may also be limited by other comorbid conditions and concomitant drug therapy in elderly patients. As AHA is a potentially treatable condition the, diagnosis must be considered in all patients with unexplained bleeding, especially in the older person.

CASE PRESENTATION

A 79-year-old-man presented to the emergency department with a 24 h history of sudden onset pain in his right groin and leg. The pain was so severe that it had prevented him from sleeping the previous night and he could not walk more than a few steps at a time. There was no history of preceding trauma. He had multiple comorbidities including type 2 diabetes

mellitus, chronic kidney disease stage 3, hypertension, gout, chronic obstructive pulmonary disease, venous leg ulcers, ischaemic heart disease and had undergone a previous carotid endarterectomy. His medications included allopurinol; humulin M3; perindopril; glycerin trinitrate spray; latanoprost; seretide inhaler; ipratropium inhaler; isosorbide mononitrate; finasteride; atorvastatin; salbutamol inhaler; aspirin; furosemide; dorzolamide and fenofibrate. Clinical examination revealed an impaired straight leg rise on the right due to pain, and erythema along the medial aspect of the right thigh. There were no other signs of bleeding. There was no personal or family history of bleeding diatheses.

Plain radiographs of the pelvis and right femur excluded any bony injury and the patient was initially treated for right leg cellulitis with antibiotics but developed worsening pain and increased swelling in his right groin and thigh over several days. MRI of the pelvis and right leg was performed and revealed a right iliacus haematoma that extended into the right abductor muscle, causing a haemoglobin drop from 103 to 84 g/L. The prothrombin ratio and platelet count were normal but the activated partial thromboplastin time (aPTT) was increased at 2.38 (normal range 0.8–1.2) in the absence of a detectable lupus anticoagulant (dilute Russell's viper venom time). Mixing studies were performed but the aPTT failed to fully correct with 50:50 plasma mixing suggesting the presence of a specific coagulation factor inhibitor rather than a deficiency. Subsequently, plasma factor VIII was found to be low at 22 iu/dL (with a normal factor IX), normal range 50–150 iu/dL. While this level is not usually associated with significant bleeding complications in haemophilia, the presence of a clinically significant inhibitor of factor VIII was confirmed by demonstrating a lack of factor VIII increment with factor VIII replacement. The inhibitor and its plasma titre were detected by the specialist Bethesda assay, and the titre was found to be 168.9 BU/mL. This assay is obtained at the time of diagnosis to monitor disease progression and assess the risk of recurrent bleeding; the titre however does not directly correlate with disease severity and should not guide acute intervention. Further investigations and clinical examination did not reveal an underlying malignancy or primary autoimmune disease.

TREATMENT

Having established the diagnosis of idiopathic AHA, the patient was given a two unit packed red cell transfusion to correct the anaemia, and

CrossMark

To cite: Patel N, Wyrko Z, Naqvi S, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-206911

haemostasis was achieved using an activated prothrombin complex concentrate (factor VIII inhibitor bypass activity (FEIBATM)) for 5 days at a dose of 6000 units a day (50 units/kg, cumulative dose 30 000 units). To eliminate the inhibitory autoantibody, the patient was treated with immunosuppressive therapy in the form of high-dose prednisolone 1 mg/kg and cyclophosphamide (100 mg once a day) for 6 weeks. The patient required a period of inpatient rest and rehabilitation to allow the haematomas to resolve but was discharged home once independent mobility had been achieved. His aPTT corrected to 1.2 following treatment.

OUTCOME AND FOLLOW-UP

At 6 months following discharge the soft tissue haematomas had resolved and the patient had required one further in-patient admission 2 weeks following discharge with recurrent epistaxis, requiring further treatment with FEIBA (4000 units a day for 2 days). He experienced two further episodes of bleeding over the forthcoming months including one soft tissue bleed into the left arm and a subungual haematoma each requiring 2 days of treatment with FEIBA 4000 units a day.

With immunosuppressive therapy, the factor VIII level returned to the normal range but the inhibitor was still detectable at a level of 13 units/mL 12 weeks following treatment. At this stage substitution of cyclophosphamide with ciclosporin A as a second-line therapy was considered but following explanation of the risks versus benefits of a change in treatment the patient opted to continue with cyclophosphamide. At 6 months factor VIII inhibitor was still detectable at 11 units/mL. The patient remains under active observation by the haematology team and continues on oral cyclophosphamide with the therapeutic aim of inhibitor eradication. The patient has not developed any side effects of treatment.

DISCUSSION

AHA is a rare bleeding disorder but one whose incidence increases with age to 15 per million per year in individuals aged over 85 years,³ with over 80% of patients diagnosed being aged over 60 years.⁴ It is an acquired autoimmune disease characterised by the immune-mediated development of autoantibodies directed against functional epitopes on factor VIII. These inhibitory autoantibodies have either a neutralising effect on factor VIII or result in its enhanced clearance from plasma, reducing functional levels.⁵ This specific coagulation defect leads to haemorrhagic complications most commonly subcutaneous, deep muscle and retroperitoneal bleeding. However, mucosal (gastrointestinal, lung and urogenital) and intracranial bleeds have also been reported.^{2,4}

The estimated mortality of AHA is 8–22%⁶ but has improved as a result of the introduction of effective haemostatic therapies and use of immunosuppressive agents. In the elderly the mortality has remained high at 50% mortality at 1 year following diagnosis.⁷ There are a number of reasons for the higher mortality observed in this age group including diagnostic delay as a result of poor recognition of the condition compounded by presence of comorbid conditions, and use of concomitant drug therapy which can be a cause of bleeding in the elderly. In addition, drug intolerance, adverse drug effects and performance status may preclude the use of effective therapy.⁸ Approximately 50% of cases are idiopathic, but associations have been demonstrated with autoimmune disease, drugs (eg, penicillin), pregnancy and malignancy,⁹ the latter more common with increasing age. The difficulty in diagnosis is further exemplified by reports of AHA

masquerading as other conditions such as angio-oedema and haemorrhagic stroke.^{10,11}

The diagnosis must be considered in patients with bleeding in the context of an isolated prolonged aPTT. Other clinical clues include the spontaneous onset of bleeding in patients with no personal or familial history of bleeding disorders. Diagnosis is confirmed when the aPTT does not correct with plasma mixing studies (suggesting the presence of a coagulation factor inhibitor in the patient's plasma), a lupus anticoagulant is excluded, and factor VIII inhibitor autoantibodies are identified in the plasma and quantified using a specialist Bethesda assay.¹²

The highest mortality from haemorrhagic complications is observed in the first few weeks following diagnosis further reinforcing the need for prompt recognition and initiation of treatment.¹³ Appropriate treatment should be guided by specialist haematology advice and is based on consensus guidelines.¹⁴ Treatment has two goals: first to establish haemostasis and second to eradicate the autoantibody inhibitor by immunosuppression. The largest observational study to investigate bleeding control in AHA demonstrated factor VIII inhibitor bypassing agents, such as recombinant activated factor VII or activated prothrombin complex concentrate (FEIBATM), to be more efficacious compared with replacement therapy with factor VIII or desmopressin.¹⁵ High-dose steroids and cyclophosphamide have been found to be the best combination in inducing remission of disease.¹⁶ Those with AHA secondary to associated underlying condition such as malignancy should receive therapy directed towards the underlying disease.

In conclusion, while haemorrhage is a common presentation in the older population and usually secondary to drug therapy, AHA should be considered in the absence of another identifiable cause. AHA is an under-recognised but reversible acquired coagulopathy that requires early diagnosis and prompt initiation of treatment to prevent an adverse outcome. With an ageing population the incidence of this condition is set to rise and this case serves to increase awareness of this condition among clinicians, especially those involved in acute care of the older person, and highlight the challenges of its management.

Learning points

- ▶ Acquired haemophilia A is a potentially life-threatening condition resulting in spontaneous bleeding most commonly into soft tissues.
- ▶ The diagnosis should be considered in all elderly patients with otherwise unexplained bleeding.
- ▶ Early diagnosis is vital as treatment is effective if initiated early but early diagnosis requires a high index of suspicion.

Competing interests APC is in receipt of an NIHR Academic Clinical Fellowship.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Lambotte O, Dautremer J, Guillet B, *et al.* Acquired hemophilia in older people: a poor prognosis despite intensive care. *J Am Geriatr Soc* 2007;55:1682–5.
- 2 Franchini M, Mannucci PM. Acquired haemophilia A: a 2013 update. *Thromb Haemost* 2013;110:1114–20.
- 3 Croom KF, McCormack PL. Recombinant factor VIIa (Eptacog Alfa). *Bio Drugs* 2008;22:121–36.

- 4 Collins PW, Hirsch S, Baglin TP, *et al.* Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' organization. *Blood* 2007;109:1870–7.
- 5 Bitting RL, Bent S, Li Y, *et al.* The prognosis and treatment of acquired hemophilia: a systematic review and meta-analysis. *Blood Coagul Fibrinolysis* 2009;20:517–23.
- 6 Shetty S, Bhavne M, Ghosh K. Acquired hemophilia A: diagnosis, aetiology, clinical spectrum and treatment options. *Autoimmun Rev* 2011;10:311–16.
- 7 Girault S, Ly K, Jaccard A, *et al.* Prognosis of acquired hemophilia in older people. *J Am Geriatr Soc* 2008;56:956–8.
- 8 Tufano A, Coppola A, Guida A, *et al.* Acquired haemophilia A in the elderly: case reports. *Curr Gerontol Geriatr Res* 2010;2010:927503.
- 9 Franchini M, Gandini G, Di Paolantonio T, *et al.* Acquired hemophilia A: a concise review. *Am J Hematol* 2005;80:55–63.
- 10 Cohen AJ, Kessler CM. Acquired inhibitors. *Baillieres Clin Haematol* 1996;9:331–54.
- 11 Demissie A, Shahani L, Khan A, *et al.* Acquired haemophilia A initially diagnosed as angioedema. *BMJ Case Rep* 2013;2013:pii:bcr2013200246.
- 12 Araf S, Aleem S, Liu B, *et al.* An unusual cause of a haemorrhagic stroke: acquired haemophilia A. *BMJ Case Rep* 2013;2013:pii:bcr2013010263.
- 13 Franchini M, Targher G, Montagnana M, *et al.* Laboratory, clinical and therapeutic aspects of acquired hemophilia A. *Clin Chim Acta* 2008;395:14–18.
- 14 Collins P, Baudo F, Huth-Kühne A, *et al.* Consensus recommendations for the diagnosis and treatment of acquired hemophilia A. *BMC Res Notes* 2010;3:161.
- 15 Baudo F, Collins P, Huth-Kühne A, *et al.* Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry. *Blood* 2012;120:39–46.
- 16 Collins P, Baudo F, Knoebl P, *et al.* Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). *Blood* 2012;120:47–55.

Copyright 2014 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow