CASE REPORT

A 75-year-old woman with acquired haemophilia disguised by warfarin treatment

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Accepted 18 September 2015

SUMMARY

Acquired haemophilia is a rare coagulation disorder more commonly seen in elderly patients. Diagnosis and effective treatment can be delayed if patients are on warfarin treatment, as the bleeding symptoms may be erroneously attributed to this agent. We present a case report of a 75-year-old woman whose unexplained, severe and persistent bleeding was treated with surgical decompression and plasma transfusions, an appropriate management based on the assumption that warfarin was the cause of the bleeding. It was only when the patient's international normalised ratio returned to normal that a persistent abnormal activated partial thromboplastin time was noted. This delayed the correct diagnosis and treatment. Awareness of acquired haemophilia as a possible cause of sudden bleeding should be encouraged, and the wider dissemination of any relevant experience of similar cases would also be welcome.

BACKGROUND

Acquired haemophilia (AH) is a rare bleeding disorder arising from spontaneous production of antibodies against endogenous Factor VIII (FVIII). The causes of AH are not fully understood, although they are likely to involve a combination of irregularities within the immune system, and a range of environmental and genetic factors.^{1 2}

Clinical presentation most commonly involves recent onset of abnormal bleeding, which can be severe and life-threatening,³ and is usually spontaneous, but can also present after trauma.^{1 4} However, the pattern of bleeding seen with AH is often quite different from that of congenital haemophilia. Bleeds into the skin and soft tissue are the most common types: the European Acquired Haemophilia Registry (EACH2) found that, of 474 bleeding episodes recorded, 53.2% were subcutaneous bleeds and 50.2% were deep muscle or retroperitoneal bleeds.⁴ Joint bleeds, a frequent symptom of congenital haemophilia A, were rare and experienced by just 4.9% of patients.⁴

Incidence of AH is estimated to be 1.5 per million/year and is much more common in the elderly patient population (presenting at a median age of 75–80 years).³ In people aged over 85 years, the incidence rises to 14.7 per million.¹ Such rarity makes diagnosis and treatment of the condition all the more difficult, given that patients may present in centres with little or no experience of AH, leading to possible delays or suboptimal management. The UK Haemophilia Centre Doctors'

Organisation (UKHCDO) guideline states that diagnosis of AH should be considered if acute or recent bleeding is accompanied by an unexplained, prolonged activated partial thromboplastin time (APTT).³

A further challenge to diagnosis, however, can arise when the clinical and laboratory symptoms of AH arise in a patient on warfarin treatment. This can lead to an assumption that spontaneous bleeding is attributable to the warfarin, and the correct diagnosis of AH is delayed or missed. There have been reports of such cases published previously,^{5–7} and we present a further example of a patient who presented to our centre, with spontaneous, unresolved bleeding, and whose diagnosis of AH was initially masked by the fact that she was on warfarin therapy.

CASE PRESENTATION

A 75-year-old woman presented with bruising and swelling on the right side of her chest, bilateral leg oedema and a decline in her level of mobility. The swelling had been present for 24 h and was increasing in size. No preceding trauma, injuries or falls were reported. The patient's medical history included atrial fibrillation (AF), for which she had been on warfarin for 2 years on presentation.

As well as AF, her medical history included hypertension, congestive cardiac failure, hypercholesterolaemia, lymphoedema and chronic inflammatory demyelinating neuropathy (CIDP). In addition to warfarin, the patient was on a range of medications for these conditions, including prednisolone 5 mg for the CIDP.

On examination, a firm palpable swelling of about 5×8 cm was documented over the right pectoralis muscle, extending into the right axilla. The swelling was non-pulsatile, mildly tender, with no erythema and no warmth. Some bruising was noted in the right axilla and the centre of the chest wall. The admitting physician suspected a right pectoral muscle rupture with bruising secondary to warfarin therapy.

Following admission, the patient's coagulation screening showed an international normalised ratio (INR) and prothrombin time (PT) within the therapeutic ranges (INR=2.49; PT=26.1 s), but an abnormally prolonged APTT of 73 s (table 1). Warfarin is a vitamin K antagonist and thus affects vitamin K-dependent coagulation factors including factor IX, the reduction in which would be expected to prolong APTT. However, an APTT of 73 s is disproportionately longer than what would routinely be seen in patients on warfarin. Despite

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To cite: Lawless S, Benson G. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-211254

Table 1 Coagulation screening results from admission to recovery

	On admission	D1	D2	D4	D8	D10 AH confirmed	D17	D38 Inhibitor not detected	D52
PT (s) NR 9.3–11.8	17.8	15.1	13.5	11.9	10.3	10.0	10.3	10.3	9.7
APTT (s) NR 23–32	56.4	60.9	64.2	68.7	58.8	58.5	50.4	26.8	22.2
Fibrinogen (g/L)	4.0	5.8	6.2	6.5	6.5	6.5	2.3	3.8	4.8

AH, acquired haemophilia; APTT, activated partial thromboplastin time; NR, normal range; PT, prothrombin time.

discontinuation of the patient's warfarin, the bleeding into the breast continued for several days after admission and a decision was made to drain the haematoma. However, <25 mL of fluid was aspirated, so it was decided to proceed with surgical decompression.

Ten days postsurgery, there was persistent bleeding combined with low haemoglobin levels, necessitating several transfusions with packed red blood cells and fresh frozen plasma. Coagulation and blood count readings remained abnormal despite several days of transfusions. At the same time, the breast haematoma was again increasing in size and becoming tense and tender, and further surgery seemed indicated.

On this occasion, however, following consultation between the surgical and haematology teams, further tests were requested to investigate FVIII levels and exclude the possibility of an inhibitor. A 50:50 mix analysis of APTT showed poor correction (from 58.5 to 56.9 s) and FVIII assay showed a severe deficiency (table 2), suggesting the possibility of AH. This was confirmed by a Bethesda assay, showing an antibody titre of >200 Bethesda Units (BU). Plans for further decompression surgery to control the patient's bleeding were therefore abandoned and, instead, treatment with recombinant factor VIIa (rFVIIa, NovoSeven) 8 mg every 3 h was promptly started, together with prednisolone 1 mg/kg (an increase from the 5 mg at presentation) as well as oral cyclophosphamide at 2 mg/kg. Following stabilisation of the bleed, rFVIIa was discontinued, with immune suppressive therapy continuing until eradication of the inhibitor occurred, in line with standard guidelines into management of AH.

The patient's FVIII levels gradually recovered over subsequent weeks, and she was able to return to theatre for evacuation and washout of her haematoma. Inhibitor titre was recorded as below the level of detection 5 weeks from its initial confirmation. The patient was kept in the rehabilitation ward for several weeks, while her cyclophosphamide and prednisolone were gradually reduced to her presenting dose of 5 mg with the cyclophosphamide stopped, and was eventually discharged, approximately 4 months after her original presentation and admission. The patient continues to be monitored at the haematology clinic and her FVIII levels remain normal. Her AF is now managed with apixaban 2.5 mg two times per day, as this treatment reports no effect on the coagulation screening and may make it easier to assess the patient's ongoing remission.

Table 2 Factor VIII assay results over the admission and treatment period

	D10	D17	D24	D38	D52	D60	D67	D72	D100
Factor VIII levels (iu/mL)	0.02	0.06	0.42	1.06	2.09	1.62	1.81	1.84	1.28

DISCUSSION

Given how rare AH is, it is not surprising that there are few reported instances of patients whose diagnosis is delayed, because warfarin overdose seems by far be the most likely explanation for sudden onset of bleeding in this population. However, as this case demonstrates, the possibility of AH in elderly patients on anticoagulant therapy should be kept in mind.

Warfarin is known to prolong both PT and APTT,^{8 9} so, although assuming warfarin therapy to be the cause of unexplained bleeds may seem reasonable, abnormally prolonged APTT should always be investigated. There is also a need to establish a reference range for APTT in patients undergoing warfarin treatment. In addition, there is often an inherent delay in making a diagnosis of AH, because it is uncommonly seen and can be mistaken for other acquired bleeding disorders.¹⁰ This makes it all the more important that clinicians likely to be presented with such cases are fully aware of the possibility of AH being masked by the fact that a patient is on warfarin therapy. This is particularly true when it comes to elderly patients, given that prevalence of AH increases with age.³

The patient discussed here presented with spontaneous, persistent and heavy bleeding in her breast. Although her initial abnormally prolonged APTT was a clear sign of abnormal coagulopathy, the interpretation that it was warfarin-induced led to inappropriate treatment and delay in seeking advice from the haematology team—despite the fact that standard guidelines and protocols were followed at all times.

Vigilance regarding elderly patients on anticoagulants should perhaps extend beyond warfarin to the new oral anticoagulants or NOACs (ie, dabigatran, apixaban and rivaroxaban), of which use is likely to increase in coming years. Each of these drugs is known to affect clotting parameters. Both apixaban and rivaroxaban prolong INR, PT and APTT, with changes observed in these tests being small but highly variable.^{11 12} Similarly, dabigatran prolongs thrombin time and APTT.¹³

Unlike with warfarin, no regular monitoring is required with the NOACs, and yet APTT can be highly sensitive to their activity, possibly leading to lower thresholds for considering the possibility of other causes of unusual bleeding.

We would argue that, for any patient presenting with unusual or unexplained bleeding, a full coagulation screening should be performed, and not just an INR reading, if the patient is on warfarin. Clinicians should be mindful that a disproportionate prolongation of APTT in patients on warfarin might not be automatically attributable to that treatment, but may in fact be caused by AH. A simple APTT mixing study should be considered to aid accurate diagnosis.

Further observations on this area would be very welcome, given the small number of cases involved, and the desirability of health professionals pooling their knowledge and experience of what is a very challenging clinical scenario.

Learning points

- ▶ Acquired haemophilia is a rare disorder, but one that can be easier excluded further to the recognition of a prolonged activated partial thromboplastin time with a routine coagulation screen.
- ▶ It is necessary to understand the effects of oral anticoagulants on the routine coagulation screen and how they may mask alternative diagnoses.
- ▶ Management of acquired haemophilia requires referral on to a haemophilia comprehensive care centre for inhibitor eradication as well as haemostasis management.

Acknowledgements The authors would like to thank the patient and her family, and the laboratory and breast teams at Belfast City Hospital. The development of this article was supported by an educational grant from Novo Nordisk Ltd, which covered the services of a medical writer, provided by Cathy Garcia.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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