Case Reports

Acquired haemophilia: an easy diagnosis to miss in a patient taking warfarin

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Abstract:
Acquired Haemophilia (AH) is an autoimmune bleeding disorder, which despite being rare, can be fatal. It occurs in patients with previously normal haemostasis who spontaneously develop IgG autoantibodies against factor VIII. Unlike congenital haemophilia, it manifests as spontaneous bleeding into skin and soft tissues. The presentation can be masked in patients who are receiving warfarin where the bleeding is often attributed to warfarin therapy, as in the case described in this report. Consideration of AH is important in patients taking anticoagulants, when coagulopathy and bleeding fails to correct with usual measures.

Key points
- It is important to check a full clotting screen in patients who present with bleeding while receiving anticoagulants like warfarin. This may help in identifying the cause of bleeding which may be wrongly attributed to the anticoagulant.
- Acquired haemophilia should always be suspected in patients presenting with spontaneous skin and soft tissue bleeding with no apparent cause and past history of bleeding.
- Acquired haemophilia can be life-threatening and early diagnosis and treatment is therefore essential.

Case History:

A 79 year-old gentleman was transferred from a District General Hospital with bleeding into the skin and soft tissues. The patient had been admitted a week previously, with groin pain for 4-5 weeks and large bruises for 5 days. These occurred spontaneously at different sites including from groin to knee, and shins with blackening of his right toes. The patient had a background history of atrial fibrillation, for which he was taking Warfarin, with good control of his INR in the range 2-3 in the weeks preceding his admission. He had previously undergone AV nodal ablation and had a permanent pacemaker in-situ, along with type 2 diabetes (on insulin M3), hypothyroidism, hypertension, hypercholesterolemia and stable chronic kidney disease. His other medications included Levothyroxine, Candesartan, Amlodipine, Atorvastatin, Oxycodone and Sertraline.

Examination at the time of his original admission revealed an irregularly irregular pulse of 60/min, but was otherwise unremarkable aside from the bruising. Foot pulses and neurological examination were normal, with no evidence of compartment syndrome. The patient's blood results showed haemoglobin of 101 g/l, white cell count of 11.3 x 109/l, and platelet count of 320 x 109/l. Renal function was unchanged from his baseline and liver function was normal. The INR was 2.0 (APTT was not measured) and serum glucose was 15.7 mmol/l.

The bleeding episodes were attributed to warfarin, which was discontinued, and the patient was treated with intravenous vitamin K before being transferred to our hospital. Repeat bloods after treatment with vitamin K showed haemoglobin of 84 g/l, platelet count of 407 x 109/l, normal prothrombin time (PT) of 15.5s (normal 12-15.5 seconds), and prolonged APTT (Activated Partial Thromboplastin Time) of 50.7s (N: 28-35.9s).



Figure 1. Abdominal CT showing left obdurator haematoma (indicated by arrow)

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Table 1. Factor VIII Assay results

Time after admission	Factor VIII assay (N: 50-170 u/dl)
Day 1	11
Day 13	8
Day 19*	14
2 and half months after admission	31
4 months	58
5 months	62
8 months	141
11 months	136

*Patient was discharged on day 21- two days after this result

The patient underwent further investigations in our hospital. A CT scan showed left obturator muscle haematoma with no evidence of occult malignancy (figure 1). APTT of patients plasma incubated separately at 37 degrees for 1 hour was 41.4s and incubation of 50:50 mixture of Test Plasma with normal plasma showed no correction with an APTT of 39s suggesting the presence of an inhibitor. Lupus anticoagulant was negative. Factor VIII assay was then carried out which demonstrated lower levels of 11μ/dl (normal range 50-170 u/dl) with a Factor VIII inhibitor level (using Bethesda assay) of 2.76 u/ml. A diagnosis of acquired haemophilia (AH) was made on the basis of these clinical and laboratory findings.

The patient received two units of blood; as he had no further major bleeds after his hospitalisation, no prohaemostatic factors were administered. The decision was taken not to administer steroids for the treatment for AH because of his diabetes. He was commenced on intravenous Rituximab at a dose of 375 mg/m^2 once weekly for 4 weeks starting from the 9th day of admission to our hospital. The patient was discharged on the 21st day of admission with a plan to monitor Factor VIII every week and to recommence warfarin once the Factor VIII level was > 30. Over the next 8 months, the patient's factor VIII level gradually improved to normal (see Table 1) and no further bleeding was reported.

Discussion:

Acquired Haemophilia is a rare, but potentially fatal, bleeding disorder which develops due to the development of antibodies against clotting factor VIII.[1] The incidence of this condition is thought to be 1.3 to 1.5 cases per million per year with a predilection for older individuals except for the postpartum period.[2] Many of the cases of AH do not have a precipitating cause (idiopathic), although malignancies and autoimmune conditions may be responsible in some cases.[3]

The diagnosis of AH is not often considered due to its rarity. However, when patients present with bleeding complications while receiving anticoagulants like warfarin, a full coagulation screen (PT, INR and APTT) should be undertaken rather than just the INR. It should also be noted that extensive and unusual-site bleeding is not commonly observed in patients taking warfarin and should raise the suspicion of a co-existing problem like AH.

Once a very prolonged APTT is noted, mixing studies are performed where the patient's plasma is mixed with normal plasma. If the APTT remains abnormal, it suggests the diagnosis of AH in the absence of lupus anticoagulant. The confirmatory tests are factor VIII assay which will show much reduced levels and an inhibitor assay which demonstrates, as in this case the antibodies to the coagulation factor.[4, 5]

The characteristic feature of AH is bleeding without any trauma or with minor trauma. Occasionally, prolonged bleeding is first noted after a surgical procedure.[3] When bleeding occurs in closed spaces like muscles, it may cause compartment syndrome.[4] Other types of bleeding can also occur with AH including ecchymosis, epistaxis, gastrointestinal bleeding, and haematuria.[6] However, haemarthrosis, common in congenital haemophilia, is very rare in AH.[2] In some cases of AH, bleeding can be life or limb-threatening and should be treated as a medical emergency. In one study, 87% of patients had major bleeding while 22% died from complications of AH.[7] Delayed diagnosis of AH is one of the biggest factors leading to life threatening haemorrhage.[8]

There have been a few reported cases of spontaneous bleeding in patients due to AH, masked initially by warfarin therapy.[9,10] Spontaneous bleeding with warfarin has been reported, even in patients whose INR is within a normal therapeutic range. However, an inappropriately prolonged APTT should always be investigated thoroughly.

The pathogenesis of AH is the formation of antibodies to the coagulation factor VIII. As such, management requires two strategies – dealing with the bleeding episode with pro-haemostatic agents and eradication of the antibody with immunosuppressive drugs. Pro-haemostatic agents used are of two types; recombinant factor VIIa and activated prothrombin complex concentrate, which bypass the step in the coagulation cascade where FVIII is required. Prednisolone (1 mg/kg) or steroid sparing agents like cyclosporine or mycophenolate may be used to eliminate the inhibitor.[4,5] In the case of failure or contraindications of long-term steroids (diabetes or osteoporosis), the monoclonal antibody, Rituximab may be tried with one systematic review

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suggesting this agent to be as the first line treatment in post-partum AH.[12,13]

Conflicts of interests

None

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