CASE REPORT

Aspirin unmasking acquired haemophilia A in a patient with prostate cancer

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SUMMARY

A 72-year-old man, on treatment for prostate cancer, attended the emergency department with his 2nd episode of spontaneous extensive bruising and haematomas. His first presentation was 2 months prior but this was thought to be because of his aspirin and he improved when aspirin was discontinued. On this occasion aspirin had been restarted 7 days before he developed his symptoms. His blood investigation was significant for a much raised activated partial thromboplastin time (aPTT). On his 3rd day of admission he deteriorated clinically with a drastic drop in his haemoglobin and worsening tense haematomas. Blood investigations confirmed the diagnosis of acquired factor VIII deficiency and he subsequently received treatment with factor VIII inhibitor bypassing activity, steroids and immunosuppressants.

under treatment with leuporelin, a gonadotropin-releasing hormone (GnRH) analogue. Leuporelin was started only a month preceding his presentation. He had also received a 3-week course of beclutamide, a non-steroidal antiandrogen, before starting leuporelin. His most recent images (MRI pelvis, CT brain, thorax and abdomen and bone scans) did not report any evidence of metastasis but his prostate-specific antigen (PSA) was 43.7 ng/mL signifying biochemical recurrence. He had a long-term urinary catheter following urinary retention after a prostate biopsy.

On clinical examination, he appeared well and was haemodynamically stable. Large areas of bruising were noted over his right axilla, right arm, anterior chest wall and his right lateral thoracic wall. These bruised areas were hard to touch but non-tender. He was admitted for further evaluation and his aspirin was once again stopped.

BACKGROUND

Haemophilia A is an X linked inherited coagulopathy involving deficiency of coagulation factor VIII (FVIII) leading to increased bleeding, whereas, acquired haemophilia A (AHA) as the name suggests is a deficiency of FVIII secondary to the presence of an inhibitor, an autoantibody which depletes FVIII. AHA is a very rare bleeding disorder which is potentially life threatening especially if not diagnosed promptly. Owing to the rarity of this condition, diagnosis may be delayed especially in elderly patients who may have comorbidities and receiving anticoagulants on which bleeding episodes may be blamed.^{1 2}

If AHA is diagnosed promptly there are treatment options which prove to be lifesaving. Ultimately elimination of the FVIII inhibitor is the cure.

CASE PRESENTATION

A 72-year-old man, a lifelong non-smoker, presented under the general medical take with a 1-day history of spontaneous extensive bruising and haematomas which had started 7 days after his prophylactic low-dose aspirin was reintroduced. This episode was his second presentation. The first was 2 months prior and had resolved after his aspirin was stopped in the community hospital (he had been on low-dose aspirin for 15 years). There were no other signs of active bleeding except macroscopic haematuria noted in his urinary catheter bag 4 days preceding his haematomas.

He had a medical history of hypertension, hyperthyroidism and stage 2 prostate adenocarcinoma, Gleason grade 4+4, diagnosed 3 years prior and

INVESTIGATIONS

His complete blood count showed anaemia with haemoglobin of 10.6 g/dL (13–18 g/dL). The rest of his blood counts were unremarkable. His liver and renal profiles were normal but his C reactive protein level was raised to 138 mg/L (<5 mg/L). A coagulation screen revealed an aPTT of 86.7 s (22.1–29.1 s) and only partially corrected when his plasma was mixed with an equal volume of pooled normal plasma, an aPTT ratio of 3.39 (1.5–2.5) and a fibrinogen count of 6.3 g/L (1.5–4 g/L). International normalised ratio (INR) prothrombin time (PT) and platelet count were all within normal laboratory limits. On review of his most recent coagulation screen, the first sign of a raised aPTT was 3 months prior with a value of 29.6 s and a significant increase to 70.5 s 2 months after.

Following haematology review, coagulation factor quantification as well as inhibitor levels were requested. On day 3 of his admission and while awaiting the results of the above blood tests, he deteriorated further with his haemoglobin dropping from 10 to 6 g/dL which corresponded with the extension of his haematomas. His aPTT had increased to >152 s.

His blood tests returned a significantly reduced FVIII level of 0.01 IU/mL (normal value 0.6–1.36 IU/mL). Levels of factors IX, XI, XII were normal. An inhibitor of FVIII was identified with a titre of 125 BU (Bethesda Units), confirming a diagnosis of AHA, possibly secondary to malignancy. He was transferred to a tertiary centre for further management.

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DIFFERENTIAL DIAGNOSIS

In view of the close relationship of aspirin to his two episodes, an aspirin-induced disorder was suspected but this would not be consistent with his aPTT result—though aspirin might have contributed in unmasking the underlying pathology. Von Willebrand disease and antiphospholipid syndrome were excluded by a normal VW screen and negative lupus anticoagulants. disseminated intravascular coagulopathy (DIC) was initially considered but INR, platelet count and fibrinogen level did not support this.

TREATMENT

He was transfused 2 units of red blood cells, given repeated infusions of FVIII inhibitor bypassing activity (Feiba) 80 units/kg and started on high-dose prednisolone. After 4 weeks of steroid therapy, his FVIII level remained at <0.01 iu/mL. In view of this, he was started on cyclophosphamide 1.5 mg/kg daily and rituximab 375 mg/m² weekly. His factor level responded to this new treatment regime. His steroid therapy was slowly weaned off.

His 5-month long hospital stay was complicated by an upper gastrointestinal bleed requiring recommencement of Feiba, steroid-induced diabetes managed with insulin sliding scale, various episodes of neutropenic sepsis for which he received broad spectrum antibiotics, prostate abscess needing ultrasound-guided drainage, severe herpetic stomatitis treated with acyclovir and acute kidney injury. He had an intensive care unit admission for haemodynamic compromise secondary to severe sepsis. Cyclophosphamide was discontinued because of neutropenia and he received granulocyte-colony stimulating factor (G-CSF) on alternate days for persistent neutropenia. He underwent physiotherapy as part of his treatment.

For his prostate cancer, he was continued on 6-monthly leuporelin and bicalutamide. On this hormone therapy his PSA maintained a steady decline and was <0.1 ng/mL (0–4.1 ng/mL) 1 year after his acquired haemophilia A presentation.

OUTCOME AND FOLLOW-UP

Remission was monitored with FVIII levels. On discharge, his FVIII level had an upward trend, measuring 0.27 iu/mL. He was readmitted a week later with further neutropenic sepsis and acute kidney injury. He was treated with broad-spectrum antibiotics and received further G-CSF. A bone marrow biopsy was performed and reported trilineage haematopoiesis with some reactive features. His neutropenia was likely secondary to his immunosuppressants. At this time, his AHA was in remission with a FVIII level of 1.05 iu/mL. His rituximab was discontinued and a 3-weekly intravenous immunoglobulin 400 mg/kg was started as maintenance therapy. He was discharged after spending 4 months in hospital secondary to his multiple infections.

A 2 weekly follow-up with repeat measurement of FVIII levels, an outpatient weekly repeat full blood count and G-CSF injections was planned. He is also required to attend the day services ward for intravenous immunoglobulin infusions every 3 weeks.

He continues follow-up with urology and oncology for his prostate cancer.

DISCUSSION

With an incidence of 0.2–1 per 1 million cases per year,¹ acquired haemophilia is a rare, albeit a life-threatening bleeding

disorder. AHA has no racial or gender discrimination; however, there is a biphasic age distribution with peaks occurring in females between the ages of 20 and 30 years and another peak in males over the age of 60 years.² AHA is an autoimmune condition with autoantibodies acting against clotting factors. Autoantibodies to FVIII are the most common form of acquired haemophilia. These antibodies may arise in association with other autoimmune conditions such as systemic lupus erythematosus.³ Medication-associated AHA has been reported, an example of which is clopidogrel.⁴ AHA has also been linked to pregnancy and the postpartum period.⁵ Malignancy makes up 10% of patients with AHA where it occurs as part of a paraneoplastic phenomenon in solid tumours or haematological malignancies.² Some cases of AHA are diagnosed prior to discovery of an underlying malignancy. In 50% of cases an associated disorder or cause is not found.^{1 2}

AHA is a very rare disease complicating malignancy, pathogenesis of which is unknown.^{2 6 7} One of the most common malignant association is prostate cancer. A close second is lung cancer.²

AHA should be suspected in patients with malignancies who present with a new onset bleeding disorder.⁸ This is especially tricky in those with a history of venous thromboembolism who are on treatment with an anticoagulant such as heparin which is expected to raise aPTT. Suspicion is supported by a raised aPTT when the patient's plasma is mixed with an equal volume of normal plasma. In the absence of an inhibitor aPTT is corrected significantly but if an inhibitor to a clotting factor is present aPTT is only partially corrected. Diagnosis however, is confirmed by a reduced serum FVIII level and the presence and quantification of clotting factor inhibitor in BU.⁹

Management of AHA is focused on treating bleeding episodes and eliminating inhibitors. Bleeding episodes are managed with products that bypass the inhibitor.¹ In our case Feiba was used. Other possible options are recombinant factor VIIa which promotes homeostasis by activating the extrinsic pathway of the coagulation cascade and recombinant FVIII porcine sequence which is not affected by human FVIII inhibitor. Human FVIII and desmopressin may be used in cases of low titre inhibitor.^{1 7 9–11} While human FVIII has been used in low-inhibitor levels, doses much larger than needed for congenital haemophilia are frequently used. Human FVIII and desmopressin alone may not offer sufficient haemostasis in AHA and an agent that bypasses the inhibitor is often required in these cases.^{1 11} The main treatment goal is centred on elimination of the autoantibody/inhibitors using immunosuppressants.^{1 9 10} In our case, high-dose corticosteroids, cyclophosphamide and rituximab were used. Plasmapheresis is also a recognised way of eliminating FVIII inhibitors.⁷ Complication of treatment with immunosuppressants limits their use in some cases and especially in the elderly population.⁹ Such complications and the management of these were experienced in the treatment of our patient. His cyclophosphamide and rituximab were stopped following persistent neutropenia complicated by severe and recurrent sepsis. Fortunately, his FVIII level maintained an upward trend and remained within normal limits.

Some reported cases suggest improvement in symptoms and prognosis following treatment of the underlying cancer.^{2 8}

An important distraction in the presented case is the close relation of aspirin discontinuation and reintroduction to our patient's two presentations. This undoubtedly delayed diagnosis as his symptoms were so closely related to aspirin that it was thought to be to aspirin-induced haematomas. There are reports of antiplatelets causing AHA but clopidogrel being more commonly reported than aspirin.⁴ On the literature review, there is

no referencing of aspirin in association with AHA. Was aspirin involvement just a coincidence or did it act synergistically with the background coagulopathy? If aspirin was not a factor in our patient's history, would his presentation have been any different?

Learning points

- ▶ Patients with malignancy and a new onset of bleeding disorder should be suspected for acquired haemophilia.
- ▶ In the presence of non-traumatic bruising and haematomas in a patient on antiplatelets or anticoagulants, a full coagulation profile should be performed and where a prolonged aPTT is found, a 50/50 mix with normal plasma should be performed to exclude the presence of an inhibitor.
- ▶ In patients with idiopathic acquired haemophilia A, a search for an underlying malignancy would be good practice.
- ▶ Physicians should be aware of treatment options available, complications of treatment and the management of these complications.

Contributors JOO is the admitting doctor and was involved in patient consent, summary, case presentation, differential diagnosis, learning points, discussion, referencing and treatment. AZK as an admitting consultant was involved in learning point and discussion. FK contributed to the discussion, gathering patient information, investigations and summary, FM contributed to the background, treatment, discussion and referencing.

Competing interests None declared.

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