Case History

A 68 year old lady presented to A&E with mild bruise and pain on left leg after minor scratch. She was discharged home and referred to outpatient haematology clinic.

Three days later, she was admitted with extensive bruises, pain and swelling of the entire left leg. She also felt weak and tired. Examination revealed extensive bruises over the posterior aspect of thigh and buttock and knee. The rest of the examination was normal.

She has Crohn’s disease, type 2 DM, Glaucoma and Hypertension.

Medications: Lisinopril, Rosuvastatin, Metformin SR (She is not on warfarin or NOAC)

Investigations

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 4 Admission</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Ref. Range</th>
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<tbody>
<tr>
<td>Haemoglobin</td>
<td>90</td>
<td>70</td>
<td>101</td>
<td>97</td>
<td>115-365</td>
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<tr>
<td>Total White cell</td>
<td>13</td>
<td>14</td>
<td>15.8</td>
<td>20.3</td>
<td>4-11</td>
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<tr>
<td>Platelet</td>
<td>323</td>
<td>407</td>
<td>361</td>
<td>424</td>
<td>150-450</td>
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<tr>
<td>MCV</td>
<td>91.1</td>
<td>92.8</td>
<td>91.1</td>
<td>92.4</td>
<td>80-100</td>
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<tr>
<td>Neutrophil</td>
<td>10.1</td>
<td>10.5</td>
<td>13.51</td>
<td>16.88</td>
<td>1.7-7.5</td>
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<td>PT</td>
<td>9.9</td>
<td>9.9</td>
<td>9.8</td>
<td>9.12</td>
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<tr>
<td>aPTT</td>
<td>63.1</td>
<td>71.9</td>
<td>73.7</td>
<td>60.6</td>
<td>21-30</td>
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<tr>
<td>aPTT ratio</td>
<td>2.4</td>
<td>2.7</td>
<td>2.8</td>
<td>2.3</td>
<td>0.8-1.2</td>
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<tr>
<td>Fibrinogen</td>
<td>4.9</td>
<td></td>
<td>1.5-4</td>
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<td>Mixing Studies</td>
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<td></td>
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<tr>
<td>Factor VIII</td>
<td>&lt;1*</td>
<td></td>
<td>50-150</td>
<td></td>
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<tr>
<td>Factor IX</td>
<td>120*</td>
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<td>50-150</td>
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<tr>
<td>Factor XI</td>
<td>Normal range*</td>
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<tr>
<td>Factor XII</td>
<td>Normal range*</td>
<td></td>
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</table>

*Results obtained later
UE, LFT, CRP and Bone profile are normal.
CT angiogram of both lower limbs showed acute haematoma within lateral aspect of left rectus muscle: 4x1cm in diameter extending over a length of 17cm.

Urgent review by Haematologist
Immediate Treatment
RBC 2 units, FFP 3 units
Prednisolone 80mg od (1mg/kg)
FEIBA (Factor Eight Inhibitor Bypassing Activity) 4000 units for 3 days
Factor assays later reported Factor VIII deficiency.

She was also referred to orthopaedic surgeons to exclude compartment syndrome.

Diagnosis: Acquired Haemophilia A (AHA) (Factor VIII inhibitors)

Learning Points

The diagnosis of AHA should be considered if acute or recent onset of bleeding is accompanied by an unexplained prolonged activated partial thromboplastin time (aPTT)

Delay in diagnosis and treatment is common putting patients at unnecessary risk of severe bleeding. In Knob et al, 2012 study diagnostic delays were more than 12 days in 25% and more than 4 weeks in 10% of cases.

Avoid iatrogenic bleeding: Avoid IM injections, Venepuncture and IV cannula. Minimise BP and blood glucose monitoring.

It is also important to take full drug history especially antiocoagulant and antiplatelet medications.

The severity of bleeding at presentation does not predict future bleeding and patients remain at risk of fatal bleeding until the inhibitor has been eradicated.

Discussion

What is AHA?
Acquired haemophilia A (AHA) results from immune mediated depletion or formation of inhibitors against coagulation factor VIII.
Incidence: 1.5 case/million/year, most commonly in the elderly, median age of 75-80 years
Presentation: Varies from only abnormal coagulation test without clinical bleeding to severe life threatening bleeding such as gastrointestinal, intracranial and retroperitoneal bleeds
Common presentation are bruising, retroperitoneal, muscle, gastrointestinal and urogenital bleeding where as haemarthroses are uncommon.
Associations: PMR, RA, SLE & autoimmune disorders, malignancy, SLE, pemphigoid. (no association in 50% of cases)
Mortality: 8-42%, recent study suggests 3-12% are related to treatment such as immunosuppression & infection whereas 3-8% are due to bleeding.

In this case as PT is normal, therefore patient has intact extrinsic pathway. As aPTT is prolonged, intrinsic factor abnormalities due to factor VIII, IX, XI and XII need to be excluded. Inhibitors against factor VIII and vWF are most common in contrast to other coagulation factors.

Treatment
Management of AHA should be supervised by the haematologist experienced in the treatment of patients with inhibitors
Immediate Treatment
Haemostatic therapy depends on the specificity of the inhibitor. If haemostatic treatment is required it should be with a bypassing agent. The available bypassing agents are:
- recombinant factor VIIa (rFVIIa),
- the activated prothrombin complex concentrate (aPCC) and
- Factor Eight Inhibitor Bypassing Activity (FEIBA).

Eradication of the inhibitor in AHA
First, it is important to exclude malignancy.
Immunosuppression to eradicate an inhibitor should be started as soon as the diagnosis has been made, to reduce the time a patient is at risk of bleeding.
Prednisolone is the first line agent with the dose of 1 mg/kg/d either alone or combined with cyclophosphamide 1-2 mg/d orally. Rituximab can be used as a single agent but it may have limited efficacy. It can be combined with other immune-suppressive agents.
Other options are calcineurin inhibitors, multiple immunosuppressive agents and immune tolerance protocols.

Conclusion
AHA is rare but delay in diagnosis and treatment may result adverse outcome. Therefore it is important for a physician to recognise the condition and be familiar with interpretation of coagulation algorithms.
Early involvement of Haematologist is essential for acute haemostasis and further treatment such as eradication of inhibitors.