Question 52
A 58-year-old previously well man presents with a two-week history of spontaneous bruising and a large, painful left thigh haematoma following minimal trauma. He is on no medication and his blood count has been documented as normal 18 months earlier prior to elective surgery. There is no previous history of bleeding with trauma or with surgery and no family history of bleeding disorder. Physical examination is normal apart from scattered ecchymoses and the swollen, bruised left thigh. The haematoma is confirmed on ultrasound examination.

Investigations show:

- Full blood count
  - haemoglobin: 119 g/L [135-170]
  - other parameters normal
- prothrombin time-international normalised ratio (PT-INR): 1.1 [1.0-1.3]
- activated partial thromboplastin time (APTT): 90 seconds [26-38]
- APTT 1:1 mix, normal plasma:patient plasma: 50 seconds [26-38]
- fibrinogen: 2.7 g/L [2.0-4.0]
- D-dimer: 0.2 mg/L [<0.2]
- platelet function tests (aggregometry) normal

The most likely diagnosis is:

A. haemophilia A.
B. haemophilia B.
C. primary antiphospholipid antibody syndrome.
D. von Willebrand’s disease.
E. acquired factor VIIIc inhibitor.

Key points from the question:

1. Anaemia – Hb↓
2. INR – normal
3. APTT prolonged
4. APTT 1:1 mix prolonged
   - As the addition of normal plasma does not correct the prolongation of APTT it suggests a factor inhibitor rather than a deficiency
5. Platelets normal
6. D-Dimer/ Fibrinogen normal
7. New bleeding disorder – unlikely an inherited one given his age
PATHWAYS OF COAGULATION

APTT – measure of intrinsic and common pathway
INR – measure of extrinsic and common pathway
1:1 dilution – assess whether there is factor deficiency or inhibition

Haemophilia A – Factor VIII deficiency and Haemophilia B – Factor IX deficiency
- Prolonged APTT and normal INR
- Should correct with 1:1 dilution with normal factor bc it’s a deficiency
- Would expect to have had symptoms from birth

Antiphospholipid antibody syndrome
- Prolonged APTT and normal INR
- Associated with thrombosis rather than bleeding
- Prolonged APTT is an artifact of antiphospholipid phenomenon
- Presence of antiphospholipid antibody producing lupus anticoagulant is suggested by prolonged APTT that doesn’t correct after 1:1 dilution w normal plasma
- With addition of phospholipids clotting time corrects
von Willebrand’s Disease
- Can be associated with prolonged APTT and normal INR
- But in mild disease APTT normal
- More assoc with mucosal bleeding
- Would expect to have had symptoms from a younger age
- Would expect correction with 1:1 dilution

Acquired factor VIII inhibition
- Normal INR but prolonged APTT
- Acquired inhibition fits with the failure of the 1:1 dilution to correct

- Most common autoantibodies affecting coagulation are directed against factor VIII
- In 50% associated with
  - Pregnancy or post-partum period
  - Rheumatoid arthritis
  - Malignancy (solid tumours)
  - SLE
  - Drug reactions

- Hallmark is bleeding that is first noted after a surgical procedure
- Bleeding is often sever
- Present with
  - Large hematomas
  - Extensive ecchymoses
  - Severe mucosal bleeding inc epistaxis, GI bleeding, hematuria
  - Hemarthrotheses common in hereditary factor VIII deficiency are rare

- Diagnosis
  1. Prolonged APTT with normal INR
  2. 1:1 dilution with normal plasma – persistence of prolongation of APTT suggesting an inhibitor
  3. Add source of phospholipid to the plasma
     - Correction of the APTT suggests antiphospholipid antibodies
     - If APTT doesn’t correct → Bethesda assay
  4. Bethesda Assay
     - Diagnoses factor VIII inhibitor and quantifies the antibody titre
**PATHWAYS OF COAGULATION**

**PROTHROMBIN TIME (INR)**
- Measures the functioning of the extrinsic and common pathways
- Measures activity of VII, X, V, II (prothrombin), I (fibrinogen)
- VII, X and II (prothrombin) are vit K dependent and altered by warfarin so is a measure of warfarin activity

**ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT)**
- Measures the intrinsic and common pathways of coagulation
- Sensitive for deficiencies of all coag factors except VII, XIII
- Measure of the activity of heparin
- Less sensitive than INR to deficiencies of the common pathways (X, V, II-prothrombin, I-fibrinogen)
PT or APTT on 1:1 mixture

- After an abnormality in clotting is detected need to differentiate between a factor deficiency or factor inhibition
- Mix patient’s plasma with normal pooled plasma and repeat abnormal test
- 3 principles to understand
  1. Clotting tests will give normal values when there is 50% activity of involved factor
     - so if clotting test is normal after 1:1 dilution with normal plasma cause of abnormal test was factor deficiency
  2. Most agents which inhibit factor activity will not be effectively diluted out by 1:1 dilution
     - so if test remains abnormal an inhibitor was the cause of the abnormal test
  3. Some inhibitors give normal results when tested immediately after 1:1 dilution but then become abnormal again
     - eg factor VIII inhibitors (characteristic)

- If 1:1 dilution corrects the abnormal test
  - determine deficient factors by individual factor assays

- If test is not corrected by dilution most common inhibiting factors are:
  1. Heparin
  2. antiphospholipid antibodies (though most commonly seen in hypercoag state)
  3. inhibitors against VIII, IX, X
  4. inhibitors of thrombin eg fibrin or fibrinogen degradation products
INTERPRETTING RESULTS

Normal INR and APPT
- thrombocytopenia is the most common acquired bleeding disorder
- von WILLEBREAD DISEASE
- Platelet dysfunction
- Factor XIII deficiency

Normal INR with Prolonged APTT
- characteristic of disorder of intrinsic pathway
- Inherited disorders:
  1. Factor VIII (hemophilia A, vW disease)
  2. Factor IX (hemophilia B)
  3. Factor XI (tend to bleed post-surgical procedures)
- Acquired disorders/ inhibitors:
  1. antiphospholipd antibodies (presents with thrombosis)
  2. acquired antibodies to factor VIII (acquired hemophilia), IX, XI

Prolonged INR and normal APTT
- indicates an abnormality of the extrinsic pathway and suggests factor VII deficiency
- Factor VII deficiency can be inherited or acquired
- Inherited factor VII
  - Phenotypic and molecular heterogeneity
  - Inconsistencies bw clinical picture, underlying clotting and molecular defects and response to prophylaxis with recombinant human factor VIIa
  - Can have no excessive bleeding to severe hemorrhagic tendency
- Acquired inhibitors are
- Pattern is more commonly seen due to:
  - Warfarin therapy, Early liver disease
  - Vit K deficiency, Early DIC (rare)

Prolonged INR and APPT
- Inherited disorder of common pathway or more complex acquired disorder inv multiple pathways
- Inherited disorders: deficiency of factor X, V, prothrombin or fibrinogen (rare)
- Acquired disorders:
  - Supratherapeutic doses of warfarin or heparin can prolong both
  - Vit K deficiency, liver disease, DIC
  - Factor V is vit K independent so can be used as a direct evaluation of hepatic function