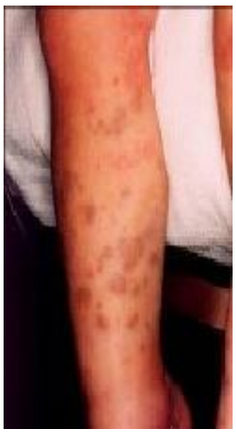
CASE SIX

Short case number: 3_30_6
Category: Immune and haemopoietic systems
Discipline: Medicine
Setting: General Practice
Topic: Bleeding disorders_thromobcytopaenia

Case



Sybilla Hanson, who is 35 years old presents with bruising on her legs, they have developed quite quickly. There is no history of trauma and she has not been unwell.

You observe that she has quite marked purpura over both legs.

Questions

1. What are the key features of your history and examination and why?
2. You are concerned that there may be a problem with haemostasis. Describe the function and the role of the vessel wall, platelets, coagulation pathway and fibrinolysis in normal haemostasis.
3. In the investigation of a possible bleeding disorder what investigations would you undertake and why?
4. Sybilla's full blood count indicates that she is thrombocytopaenic with a platelet count of 20 x 10^9/L. What is thrombocytopaenia and what are the clinical effects caused by differing levels of platelet count?
5. Sybilla is referred to a haematologist who diagnoses immune thrombocytopaenic purpura [ITP]. What is ITP and how does the clinical picture differ from Thrombotic thrombocytopaenic purpura [TTP]?
6. Outline the stepwise approach to the management of patients with ITP.

Suggested reading:

- Kumar P, Clark ML, editors. Kumar & Clark's Clinical Medicine. 9th edition. Edinburgh: Saunders Elsevier; 2016.
- Colledge NR, Walker BR, Ralston SH, Penman ID, editors. Davidson's Principles and Practice of Medicine. 22nd edition. Edinburgh: Churchill Livingstone; 2014.

ANSWERS

Question 1
What are the key features of your history and examination and why?

General
PMHx, family history, social history, history of presenting symptoms, medications, allergies.
General haematological questions

- symptoms of anaemia
- bleeding abnormalities (menstrual, GI)
- Easy bruising, purpura, thrombotic tendency
- Infection, fever
- Lymph node enlargement
- Bone pain
- Weight loss

Specifically

- Fevers
- pregnancy (risk factor for ITP)
- oral contraceptive use (risk factor for ITP)
- haematuria
- abdominal pain

Question 2
You are concerned that there may be a problem with haemostasis. Describe the function and the role of the vessel wall, platelets, coagulation pathway and fibrinolysis in normal haemostasis.
Haemostasis is a complex process, depending on interaction between the vessel wall, platelets and coagulation factors.

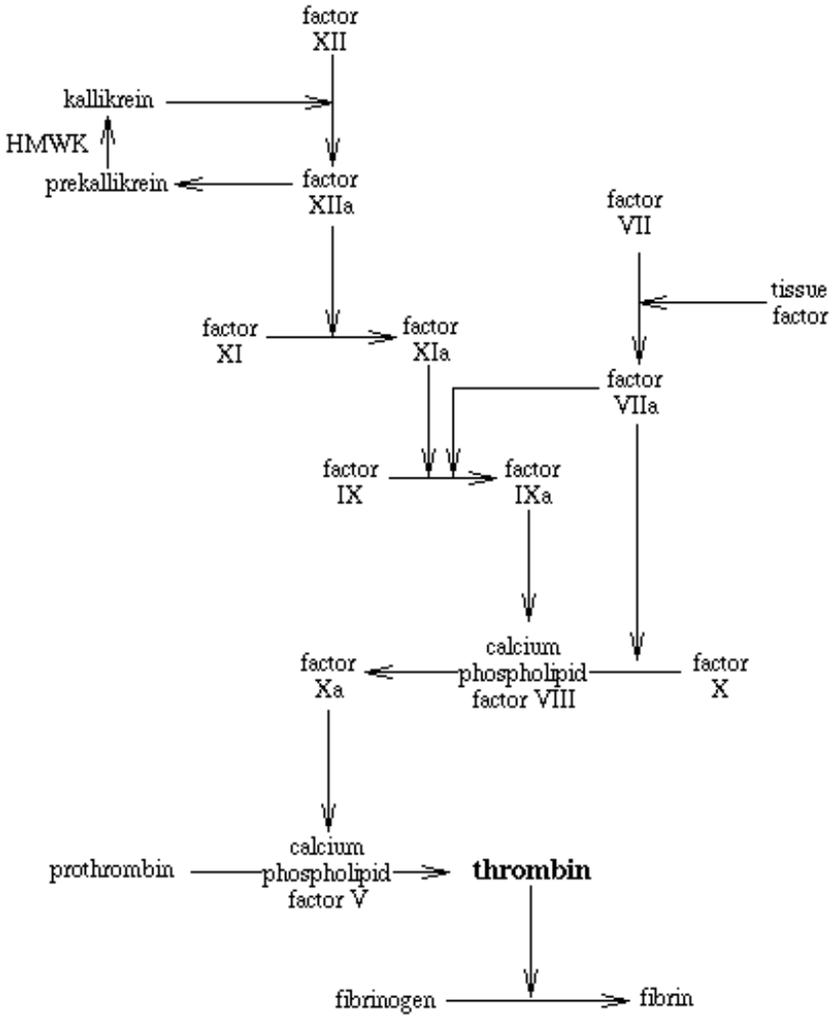
<u>Vessel Wall</u>
An immediate reflex vasoconstriction of the injured vessel and adjacent vessels results in a transient reduction of blood flow to the affected area. Damage to the endothelium of the vessel results in activation of platelets and coagulation, release of serotonin and thromboxane A from activated platelets contributes to the vasoconstriction.

<u>Platelets.</u>
Platelet adhesion to collagen is dependent on membrane receptors. Following adhesion, platelets undergo a shape changes from a disc to a sphere, spread along the subendothelium and release the contents of their cytoplasmic granules, which allow binding to fibrinogen. Fibrinogen binds platelets into activated aggregates and further platelet release occurs. A self perpetuating cycle of events is set up leading to formation of a platelet plug at the site of injury.

Coagulation and fibrinolysis.

This is a biological amplification system in which there is sequential activation of circulating precursor proteins (the coagulation factor enzymes) which results in the generation of thrombin. Thrombin causes the conversion of plasma fibrinogen to fibrin which enmeshes the platelet aggregates at the site of vascular injury. This results in the formation of stable homeostatic plugs.

Blood coagulation is considered in terms of two pathways - the intrinsic and extrinsic, which both end in a common pathway.



Question 3
In the investigation of a possible bleeding disorder what investigations would you undertake and why?

Investigations should include:

- repeat FBC and request blood film
    - this is in order to confirm thrombocytopenia is real - also this will exclude other diseases such as chronic lymphocytic leukaemia and myelodysplastic syndromes
- renal biochemistry
- liver function tests (liver disease)

- viral serology (EBV, hepatitis screen); consider HIV
- autoantibodies - thrombocytopenia may occur in conditions such as SLE
- B12, folate - deficiency may result in pancytopenia or cytopenia of particular cell line
- immunoglobulins - to exclude common variable immunodeficiency
- clotting studies - also related to liver function

Bone marrow will be a secondary care investigation.

Question 4
Sybilla's full blood count indicates that she is thrombocytopaenic with a platelet count of 20 x 10^6/L. What is thrombocytopaenia and what are the clinical effects caused by differing levels of platelet count?

Thrombocytopaenia is a decrease in the number of platelets in the blood - it reduces the ability of the blood to clot and is thus a bleeding diathesis. It is defined as a platelet count less than 100 x 10^9/L (<100,000 per cubic mm).

Thrombocytopaenia and functional platelet abnormalities result in a bleeding tendency:

- spontaneous cutaneous purpura or ecchymoses
- mucous membrane bleeding
- nose bleeds, especially in children
- menorrhagia
- post-partum haemorrhage

Rare complications usually only occur when the platelet count is below 30x10^9:

- retinal or subconjunctinal haemorrhage
- gastrointestinal bleeding
- intracranial bleeding

Question 5
Sybilla is referred to a haematologist who diagnoses immune thrombocytopaenic purpura [ITP]. What is ITP and how does the clinical picture differ from Thrombotic thrombocytopaenic purpura [TTP]?

Immune thrombocytopenic purpura (ITP) is a clinical syndrome in which a decreased number of circulating platelets (thrombocytopenia) manifests as a bleeding tendency, easy bruising (purpura), or extravasation of blood from capillaries into skin and mucous membranes (petechiae).

In persons with immune thrombocytopenic purpura (ITP), platelets are coated with autoantibodies to platelet membrane antigens, resulting in splenic sequestration and phagocytosis by mononuclear macrophages. The resulting shortened life span of platelets in the circulation, together with incomplete compensation by increased platelet production by bone marrow megakaryocytes, results in a decreased platelet count.

Thrombotic thrombocytopenic purpura is an uncommon syndrome characterised by:

- fever
- microangiopathic haemolytic anaemia
- thrombocytopenia
- neurologic and renal abnormalities

The cause is unknown but it often follows infection or in women, oral contraception or pregnancy. Young adults from 20 to 50 years are predominantly affected, with a slight female preponderance.

There is evidence that affected patients may have a platelet agglutinating factor; be unable to produce prostacyclin, an antiplatelet substance, because of vascular endothelial cell defects; and have impaired fibrinolytic potential. In chronic relapsing TTP, patients may also have a structurally altered von Willebrand's Factor, the significance of which is unknown.

It is now believed that thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome represent a spectrum of disease.

Question 6
Outline the stepwise approach to the management of patients with ITP.

Adult acute ITP rarely resolves without treatment and 5-10% of patients develop a chronic ITP. The efficacy of steroids or intravenous immunoglobulin in reducing the duration of thrombocytopenia and the percentage of patients progressing to chronic ITP is unclear.

Chronic ITP rarely resolves spontaneously. First line treatment is with prednisolone:

- it is mandatory to perform a bone marrow aspiration before commencing steroids, to rule out leukaemia
- 20% of patients have a complete response
- 30% have a partial response and run a moderate thrombocytopenia of 30-100 requiring no further treatment or small doses of steroids
- the remaining 50% of patients, of which 30% would have initially shown a partial response to steroids, require splenectomy

Splenectomy has a 90% initial response rate. However, 30% of patients relapse. These patients may benefit from treatment with cyclophosphamide, azathioprine, vincristine or danazol.

Patients with chronic ITP who require surgery may be given intravenous immunoglobulins which produce a transient rise in platelet count by blocking receptors on splenic macrophages.

Platelet transfusions are largely ineffective as exogenous platelets survive no better than endogenous ones. Transfusion should be given only in life-threatening haemorrhage to enhance haemostasis.