CASE FOUR

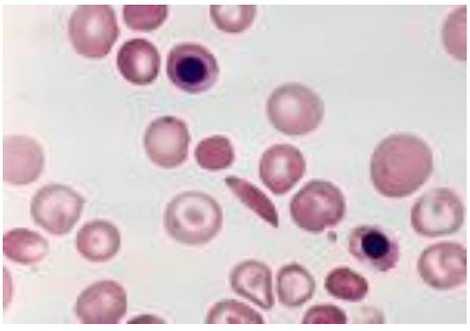
Short case number: 3_30_4
Category: Immune and haemopoietic systems
Discipline: Medicine
Setting: Emergency Department
Topic: Haemolytic Anaemias [SDL]

Case

You are the intern in the emergency department; Ambrose Okeke who is 25 years old is visiting from South Africa. He presents with severe pain in his left leg which has not been relieved by panadeine forte. Ambrose has sickle cell disease and many episodes of similar pain which occasionally require analgesia with narcotics.
You observe that he is in obvious pain and note that his temperature is elevated at 37.8^{0}C.

Questions

1. What is the underlying pathophysiology of the severe bone pain experienced in patients with sickle cell disease? Detail the pathophysiology of the following clinical features seen in sickle cell disease; anaemia, splenic sequestration and bone marrow aplasia.
2. You recall that sickle cell disease causes a haemolytic anaemia, what is pathophysiology is seen in haemolytic anaemias and what are the consequences of haemolysis?
3. What is the fate of haemoglobin in the plasma following haemolysis?
4. In a flow chart summarise that investigations that assist in determining the cause of haemolysis.



5. Investigations demonstrate that Josef is anaemic with a haemoglobin of 80g/L with a high reticulocyte count. His blood film is seen here. What features can be seen on the blood film?
6. Describe the haemoglobin abnormality seen in sickle cell disease and the pathogenesis of sickle syndromes that result in the sequelae of sickling.
7. What are the principles of management of an acute painful crises in patients with sickle cell disease?
8. Outline the long term problems seen with sickle cell anaemia and their underlying pathophysiology.

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 is the underlying pathophysiology of the severe bone pain experienced in patients with sickle cell disease? Detail the pathophysiology of the following clinical features seen in sickle cell disease; anaemia, splenic sequestration and bone marrow aplasia.

Symptoms in sickle cell disease vary from a mild asymptomatic disorder to a severe haemolytic anaemia and recurrent severe painful crises. The condition may present in childhood with anaemia and mild jaundice. In the older patient, vaso-occlusive problems occur owing to the sickling in the small vessels of any organ, mimicking many medical and surgical emergencies. Typical infarctive sickle crises include

- Bone pain
- Pleuritic chest pain
- Cerebral – hemiparesis, fits
- Spleen – painful infarcts
- Penis – priapism
- Liver – pain and abnormal liver function tests.

Question 2

You recall that sickle cell disease causes a haemolytic anaemia, what is pathophysiology is seen in haemolytic anaemia and what are the consequences of haemolysis?

Haemolytic anaemias are caused by increased destruction of red cells. The red cell normal survives about 120 days, but in haemolytic anaemias the red cell survival times are considerably shortened.

There is no definite explanation why red cells are removed from the circulation at the end of their life span. Breakdown of normal red cells occurs in the macrophages of the bone marrow, liver and spleen.

<u>Consequence of haemolysis.</u>

Shortening of red cell survival does not always cause anaemia as there is a compensatory increase in red cell production by the bone marrow. If the red cell loss can be contained within the marrow's capacity for increased output, then a haemolytic state can exist without anaemia. The bone marrow can increase its output by six to eight times. In addition, immature red cells are released prematurely.

Question 3

What is the fate of haemoglobin in the plasma following haemolysis?

Some intravascular haemolysis may occur in sickle cell disease owing to increased mechanical fragility of the severely damaged cells. The average red cell survival correlates with the percentage of irreversibly sickled cells in circulation and is shortened to approximately 20 days.

When red cells are rapidly destroyed within the circulation, haemoglobin is liberated. This is initially bound to plasma haptoglobins but these soon become saturated. Excess free plasma Hb is

filtered by the renal glomerulus and enters the urine, although small amounts are reabsorbed the renal tubules. In the renal tubular cell, Hb is broken down and becomes deposited in the cells as haemosiderin. The liver plays an important role in removing HB bound to haptoglobin and haemopexin and any remaining free Hb.

Question 4
In a flow chart summarise that investigations that assist in determining the cause of haemolysis.

- full blood count:
  - reticulocytosis - present if there is increased red cell production
- blood film:
  - polychromasia, macrocytosis: increased red cell production
  - spherocytosis: hereditary spherocytosis
  - elliptocytosis: hereditary elliptocytosis
  - sickle cells
- bilirubin - increased in unconjugated bilirubin if there is increased red cell destruction (also increased urinary urobilinogen and reduced haptoglobin)
- LDH: increased if red cell destruction
- urine:
  - urobilinogen: high if increased RBC destruction
  - haemoglobinuria, haemosiderinuria: present in intravascular causes of RBC destruction

Question 5
Investigations demonstrate that Josef is anaemic with a haemoglobin of 8g/dl with a high reticulocyte count. His blood film is seen here. What features can be seen on the blood film?

Diagnosis of sickle cell anaemia is on the basis of:

- history and examination
- blood - shortened red cell survival results in:
  - low haemoglobin, usually around 8 or 9 g/dl
  - *normochromic normocytic anaemia of moderate degree and sickle cells present.(as seen)*
    - Normocytic anaemia occurs when the overall haemoglobin levels are decreased, but the red blood cell size (Mean corpuscular volume) remains normal.
  - *target cells and sickle cells on the blood film (as seen on this slide)*
    - Target cells are red cells with a central area of increased staining, surrounded by a ring of hypodense staining and then a further ring of dense staining at the edge of the cell, giving an appearance akin to an archery target.
    - Sickle cells describe a red cell with an abnormal morphological shape. The name describes their shape.
  - the reticulocyte count is usually elevated to 10-20%
    - Reticulocytes are young, oversized red cells that are present when the marrow is actively producing red cells. They are the intermediary between the nucleated red blood cell and the mature red blood cell. Small numbers of reticulocytes are found in normal peripheral blood. They are usually expressed as a percentage of total red cells.
- the diagnosis is confirmed by identification of HbS on a haemoglobin electrophoresis gel

Question 6
Describe the haemoglobin abnormality seen in sickle cell disease and the pathogenesis of sickle syndromes that result in the sequelae of sickling.

The most important structural abnormality of the Hb chain is sickle cell haemoglobin (Hb S). Hb S results from a single – base mutation of adenine to thymine which produces a substitution of valine for glutamine at the sixth codon of the b globin chain. In the homozygous state (sickle cell anaemia) both genes are abnormal Hb SS, where as in the heterozygous state (sickle cell trait) only one chromosome carries the gene. As the synthesis of Hb F is normal, the disease usually does not manifest itself until the Hb F decreases to adult levels at about 6 months of age.

Clinical presentation depends on whether the onset of haemolysis is gradual or abrupt and on the severity of erythrocyte destruction. A patient with mild haemolysis may be asymptomatic. In more serious cases, the anaemia can be life threatening, and patients can present with angina and cardiopulmonary decompensation. The clinical presentation also reflects the underlying cause for haemolysis.

Question 7
What are the principles of management of an acute painful crisis in patients with sickle cell disease?

Painful sickle cell crises are acute exacerbations of sickle cell disease characterised by severe generalised bone pain due to infarction of the marrow. Almost any bone may be involved and there is a tendency for the infarcts to become infected. Sometimes infection may occur with unusual organisms such as Salmonella.

Treatment is required when crises occur for the control of pain, the maintenance of hydration, correction of anaemia and prevention and treatment of infection.

Question 8
Outline the long term problems seen with sickle cell anaemia and their underlying pathophysiology.

Long term problems include

- Susceptibility to infections – particularly strep pneumoniae which can cause a fatal meningitis (Splenic function is impaired, even though splenomegaly is present. This may be due to the extensive erthrophagocytosis causing a blockade of the mononuclear phagocyte system. In adults, splenic infarcts also significantly reduce the size and function of the organ. This functional splenectomy leads to increased susceptibility to blood borne infections, in particular by encapsulated organisms such as Strep Pneumoniae and haemophilus influenzae.)
- Chronic leg ulcers, due to ischaemia
- Gallstones, pigment stones from persistent haemolysis
- Aseptic necrosis of bone, particularly of the femoral heads
- Blindness, due to retinal detachment
- Chronic renal disease.