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Please read this section first

The HPCSA and the Med Tech Society have confirmed that this clinical case study, plus your routine review of your EQA reports from Thistle QA, should be documented as a "Journal Club" activity. This means that you must record those attending for CEU purposes. Thistle will **not** issue a certificate to cover these activities, nor send out "correct" answers to the CEU questions at the end of this case study.
The Thistle QA CEU No is: **MTS 17/011**
Each attendee should claim **THREE** CEU points for completing this Quality Control Journal Club exercise, and retain a copy of the relevant Thistle QA Participation Certificate as proof of registration on a Thistle QA EQA.

DIFFERENTIAL SLIDES LEGEND

CYCLE 50 SLIDE 2

HAEMOLYTIC ANAEMIA

Haemolytic anaemia is a form of anaemia due to hemolysis, the abnormal breakdown of red blood cells (RBCs), either in the blood vessels (intravascular hemolysis) or elsewhere in the human body (extravascular haemolysis). It has numerous possible causes, ranging from relatively harmless to life-threatening. The general classification of haemolytic anaemia is either inherited or acquired. Treatment depends on the cause and nature of the breakdown.

Symptoms of haemolytic anaemia are similar to other forms of anaemia (fatigue and shortness of breath), but in addition, the breakdown of red cells leads to jaundice and increases the risk of particular long-term complications, such as gallstones and pulmonary hypertension.

Basic features

Haemolytic anaemia involves the following:

- Abnormal and accelerated destruction of red cells and, in some anaemias, their precursors.
- Increased breakdown of haemoglobin, which may result in:
  - increased bilirubin level (mainly indirect-reacting) with jaundice.
  - increased faecal and urinary urobilinogen.
  - Haemoglobinaemia, methemalbuminaemia, hemoglobinuria and haemosiderinuria (where there is significant intravascular hemolysis).
- Bone marrow compensatory reaction:
  - Erythroid hyperplasia with accelerated production of red cells, reflected by reticulocytosis, and slight macrocytosis in peripheral blood.
  - Expansion of bone marrow in infants and children with severe chronic hemolysis - changes in bone configuration visible on X-ray.
- The balance between red cell destruction and marrow compensation determines the severity of anaemia.

Signs and symptoms

In general, signs of anaemia (pallor, fatigue, shortness of breath, and potential for heart failure) are present. In small children, failure to thrive may occur in any form of anaemia. Certain aspects of the medical history can suggest a cause for haemolysis, such as drugs, consumption of fava beans, the

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presence of prosthetic heart valve, or other medical illness. Chronic haemolysis leads to an increased excretion of bilirubin into the biliary tract, which in turn may lead to gallstones.

The continuous release of free haemoglobin has been linked with the development of pulmonary hypertension (increased pressure over the pulmonary artery); this, in turn, leads to episodes of syncope (fainting), chest pain, and progressive breathlessness. Pulmonary hypertension eventually causes right ventricular heart failure, the symptoms of which are peripheral oedema (fluid accumulation in the skin of the legs) and ascites (fluid accumulation in the abdominal cavity).

Causes

They may be classified according to the means of hemolysis, being either intrinsic in cases where the cause is related to the red blood cell (RBC) itself, or extrinsic in cases where factors external to the RBC dominate. Intrinsic effects may include problems with RBC proteins or oxidative stress handling, whereas external factors include immune attack and microvascular angiopathies (RBCs are mechanically damaged in circulation).

Intrinsic causes

Hereditary haemolytic anaemia can be due to membrane defects:

- Defects of red blood cell membrane production (as in hereditary spherocytosis and hereditary elliptocytosis).
- Hereditary (inherited) haemolytic anaemia can be due to defects in haemoglobin production (as in thalassemia, sickle-cell disease and congenital dyserythropoietic anaemia).

Hereditary (inherited) haemolytic anaemia can be due to enzyme defects:

- Defective red cell metabolism (as in glucose-6-phosphate dehydrogenase deficiency and pyruvate kinase deficiency).

Acquired due to paroxysmal nocturnal hemoglobinuria:

- Paroxysmal nocturnal hemoglobinuria - PNH is a rare, acquired, potentially life-threatening disease of the blood characterized by complement-induced intravascular haemolytic anaemia.

Extrinsic causes

Acquired haemolytic anaemia may be caused by immune-mediated causes, drugs and other miscellaneous causes.

- Immune-mediated causes could include transient factors as in Mycoplasma pneumoniae infection (cold agglutinin disease) or permanent factors as in autoimmune diseases like autoimmune haemolytic anaemia (itself more common in diseases such as systemic lupus erythematosus and chronic lymphocytic leukaemia)
- Any of the causes of hypersplenism (increased activity of the spleen) such as portal hypertension
- Acquired haemolytic anaemia is also encountered in burns and as a result of certain infections.
- Lead poisoning resulting from the environment causes non-immune haemolytic anaemia.
- Runners can suffer haemolytic anaemia due to "footstrike hemolysis", owing to the destruction of red blood cells in feet at foot impact.
- Low-grade haemolytic anaemia occurs in 70% of prosthetic heart valve recipients, and severe haemolytic anaemia occurs in 3%
- March hemoglobinuria

Pathophysiology

In a healthy person, a red blood cell survives 90 to 120 days in the circulation, so about 1% of human red blood cells break down each day. The spleen (part of the reticulo-endothelial system) is the main organ that removes

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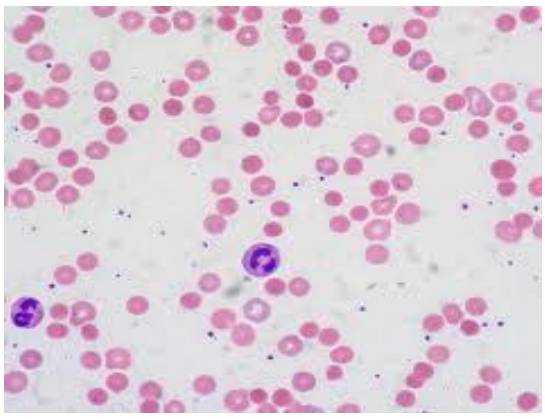
old and damaged RBCs from the circulation. In healthy individuals, the breakdown and removal of RBCs from the circulation is matched by the production of new RBCs in the bone marrow.

In conditions where the rate of RBC breakdown is increased, the body initially compensates by producing more RBCs; however, breakdown of RBCs can exceed the rate that the body can make RBCs, and so anaemia can develop. Bilirubin, a breakdown product of haemoglobin, can accumulate in the blood, causing jaundice, and be excreted in the urine causing the urine to become a dark brown colour.

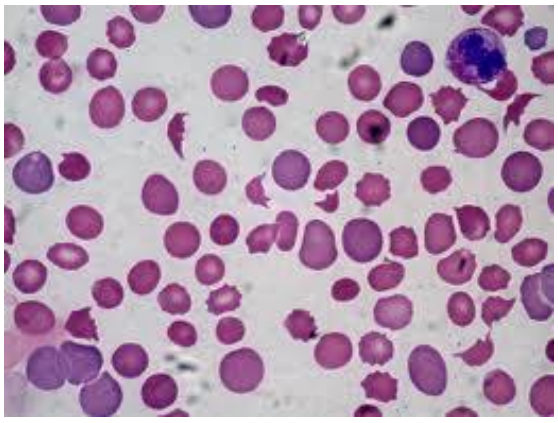
The distinguishing feature of intravascular hemolysis is the release of RBC contents into the blood stream. The metabolism and elimination of these products, largely iron-containing compounds capable of doing damage through Fenton reactions, is an important part of the condition. Free haemoglobin can bind to haptoglobin, or it may oxidize and release the heme group that is able to bind to either albumin or haemopexin. The heme is ultimately converted to bilirubin and removed in stool and urine. Haemoglobin may be cleared directly by the kidneys resulting in fast clearance of free haemoglobin but causing the continued loss of haemosiderin loaded renal tubular cells for many days.

Diagnosis

- Peripheral blood smear microscopy:
  - fragments of the red blood cells ("schistocytes") can be present
  - some red blood cells may appear smaller and rounder than usual (spherocytes)
  - reticulocytes are present in elevated numbers (polychromasia).
- The level of unconjugated bilirubin in the blood is elevated. This may lead to jaundice.
- The level of lactate dehydrogenase (LDH) in the blood is elevated
- Haptoglobin levels are decreased
- If the direct Coombs test is positive, hemolysis is caused by an immune process.
- Haemosiderin in the urine indicates chronic intravascular hemolysis. There is also urobilinogen in the urine.



spherocytes



schistocytes, spherocytes, polychromasia

Treatment

Definitive therapy depends on the cause:

- Symptomatic treatment can be given by blood transfusion, if there is marked anaemia.
- In severe immune-related haemolytic anaemia, steroid therapy is sometimes necessary.
- Sometimes splenectomy can be helpful where extravascular hemolysis is predominant (i.e. most of the red blood cells are being removed by the spleen).

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References

1. Essential Haematology , edition 5 , AV Hoffbrand, JE Petit, and PAH Moss
2. http://en.wikipedia.org/wiki/Hemolytic_anemia

Questions

1. Discuss the causes of haemolytic anaemia.
2. Discuss the lab findings in a patient diagnosed with Haemolytic anaemia.
3. Discuss the pathogenesis of Haemolytic anaemia.