A 24-year-old woman who has recently arrived in Australia from Vietnam, presents for evaluation of abnormal menstrual bleeding. There are no abnormalities on examination.

Investigations show:

Full blood count

- haemoglobin: 113 g/L [120-155]
- red cell count: 5.2 x 10^12/L [4.1-5.2]
- mean corpuscular volume (MCV): 71 fl [80-95]
- mean corpuscular haemoglobin (MCH): 22.0 pg [27.0-32.5]
- mean corpuscular haemoglobin concentration (MCHC): 310 g/L [325-360]
- white cell count: 6.6 x 10^9/L [3.5-9.5]
- differential: normal
- platelet count: 212 x 10^9/L [130-330]

Blood film shows red cell microcytosis and hypochromasia but is otherwise normal.

Haemoglobin (Hb) electrophoresis (cellulose acetate, pH 8.6):

- HbA2: 2.7% [1.8-3.5]
- HbF: 0.4% [0-2.0]

No abnormal bands

HbH preparation: HbH inclusions present

Serum biochemistry:

- iron: 8 µmol/L [7-32]
- transferrin: 3.2 g/L [2.1-3.6]
- ferritin: 15 µg/L [7-280]

The most likely diagnosis is:

A. homozygous alpha+ thalassemia (−α/−α).
B. early iron deficiency.
C. congenital sideroblastic anaemia.
D. sickle cell anaemia.
E. heterozygous beta thalassaemia.

Answer: A

Key points from question:
• Microcytic hypochromic anaemia
• FBC otherwise normal
• HbA2 and Hb F normal so it can’t be β thalassemia
• No abnormal bands on Hb electrophoresis makes sickle cell unlikely BUT not impossible bc sickling tests haven’t been done
• Normal Iron studies excludes sideroblastic anaemia (also wrong sex and age group) and makes iron deficiency unlikely
• Hb H inclusions is characteristic of α thalassemia Hb H disease but can occur in α thal trait

**ALPHA THALASSEMIA**

• 4 genes on Chr 16 that code for α chain
• 2 genes on each chromosome and they are inherited in pairs
• Syndrome is dependent on number of deletions
• AND whether the deletions are on the same chromosome

**α thalassemia – one deletion**
• asymptomatic silent carrier

**α thalassemia trait – 2 deletions**
• microcytic anaemia mild (asymptomatic)

**Hb H disease – 3 deletion**
• Hb A is only 25-30% normal
• In adults β chains accumulate and form β₄ (HbH)
• HbH forms few inclusions in erythroblasts but does precipitate in circulating RBCs
• → moderate to severe hemolytic anaemia with milder ineffective erythropoiesis
• Survival into mid adulthood w/o transfusion is common; may need transfusion during illness

**Hydrops fetalis – 4 deletions**
• Total absence of α globin synthesis
• Get no physiologically useful Hb past embryonic stage
• Excess γ globin forms tetramers γ₄ (Hb Barts) has high O₂ affinity
• Delivers almost no oxygen to fetal tissue
• → tissue asphyxiation and oedema (hydrops fetalis) with intrauterine death

**Diagnosis of Alpha Thalassemia**
• Microcytic, hypochromic anaemia
• Normal Hb A2 and HbF
• Hb H inclusions occur in Haemoglobin H disease and occasionally α thal trait
• DNA diagnosis is available

**SICKLE CELL ANEMIA**
Year 2001 Paper two: Questions supplied by Miranda

- Sickle cell syndromes are due to a mutation in the β globin gene
- Changes 6th amino acid from glutamine to valine
- Resulting molecule is Hb S
- When Hb S is deoxygenated it reversibly polymerises leading to
  - ↓ flexibility of the RBC membrane
  - ↑ viscosity
  - Dehydration due to K+ leakage and calcium influx
- Also causes the sickle like shape of the cell
- With repeated sickling the RBC loses the pliability to traverse small capillaries leading to
  - Hemolysis
  - Microvascular occlusion (this predominates the clinical course)

- Homozygous: HbSS  Sickle Cell Anaemia
- Heterozygous: HbS  Sickle Cell Trait (asymptomatic)

Clinical Manifestations
- Haemolytic anaemia with reticulocytosis
- Vasoocclusion
  - Intermittent episodes of painful ischaemia “painful crisis”
  - Most common manifestation
  - Can develop anywhere; duration of hours to weeks
  - Provoked by fever, infection, ↑ exercise, change in temp, hypoxia

- Repeated microinfarction leads to end organ damage
  - Splenic, retinal, renal, pulmonary, bone and joint infarcts
  - Renal failure common late cause of death in adults
  - Stroke is common in children but rare in adults
  - Chronic leg ulcers

- Heterogenous syndrome
- Symptoms ameliorated by co-inheritance of HbE, thalassemia, HbC

Diagnosis:
- Hb electrophoresis
  - Important to distinguish bw sickle thalassemia, Hb SC as have better prognosis
- Need to genotype family

Factors associated with ↑ morbidity and ↓ survival
Year 2001 Paper two: Questions supplied by Miranda

1. > 3 painful crises/year requiring hospitalisation
2. chronic neutrophilia
3. history of splenic sequestration or hand foot crisis
4. 2nd episode of acute chest syndrome

Treatment:
- Of acute painful crisis: hydration, analgesia and evaluate for underlying cause
- Hydroxyurea used in those with severe symptoms
- BM transplant only safe and effective in children

CONGENITAL SIDEROBLASTIC ANAEMIA
- X linked
- Due to deficient activity of erythroid form of ALA synthetase → ineffective erythropoiesis
- Typically male
- Develop refractory haemolytic anaemia, pallor and weakness in infancy
- Secondary hypersplenism
- Become iron overloaded and can develop hemosiderosis
- Severity depends on residual ALA synthetase activity
- Hypochromic, microcytic anaemia with anisocytosis, poikilocytosis and polychromasia
- Pyroxidine supplementation is treatment