Question 38

Within two hours of vigorous exercise, a 20-year-old man presents with sudden onset of severe left lateral lower chest pain, dyspnoea and anxiety. Physical examination shows him to be febrile and anaemic and there is local tenderness over the left lateral lower ribs.

Full blood examination shows:

- Haemoglobin: 75 g/L [128-175]
- Mean corpuscular volume (MCV): 81 fL [80-97]
- White cell count: 13.6 x 10^9/L [3.9-12.7]
  - Neutrophils: 11.2 x 10^9/L [1.9-8.0]
  - Lymphocytes: 0.9 x 10^9/L [0.9-3.3]
  - Monocytes: 1.0 x 10^9/L [0.3-1.1]
  - Eosinophils: 0.4 x 10^9/L [0-0.5]
  - Basophils: 0.1 x 10^9/L [0-0.1]
- Platelet count: 180 x 10^9/L [150-396]
- Reticulocyte count: 200 x 10^9/L [9-116]

The blood film is shown below.

The most likely diagnosis is:

A. Thrombotic thrombocytopenic purpura.
B. Sickle crisis.
C. Plasmodium falciparum malaria.
D. Autoimmune haemolysis.
E. Glucose-6-phosphate dehydrogenase deficiency.

Anaemia and reticulocytosis
Blood film – sickle cells
Sickle Cell anaemia

Vaso-occlusive phenomena and hemolysis are the clinical hallmarks of sickle cell disease (SCD), an inherited disorder due to homozygosity for the abnormal hemoglobin, hemoglobin S (HbS). Vaso-occlusion results in
recurring painful episodes (previously called sickle cell crisis) and a variety of serious organ system complications that can lead to life-long disabilities and/or early death.

Hemoglobin S (HbS), results from the substitution of a valine for glutamic acid as the sixth amino acid of the beta globin chain, which produces a hemoglobin tetramer (alpha2/beta S2) that is poorly soluble when deoxygenated. The polymerization of deoxy HbS is essential to vaso-occlusive phenomena. The polymer assumes the form of an elongated rope-like fiber which usually aligns with other fibers, resulting in distortion into the classic crescent or sickle shape (show histology 1) and a marked decrease in red cell deformability.

Clinical manifestations

The clinical manifestations of sickle cell disease vary markedly among the major genotypes.

- most severe in patients with SCD (homozygosity for HbS),
- intermediate severity in hemoglobin SC disease (HbSC, combined heterozygosity for hemoglobins S and C
- generally benign in those with sickle cell trait (heterozygosity for HbS).
- Among patients with sickle cell-beta thalassemia, the disease varies with the quantity of hemoglobin A, often being quite severe in patients with sickle cell-beta (0) thalassemia and less severe in patients with sickle cell-beta (+) thalassemia.
- Among patients with coexisting alpha thalassemia, the anemia is less severe (because of a lower cellular hemoglobin concentration) but the effects on the clinical manifestations are variable.
- Patients with homozygous SCD are typically anemic and often lead a life punctuated by recurrent painful vasoocclusive episodes. Clinical signs and symptoms typically develop at an early age. Dactylitis (acute pain in the hands and/or feet) common initial symptom,

Pathology

The chronic hemolysis of sickle cell disease is usually associated with a mild to moderate anemia (hematocrit 20 to 30 percent), reticulocytosis of 3 to 15 percent (accounting for the high or high-normal mean corpuscular volume [MCV]), unconjugated hyperbilirubinemia, elevated serum lactate dehydrogenase, and low serum haptoglobin

The peripheral blood smear may reveal sickled red cells, polychromasia indicative of reticulocytosis, and Howell-Jolly bodies reflecting hyposplenia secondary to repeated splenic infarctions. The red cells are normochromic unless there is coexistent thalassemia or iron deficiency. If the age-adjusted MCV is not elevated, the possibility of sickle cell-beta thalassemia, coincident alpha thalassemia, or iron deficiency should be considered

Peripheral smear from a patient with sickle cell anemia shows multiple spindly sickle cells (blue arrows), a nucleated red blood cell in the upper left, and a Howell-Jolly body (black arrow), which is a nuclear fragment.
Anemia — The anemia of SCD is usually a chronic, reasonably well compensated hemolytic anemia with an appropriate reticulocytosis.

A number of factors other than chronic hemolysis can contribute to the anemia. These include:

- Inappropriately low serum erythropoietin (EPO) concentrations, which may result in deficient compensation for hemolysis
- Folate and/or iron deficiency resulting from increased utilization of folate and enhanced urinary losses of iron.

Acute severe anemia — There are three settings in which an acute fall in hemoglobin concentration may be superimposed upon the chronic anemia: splenic sequestration crisis; aplastic crisis; and hyperhemolytic crisis. Affected patients with these complications usually present with pallor, weakness, and lethargy; fatalities are not uncommon.

Splenic sequestration crisis — With splenic sequestration crisis, vaso-occlusion within the spleen and splenic pooling of red cells produce a marked fall in hemoglobin concentration accompanied by persistent reticulocytosis and a rapidly enlarging spleen. There is a risk of hypovolemic shock, particularly in children. Although primarily associated with aplastic crisis, parvovirus B19 infection may also be a risk factor for splenic sequestration.

Aplastic crisis — An aplastic crisis is characterized by the transient arrest of erythropoiesis, leading to abrupt reductions in hemoglobin concentration and red cell precursors in the bone marrow, and a markedly reduced number of reticulocytes in the peripheral blood (ie, reticulocytes <1.0 percent and an absolute reticulocyte count <10,000 per microL).

Impaired erythropoiesis can be associated with a variety of infections. Most cases in children follow infection with human parvovirus B19, which specifically invades proliferating erythroid progenitors.

Hyperhemolytic crisis — Hyperhemolytic crisis refers to the sudden exacerbation of anemia with reticulocytosis. This complication is rare, its cause is unknown, and some experts doubt its existence.

**TTP**
- red cell fragments, microangiopathic DIC

**classic pentad of clinical features**
- Thrombocytopenia
- Microangiopathic hemolytic anemia
- Neurologic symptoms and signs
- Renal function abnormalities
- Fever
Peripheral blood smear from a patient with a microangiopathic hemolytic anemia with marked red cell fragmentation. The smear shows multiple helmet cells (small black arrows), other fragmented red cells (large black arrow); microspherocytes are also seen (blue arrows). The platelet number is reduced; the large platelet in the center (red arrow) suggests that the thrombocytopenia is due to enhanced destruction.

**Plasmodium falciparum malaria**

Thick and thin films – parasites
autoimmune haemolysis.

Spherocytes and positive coombs
(hereditary spherocytosis – spherocytosis negative coombs

This peripheral blood smear from a patient with AIHA due to a warm-reactive IgG antibody demonstrates the presence of many dark red small microspherocytes (red arrows) and larger spherocytes (black arrow) (x1000). Many large irregular blue-tinted red cells are also present, representing reticulocytes (blue arrows).

glucose-6-phosphate dehydrogenase deficiency.

Heinz body

Glucose 6-phosphate dehydrogenase (G6PD) deficiency, an X-linked disorder, is the most common enzymatic disorder of red blood cells in humans, affecting 200 to 400 million people [1]. The importance of this enzyme for red cell integrity was first recognized following the observation that some African-American soldiers taking the antimalarial drug primaquine developed acute hemolytic anemia with hemoglobinuria. Subsequently, the activity of G6PD, one of the enzymes needed to maintain adequate reduced glutathione (GSH) levels, was found to be deficient in affected red cells.
Split screen view of a peripheral smear from a patient with Heinz body hemolytic anemia. Left panel: red cells with characteristic bite-like deformity (arrows). Right panel: Heinz body preparation which reveals the denatured hemoglobin precipitates.