"...pale and tired"

Gastrointestinal & Haematology Block - Case 4

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Learning Objectives:

By the end of this PBL package, students should be able to:

- Link the histological ultra-structure and biochemical design of red blood cells with their functions.
- Discuss the functions of normal haemoglobin, the types of haemoglobin, and the impact of replacing normal haemoglobin (Hb A) with other types of haemoglobin (such as HbA2, F, or S).
- Discuss the formation of red blood cells and the role of haemopiotic system in their development.
- Discuss the physiology of iron.
- Discuss the mechanisms by which anaemia might occur.
- Apply knowledge from physiology, histology, and pathology to discuss the pathogenesis of thalassaemia intermediate and beta-thalassaemia major.
- Use knowledge from basic sciences to interpret symptoms, signs and investigation results of a patient with Beta-thalassaemia.
- Construct a brief management plan showing management goals, and management options for a patient with thalassaemia.

Trigger

Ayman Ahmed, a 7- year- old primary school student, comes in with his father, to see Dr Jamal in his clinic. Aymen always feels tired. His father says,' "Aymen does not like exercising; he is always tired and prefers not to participate in any physical education classes at school. On further questioning, the father says, "Aymen used to be more active but declined in his activity over the last 10-12 months. A few days ago his mother noticed that he looked pale."

Discussion Questions:

- Are there any difficult words you do not understand?
- List the key information about Aymen.
- Identify Aymen's presenting problems.
- For each problem, make a list of possible causes (generate hypotheses).
- What further information from history and clinical examination would you like to know to help you differentiate between your hypotheses?

Trigger

Ayman Ahmed, a 7- year- old primary school student, comes in with his father, to see Dr Jamal in his clinic. Aymen always feels tired. His father says,' "Aymen does not like exercising; he is always tired and prefers not to participate in any physical education classes at school. On further questioning, the father says, "Aymen used to be more active but declined in his activity over the last 10-12 months. A few days ago his mother noticed that he looked pale."

New Terms/Difficult words

- *Looked pale*
- *Physical education classes.*

Tutor: *Encourage students to use a medical dictionary resource to discuss the meaning of each of these words.*

Problems/Hypotheses

Always tired:

- Lacks fitness.
- Anaemic.
- Has a chronic problem (e.g., heart problems, lung problems).
- Has an endocrine problem (e.g., diabetes mellitus).
- Has a problem with his skeletal muscles.
- Has a problem causing excessive catabolism.
- Psychological trouble.

Problems/Hypotheses

Does not like exercising:

- Prefers to spend his time in activities other than exercising.
- Shy/quiet
- Has a previous bad experience with exercising.
- Not confident

Problems/Hypotheses

Looks pale:

- Anaemic.
- Blood loss/hypovolaemia.
- Shock (less likely)
- Poor skin circulation.
- Strong emotions such as fear
- Blood vessels are vasoconstricted.
- Hypothyroidism.

Facilitation Questions

What are the physiological functions do we need so that we do not feel tired?

- *Normal digestion and absorption of food*
- *Normal metabolism and normal blood glucose level.*
- *Normal cardiac functions, circulation and gases exchange in the lungs.*
- *Normal red blood cells and normal transfer of oxygen to different body tissues.*
- *Normal brain functions, no psychological troubles and enough sleeping at night.*
- *Normal body functions with no pain.*

Facilitation Questions

What does a muscle need to contract?

- *A healthy motor nerve.*
- *A healthy muscle fibres.*
- *Normal synapses*
- *Normal motor end plate*
- *Acetyl Choline*
- *Energy sources such as adenosine triphosphate (ATP).*
- *Calcium, sodium, chloride, magnesium, potassium.*
- *A healthy brain and spinal cord connected to the muscles by a motor nerve.*
- *Normal circulation and normal oxygen concentration.*

Facilitation Questions

Why do we feel fatigue on exercising?

A number of changes at cellular and biochemical levels are responsible for the development of fatigue. These can be summarized as follows:

- *Acidosis.*
- *Decreased ATP production.*
- *Increased inorganic phosphate.*
- *Increased ADP.*
- *Increased cellular sodium.*
- *Increased extra-cellular potassium.*
- *Hyperthermia.*
- *Increased intracellular calcium.*
- *Muscle fibre damage*
- *Decreased muscle partial pressure of oxygen.*
- *Decreased muscle glycogen.*
- *Dehydration.*
- *Electrolyte imbalance.*
- *Increased lactate level in exercising muscles.*

Facilitation Questions

What could possibly cause tiredness and pallor together?

The most likely causes for these two problems are:

- *Low haemoglobin*
- *Abnormal haemoglobin*
- *Blood loss*
- *Decreased oxygen carried to body tissues*
- *Heart problems*
- *Lung problems (less likely)*

Facilitation Questions

How is oxygen carried to different body tissues?

The normal haemoglobin in the red blood cells is responsible for carrying oxygen.

(8)

What are red blood cells?

Red blood cells are flat, disc-shaped, and biconcave cells of about 7-8 μm in diameter and 2 μm thick at the outer edges. In adults red blood cells are formed in bone marrow from two types of unipotential progenitor cell: The burst-forming units-erythrocyte and colony-forming units-erythrocyte. The development of red blood cells in the bone marrow is stimulated by erythropoietin, IL-3, IL-9 and other factors.

Facilitation Questions

What is haemoglobin?

Haemoglobin is found only in the red blood cells. Haemoglobin is a pigment (i.e., naturally coloured). It appears reddish when combined with oxygen and bluish when lacks oxygen (deoxygenated). The main functions of haemoglobin are to carry oxygen. Other functions of haemoglobin are: (1). carrying carbon dioxide, (2). carrying nitrogen oxide (NO) and (3). Contribution to the pH-buffering capacity of blood.

Further Questions

- Any history of blood loss.
- Any history of muscle disease or heart problems.
- Any history of hospital admission or previous investigations.
- Any previous bad experiences with exercising.
- Any history of congenital problems.
- Any history of blood diseases.

Please Read Progress 1

History

Aymen used to be active in sport when he was 5-6 years old. Over the last 10-12 months he has become increasingly tired and short of breath after any brief exercising. Because of his repeated decline to participate in exercise classes, the school asked his father to sign a form that Aymen could be relieved from exercise classes. This made his parents become worried about Aymen's health and willing to check with the family doctor. Recently, Aymen's mother noticed that he looks pale and is not active as he used to be. He becomes short of breath after brief exercising.

History

Past medical history

No history of bronchial asthma. He has no history of blood loss, blood transfusion or hospital admission.

Aymen was born in a small village in Jeezan region with the assistance of a midwife. His mother was not seen by a doctor during her pregnancy.

Family history

His half-brother, Mohammad, is 16 years old.
Mohammad lives in Lebanon with his Lebanese father.
He is always ill and needs blood transfusion nearly every month. Aymen' s father can' t remember the name of the condition.

History

Allergies

Nil

Social history

Because of his tiredness, Aymen usually goes to bed early and on several occasions does not complete his homework. His school report shows a decline in his performance in most subjects. Aymen has recently moved with his family to Riyadh. The family used to live in Jeezan and, Aymen misses his friends and cousins a lot. He is not happy because he has no friends at his new school. His father wonders if this may have caused Aymen's problem.

Clinical Examination

Aymen looks pale. He has no problems with his skeletal muscles. His vital signs are normal except for increased pulse rate of 105/min (tachycardia).

Cardiovascular and respiratory systems

Normal

Abdominal examination

Liver and spleen are not palpable.

Discussion Questions

-Are there any difficult words you do not understand?

-List the key information in this progress.

-Identify any new problems and add to your list.

-For each new problem, make a list of possible causes (generate hypotheses).

-What laboratory tests would you like to order for Aymen to help you differentiate between your hypotheses?

New Terms

(Tutor: encourage students to use their medical dictionary to find out more about these words)

- Shortness of breath.
- Bronchial asthma.
- Tachycardia.

Tutor: Encourage students to use a medical dictionary resource to discuss the meaning of each of these words/phrases.

Problems/Hypotheses

Shortness of breath and tired:

- Low haemoglobin (decreased oxygen carrying capacity).
- Abnormal haemoglobin.
- Heart problem (decreased cardiac output).
- Lung problem (poor exchange of gases).
- Chronic diseases (diseases associated with increased catabolism).

Problem/Hypotheses

Not happy at school:

- Unable to adapt to the change.
- Has no friends.
- Missing his old friends.
- Not interested in learning.
- Distracted.
- Family problems.
- Learning difficulties.
- Being bullied at school.

Problem/Hypotheses

Family history of blood disease:

- Family disorders.
- Inherited genetic/chromosomal disorders.
- Most likely related to the haemopoietic system.

Problem/Hypotheses

Not happy at school:

- Unable to adapt to the change.
- Has no friend.
- Missing his old friends.
- Not interested in learning.
- Distracted.
- Family problems.
- Learning difficulties.
- Being bullied at school.

Problems/Hypotheses

Always tired:

- Lacks fitness ?/+.
- Anaemic ? ++.
- Has a chronic problem (e.g., heart problems, lung problems) (o).
- Has an endocrine problem (e.g., diabetes mellitus). ?/o
- Has a problem with his skeletal muscles. ?/o
- Has a problem causing excessive catabolism. ?/o
- Psychological trouble. /o (what is for and what is against)

Problems/Hypotheses

Does not like exercising:

- Prefers to spend his time in activities other than exercising.o
- Shy/quiet (o)
- Has a previous bad experience with exercising.o
- Not confident o

Problems/Hypotheses

Looks pale:

- Anaemic. ++
- Blood loss/hypovolaemia. o
- Shock o
- Poor skin circulation.o
- Strong emotions such as fear ?/o
- Blood vessels are vasoconstricted.o
- Hypothyroidism. o

Facilitation Questions

Have you ever donated blood?

What did move you to donate blood?

Why do some patients need blood transfusion?

- To replace blood volume loss.

- For specific red blood disorders such as β-Thalassaemia.

- For specific medical conditions such as platelet transfusion, or fresh frozen plasma.

Please Read Progress 2

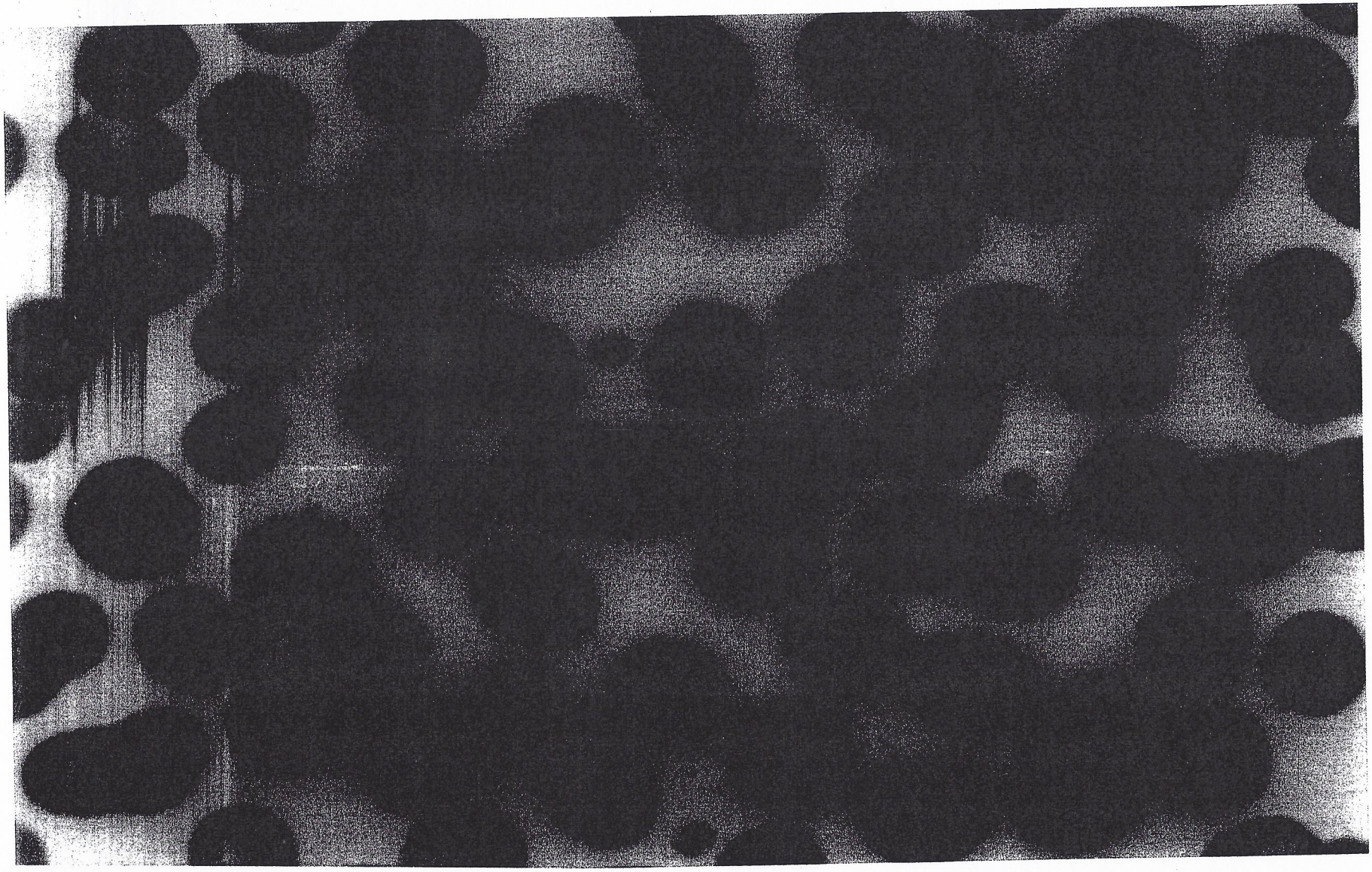
Investigations

Because of Aymen's pallor, Dr Jamal arranges for some blood tests. The results are shown below:

Blood test	Aymen's results	Normal Range
Haemoglobin (Hb)	78	130-170 g/L
Mean corpuscular volume (MCV)	78	83-101 fL
Mean corpuscular haemoglobin (MCH)	26	27-32 pg
Platelets count	200	150-400 x 10^9/L

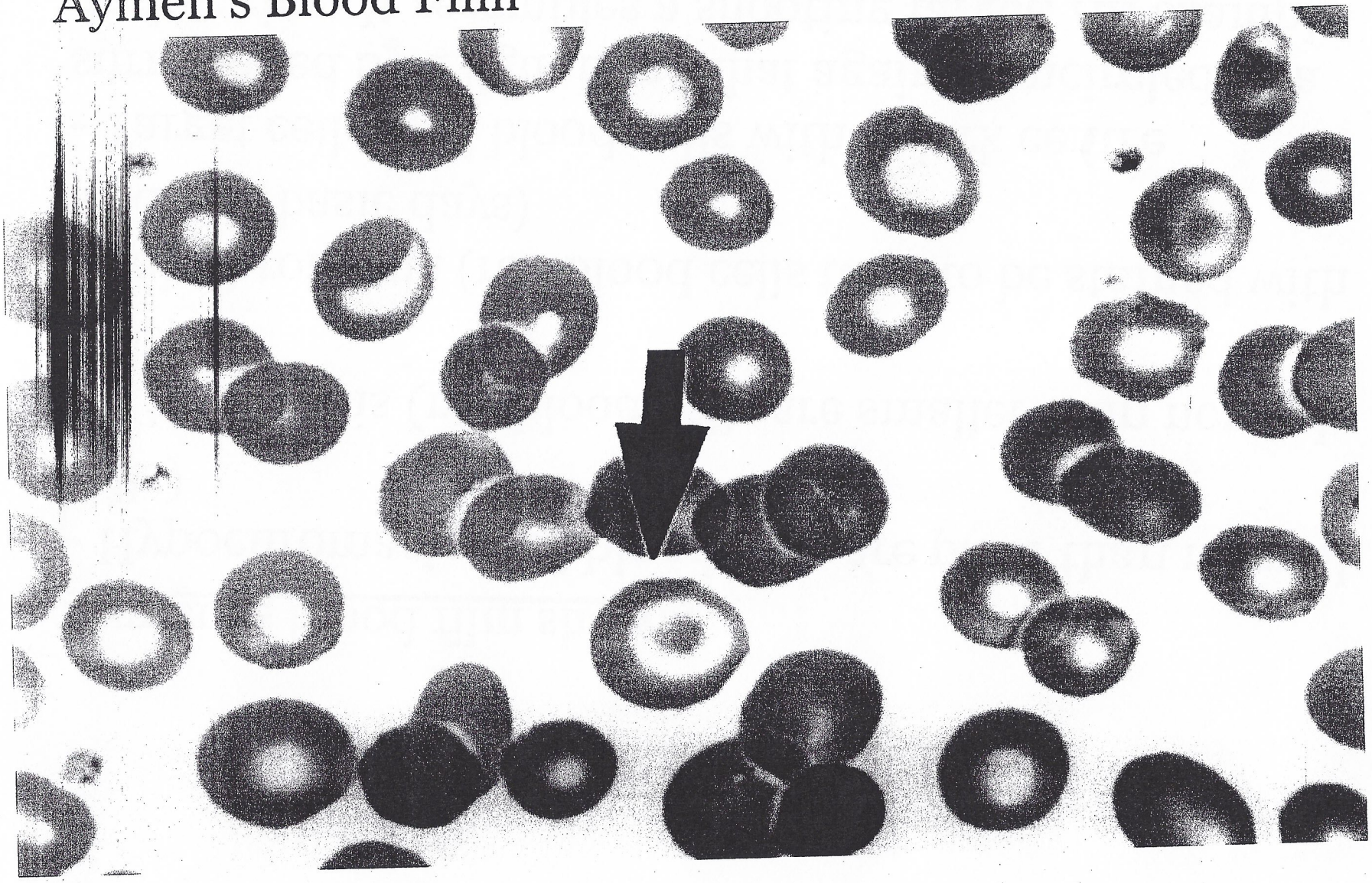
Investigations

Normal Blood Film



Investigations

Aymen's Blood Film



Blood Film Report

Aymen's blood film shows:

- Hypochromasia (red blood cells are paler than normal cells)
- Microcytosis (red blood cells are smaller than normal cells)
- Polychromasia (red blood cells tend to be stained with acid and basic days)
- Target cells (red blood cells with a dark centre surrounded by a light band that again is encircled by a darker ring. It resembles a shooting target. An example of a target cell is indicated by an arrow).
- Anisocytosis (significant variations in the size of red blood cells)

Discussion Questions

- Are there any difficult words you do not understand?
- Summarize the new information obtained from the blood tests.
- What is your interpretation of these changes?
- On the basis of the information obtained from the history, and the blood tests, do you need to make any changes to your hypotheses?
- What should Dr Jamal do next?

Difficult Words

- Haemoglobin
- Mean corpuscular volume (MCV)
- Mean corpuscular haemoglobin (MCH).

Interpretation

- Hypochromic microcytic anaemia (it might be due to iron-deficiency, or beta-thalassaemia).

- Further tests are needed to confirm or exclude iron - deficiency anaemia and the underlying cause for his enlarged liver and spleen (e.g., iron studies and haemoglobin electrophoresis).

Next Steps

- Further blood tests to assess the possibility of iron-deficiency.

- Further tests to assess other causes other than iron-deficiency (e.g., β-Thalassaemia)

Question

- Do you know a Nobel prize laureate whose work has contributed to the advancement of our knowledge in physiology and/or pharmacology related to this case? What was exactly his/her work about? Give a summary.

Please Read Progress 3

Progress 3

Because of the low MCV, MCH and the presence of microcytic hypochromic red blood cells, Dr Jamal decides to do further tests to confirm iron-deficiency anaemia. He arranges for more blood tests for Aymen.

As the results of the blood tests become available, both parents come to see Dr Jamal. See the results below.

Blood test	Aymen's results	Normal Range
Serum iron	31	9-30 µmol/L
Serum ferritin	120	10-120 µg/L
Serum transferrin	2.5	2.0-4.0 g/L

Progress 3

Dr Jamal says, "The blood tests show that Aymen has anaemia. This explains his tiredness, pallor and shortness of breath after little exercising. Anaemia means that Aymen has less than normal haemoglobin and his red blood cells are unable to carry oxygen in a way that covers the needs of his body. After reading Aymen's blood results, Dr Jamal decides to arrange for another blood test called "haemoglobin electrophoresis".

Discussion Questions

- Are there any difficult words you do not understand?
- Summarize the new information obtained from the blood tests.
- Do you think that Aymen' s anaemia is due to iron-deficiency? Explain your answers.
- In what way can the haemoglobin electrophoresis test of help?
- What are your learning issues?

New Words

- Serum iron.
- Serum ferritin
- Transferrin

Decision/Justification

His anaemia is not due to iron-deficiency. In iron-deficiency anaemia the following changes are present:

- Serum iron is decreased,
- Serum ferritin is decreased.
- Serum transferrin is increased.

Final Hypothesis

- There is evidence of anaemia (low haemoglobin).
- It is a hypochromic microcytic type of anaemia.
- It is most likely not due to iron- deficiency (iron studies results are not consistent with iron deficiency anaemia).
- It is most likely due to other congenital disorders e.g., β-Thalassaemia.

Learning Issues

Tutor: Encourage students to identify their learning issues that reflect key issues raised in the case. They might need to edit their learning issues into sentences or questions. Usually learning issues are about 5-7 key principles. See examples shown below).

Learning Issues

- Structure and function of red blood cells.
- Structure and function of normal haemoglobin (HbA2). Other types of haemoglobin and physiological differences.
- Development of red blood cells and physiological factors needed for normal development in the bone marrow.
- Physiology and metabolism of iron (iron absorption, serum iron, transferrin, and ferritin).
- Mechanisms by which anaemia may develop.
- Pathogenesis of beta-thalassaemia major. Differences between beta-thalassaemia major and thalassaemia intermediate.
- Interpretation of the patient symptoms, signs and investigation results.
- A brief management plan showing management goals, and management options.

Tutorial Two

Discussion Questions

After the students spent about 60 minutes addressing their learning issues. You might spent 10-15 minutes on these questions:

Discussion Questions:

- What changes would you expect in Aymen's haemoglobin electrophoresis? Explain your reasoning.

- How are these changes related to his presenting symptoms?

Do you know a Nobel prize laureate whose work has contributed to the advancement of our knowledge in physiology and/or pharmacology related to this case? What was exactly his/her work about? Give a summary.

Student: You could also after the completion of this case submit your work about the Nobel Prize laureate for this case to Professor Samy Azer at (sazer@ksu.edu.sa) or hand it to him.

Please Read Progress 1

الوجه الأول (29)

Progress 1

Dr Jamal meets with the family and Aymen to explain the nature of Aymen's condition. He says, "the laboratory results show that Aymen's problem is only limited to the red blood cells; other blood elements such as white blood cells and platelets are normal. The iron studies clearly indicate that Aymen's anaemia is not due to iron-deficiency, a common cause of anaemia. We believe his anaemia is most likely due to an inherited blood condition that affects red blood cells. To confirm this diagnosis we will need to do more blood tests. This test is called haemoglobin electrophoresis which usually helps in identifying the exact cause of his anaemia. "

الوجه الآخر (29)

Progress 1

Aymen's haemoglobin electrophoresis results are shown below:

Haemoglobin electrophoresis:

Haemoglobin type	Aymen's results	% of total haemoglobin
Haemoglobin A (Hb A)	52%	Over 95%
Haemoglobin A2 (Hb A2)	7%	2-3%
Haemoglobin F (Hb F)	41%	Less than 1%
Haemoglobin S (Hb S)	Absent	Absent
Other abnormal haemoglobins	Absent	Absent

Progress 1

Dr Jamal explains to Aymen' s father, "Aymen has a hereditary type of anaemia called β-Thalassaemia. This type of anaemia is not due to iron deficiency and is not treated by iron tablets. The inherited defect is in the make up of haemoglobin. Haemoglobin is a substance normally present in the red blood cells and responsible for carrying oxygen. Therefore, Aymen' s red blood cells cannot carry oxygen and deliver it to the body cells as do normal blood cells.

Aymen' s mother, Mrs Nabila, mentions that her elder son Mohammad, from another marriage, has β-Thalassaemia major. His condition was diagnosed when he was 1 to 2 months old. His condition requires repeated hospital admissions and frequent blood transfusions. Mrs Nabila says, "Mohammad' s father is my cousin". She asks Dr Jamal if Aymen will also need blood transfusions like his brother and why Mohammad' s anaemia is different from that of Aymen' s.

Discussion Questions

- Are there any terms that you do not understand?
- Summarise the key information that you have obtained from this progress.
- On the basis of the new information, how would you explain Aymen's presenting symptoms?
- Why are iron tablets not prescribed for treating patients with Thalassaemia?
- Why do you think Mohammad does not need blood transfusion? How his anaemia is different from his brother?

Difficult Words

- **Hb A:** *Comprises over 93 percent of normal adult Hb ($\alpha 2$, $\beta 2$).*
- **Hb F:** *Normal fetal haemoglobin, increased in β-Thalassaemia ($\alpha 2$, $\gamma 2$).*
- **Hb S:** *Present in Sickle-cell anaemia ($\alpha 2$, $\beta 2$ and Hb S)*

Key Information

- Increased Hb A2
- Decreased Hb A
- Increased Hb F
- No other abonormal haemoglobins.

Discussion Questions

Why Ayman' s anaemia is not severe as that of his half-brother' s Mohammad?

- *Not all β- Thalassaemias are of the same degree of severity. Accordingly, the clinical spectrum can be discussed under three main degrees:*
- *Thalassaemia minor.*
- *Thalassaemia intermedia.*
- *Thalassaemia major.*

Facilitation Questions

Will Ayman's condition require blood transfusions? Explain your reasons.

Thalassaemia intermedia usually presents with moderate anaemia, microcytosis and sometimes enlarged liver and spleen. Patients rarely require blood transfusion.

Discussion Questions

Ayman' s brother needs frequent blood transfusion as part of the treatment of his condition. What are the physiological bases behind blood transfusion?

- *The extracellular surface of the red blood cell membrane has specific inherited carbohydrate chains that act as antigens and determine the blood group of an individual. The most important of these antigens are the A and B antigens responsible for the determination of the four blood groups A, B, AB and O.*

- *Individuals who lacks either A or B antigens or both, have antibodies against the missing antigen in their serum.*

- *If blood containing the missing antigen is transfused, the donor erythrocytes are attacked by the recipient' s serum antibodies causing their lysis.*

Please Read the Closure