Learning Objectives:

Students by the end of this PBL should be able to:

- Correlate the anatomical structures and cells of the liver with their functions.
- Explain the pathology and pathogenesis of liver cirrhosis.
- Discuss the mechanisms underlying portal hypertension, portosystemic shunt, and associated complications including oesophageal varices, splenomegaly and development of ascites.
- Use basic sciences to interpret symptoms, signs and investigation results of a patient with liver cirhosis.
- Discuss the pathogenesis of haematemesis in a patient with liver cirhosis and portal hypertension
- Construct a brief management plan showing management goals and management options in a patient with liver cirrhosis.
- Discuss the pharmacology of drugs used in the management plan.

Trigger

Saif Abdullah, 58 years old business man from Damam is on a business trip for about a week in Riyadh. He is staying in a famous hotel with his business assistant. On the third day of his stay, he is found by the hotel housekeeper on the floor of his room in a pool of blood. The hotel manager calls an ambulance immediately. Saif is able to talk to the ambulance officers. He has vomited large amount of dark blood as he was preparing to go for breakfast. He has no injuries. One of the ambulance officer noticed that the sclerae of Saif' s eyes are yellow and he his increased abdominal girth.

Discussion Questions:

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

Trigger (Problem)

Saif Abdullah, 58 years old business man from Damam is on a business trip for about a week in Riyadh. He is staying in a famous hotel with his business assistant. On the third day of his stay, he is found by the hotel housekeeper on the floor of his room in a pool of blood. The hotel manager calls an ambulance immediately. Saif is able to talk to the ambulance officers. He has vomited large amount of dark blood as he was preparing to go for breakfast. He has no injuries. One of the ambulance officer noticed that the sclerae of Saif' s eyes are yellow and he his increased abdominal girth.

New Terms/Difficult words

- *Sclerae*
- *Abdominal girth*

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

Problems/Hypotheses

<u>Vomiting blood</u>

- Gastric ulcer
- Duodenal ulcer.
- Gastritis
- Oesophagitis
- Cancer of the oesophagus
- Stomach cancer
- Blood disorders
- Tears of the oesophagus

Problems/Hypotheses

Yellow sclera

1. Increased production of bilirubin
   - Haemolysis
     - Causes: out of RBCs.
     - Causes in red cell membrane.
     - Presence of abnormal haemoglobin.
   - Haematoma

2. Decreased uptake of bilirubin by the liver cell
   - Problem with the uptake process

3. Decrease or lack of conjugation of bilirubin inside the hepatocytes.
   - Congenital
   - Drugs/ toxins
   - Damage to hepatocytes (viruses, alcohol, drugs, toxins)

Problems/Hypotheses

Yellow sclera

4. Decreased efflux or secretion of conjugated bilirubin
   - Problem with the liver canaliculi
   - Congenital problems with the carrier proteins

5. Obstruction of the biliary system
   - Impacted stone
   - Carcinoma of biliary duct
   - Cancer head of pancreas.

Problems/Hypotheses

Increased abdominal girth

-Obesity (a lot of fat in the omentum).

- Abdominal organs are enlarged (liver, spleen, or other masses intra or retroperitoneal)

- Free fluid in abdominal cavity .
  - Blood
  - Ascetic fluid

- Large abdominal hernia

- Small bowel obstruction

Facilitation Questions

What could possibly be the source of blood in a vomitus?

- *Mouth cavity, tongue*
- *Nasopharynx/Nasal cavity/Respiratory*
- Oesophagus (cancer, inflammation, infection, tear, abnormal vessels- veins)
- Stomach (gastric ulcer)
- Duodenal ulcer.

What could possibly cause the sclerae to become yellow in colour?

Tutor: *if the student mention "Bilirubin" you might ask:*

What is bilirubin?

What are the sources of bilirubin

Facilitation Questions

Normally our sclerae are white in colour. What could possibly happen to make bilirubin increases in the blood and be deposited in the sclerae?

1, Increased destruction of red blood cells.
2. Decreased uptake of bilirubin by hepatocytes.
3. Problem with conjugation of bilirubin in the liver cell.
4. Problem with efflux (secretion) of conjugated bilirubin.
5. Regurgitation of conjugated bilirubin (outlet obstruction).

History

On the way to the Hospital, the assistant of Mr. Saif tells the ambulance officer that 'Mr. Saif has been unwell for the last few weeks. Two colleagues at work noticed that his eyes are yellow. He always feels tired and not fit as he used to be'. He has always been fit and he used to be a swimming champion for several years.

On further questioning, Saif responds to the ambulance officer's questions and mentions that he has noticed a progressive increases in his abdomen and he has to buy new trousers in a bigger size to fit him. Because he is always busy and travels a lot, he has no time to see his general practitioner and has not seen him for about two years.

He has no history of hyperacidity or heartburn. His symptoms suggestive of peptic ulcer. No changes in the colour of his urine.

History

Past history:

Saif has a major road traffic accident about 30 years ago and fractured both of his femurs and needed blood transfusion. Apart from this accident, there is no history of hospital admission or investigations.

Medications and allergy:

Nil

Alcohol and Smoking:

He smokes 20 cigarettes per day for over 30 years. He drinks alcohol while he is on a business trip abroad but he is not a heavy drinker.

Family history

No family history of blood diseases or blood disorders.

Social history

He is married and has 3 grown up children- 20, 22, and 25 years old. He has no financial problems. He always travels abroad and spends less time with his family.

Discussion Questions

- Are there words that you do not understand?
- Summarize key information that you have obtained from this progress.
- Identify Saif' s new problems. Provide hypotheses for each problem.
- Use the new information obtained to refine your hypothesis.
- What should the doctor do at this stage?

New Words

-Champion

-Blood transfusion

-financial

Tutor: These are general words. One member from the group might help. They might need to use the medical dictionary for "blood transfusion".

Problems/Hypotheses

Vomiting blood

-Gastric ulcers o
- Duodenal ulcer o
- Gastritis o
- Oesophagitis o
- Cancer of the oesophagus ?/o
- Stomach cancer ?/o
- Blood disorders o
- Tears of the oesophagus o
- Abnormal blood vessels in the oesophagus +/++

Problems/Hypotheses

Yellow sclera

1. Increased production of bilirubin
   - Haemolysis o
     Causes: out of RBC
     Causes in red blood cell membrane.
     Presence of abnormal haemoglobin
   - Haematoma o

2. Decreased uptake of bilirubin by the liver cell
   - Problem with the uptake process ?/+

3. Decrease or lack of conjugation of bilirubin inside the hepatocytes.
   - Congenital o
   - Drugs/ toxins /o
   - Damage to hepatocytes (viruses, alcohol, drugs, toxins) ?/+++

Problems/Hypotheses

Yellow sclera

4. Decreased efflux or secretion of conjugated bilirubin
   - Problem with the liver canaliculi ?/-
   - Congenital problems with the carrier proteins o (patient' s age)

5. Obstruction of the biliary system
   - Impacted stone ?/o (no pain)
   - Carcinoma of biliary duct ?/o/+
   - Cancer head of pancreas. ?/+

Problems/Hypotheses

Increased abdominal girth

-Obesity (a lot of fat in the omentum). ?/+

- Abdominal organs are enlarged (liver, spleen, or other masses intra or retroperitoneal) ?/+

- Free fluid in abdominal cavity .
  - Blood ?/+
  - Ascetic fluid ?/+

- Large abdominal hernia ?

- Small bowel obstruction /o

Clinical Examination

He looks pale and the sclerae of his eyes are yellow in colour. There are no palpable lymph nodes. His vital signs are summarized in the table below:

Vitals Signs	Saif's results	Normal range
Temperature	36.8 °C	36.6-37.2 °C
Pulse rate	120/min, regular	70-110/ min
Respiratory rate	22/min	12-16/min
Blood pressure	110/69 mmHg (lying) 80/55 mmHg (sitting)	100/65 – 135/80 mmHg

Clinical Examination

Gastrointestinal System Examination

- Spider naevi are found on his face, neck and both shoulders (see images 1).
- His hands shows palmar erythema (see image 2) and his nails show leuconychia (see image 3).
- He has gynaecomastia on both sides and his testicles are atrophied.
- His abdominal girth is increased and there are dilated veins and the umbilicus (caput medusae, see image 4). No umbilical or inguinal hernia.
- Abdominal palpation: The liver span is 8 cm (shrinked; normal 12-14 cm). The spleen is 3 cm below the left costal margin.
- Percussion of his abdomen: There is positive shifting dullness (indicating the presence of free fluid in the peritoneal cavity).
- A pitting oedema is noticed on his lower limbs up to 5 cm below his knees.

Discussion Questions

- Are there any terms that you do not understand?
- Summarize the key information that you have obtained from this progress.
- Refine your hypotheses and identify your most likely hypothesis.
- Work out with your group your "learning issues"?

Difficult words

- Spider naevi.
- Palmar erythema.
- Gynaecomastia.
- Caput medusae.
- Shifting dullness
- Peritoneal cavity.
- Pitting oedema.
- Haemodynamic changes.

Tutor: encourage students to use the medical dictionary.

Problems/Hypotheses

Vomiting blood

- Gastric ulcers (o)
- Duodenal ulcer (o)
- Oesophagitis (o)
- Cancer of the oesophagus (o)
- Stomach cancer (o)
- Blood disorders/bleeding tendency (o)
- Tears of the oesophagus (o)
- Abnormal blood vessels in the oesophagus (+++)

Problems/Hypotheses

Yellow sclera

1. Increased production of bilirubin
   - Haemolysis (o)
     Causes: out of RBC o
     Causes related to red blood cell membrane (o)
     Presence of abnormal haemoglobin (o)
   - Haematoma (o)

2. Decreased uptake of bilirubin by the liver cell
   - Problem with the uptake process (o)

3. Decrease or lack of conjugation of bilirubin inside the hepatocytes.
   - Congenital problems (o)
   - Drugs/ toxins (not on medications) (o)
   - Damage to hepatocytes (viruses, alcohol, drugs, toxins) (++++)- history of blood transfusion + history of alcohol intake.

Problems/Hypotheses

Yellow sclera

4. Decreased efflux or secretion of conjugated bilirubin
   - Problem with the liver canaliculi (o)
   - Congenital problems with the carrier proteins (o)

5. Obstruction of the biliary system
   - Impacted stone (o)
   - Carcinoma of biliary duct (o)
   - Cancer head of pancreas. (o)

Problems/Hypotheses

Increased abdominal girth

-Obesity (a lot of fat in the omentum). (0)

- Abdominal organs are enlarged (liver, spleen, or other masses intra or retroperitoneal) (0)

- Free fluid in abdominal cavity .
  - Blood (+/0)
  - Ascetic fluid (++++)

- Large abdominal hernia (0)

- Small bowel obstruction (0)

Facilitation Questions

What are the functions of the liver?

1. Synthetic functions:
   - Albumin
   - Coagulation factors
   - Bile salts/ cholesterol

2. Metabolic functions:
   - Carbohydrates
   - Proteins
   - Fats

3. Detoxification of drugs

4. Excretion function
   - Drugs
   - Metabolite
   - Bile

Facilitating Questions

What are the cells of the liver and what are their functions?

- *Hepatocytes.*
- *Kupffer cells (immune system)*
- *Stellate cells (stimulation causes release of cytokines and collagen)*
- *Fenestrated endothelial cells*
- *Ito cells (fat storage cells).*

Tutor: *These issues are new to the students. They might add them to their learning issues.*

Facilitating Questions

How did Mr. Saif develop an ascites (free fluid in the peritoneal cavity)? What are the underlying mechanisms?

- *Sinusoidal hypertension.*
- *Low serum albumin.*
- *Leakage of hepatic lymph.*
- *Raised serum aldosterone*
- *Renal retention of sodium and water*
- *Increased ADH.*

Tutor: *These issues are new to the students. They might add them to their learning issues.*

Facilitating Questions

How can we explain his splenomegaly?

- *Long standing congestion.*
- *Hypersplenism (long standing cases)*

How can we explain the changes in his blood pressure? What are the underlying physiological mechanisms?

- *Baroreceptors (reflex).*
- *Increased renin> increased angiotensinogen >increased angiotensin I > increased angiotensin II.*
- *Increased adrenaline*

Tutor: *These issues are new to the students. They might add them to their learning issues.*

Facilitating Questions

How would you explain his gynaecomastia and atrophied testicles?

- *Increased oestrogen (liver is not able to metabolise oestorgen)*
- *Disturbance of the hypothalamic-pituitary-gonadal axis.*

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.

Tutor: *These issues are new to the students. They might add them to their learning issues.*

Hypotheses: Ranking

Most likely:

Liver cirrhosis and the development of portal hypertension.

The development of portal hypertension resulted in porto-systemic shunt of blood (dilated abdominal veins and oesophageal varices), splenomegaly and ascites.

Several mechanisms have contributed to the development of ascites.

Less likely:

- Oesophageal cancer.
- Oesophageal tear.
- Gastric ulcer
- Duodenal ulcer
- Gastric cancer
- Blood disorders
- Obstructive jaundice
- Decreased uptake of bilirubin by hepatocytes.
- Increased haemolysis
- Umbilical/inguinal hernia.
- Intra- abdominal bleeding

Learning Issues

- Anatomical structures and functions of the liver.
- Pathology and pathogenesis of liver cirrhosis.
- Mechanisms responsible for portal hypertension and associated changes such as splenomegaly, ascites, and development of oesophageal varices.
- Common causes of vomiting blood and underlying mechanisms.
- How changes in the structure and functions of the liver resulted in the patient' s symptoms, signs and laboratory results.
- What are the investigations needed for Saif? How these investigations can help you?
- A brief management plan showing management goals, and management options.

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 is your final hypothesis? What is your evidence?
- What could possibly be the mechanisms underlying Saif' s presenting problems?
- What should the doctor do at this stage?

Discussion Questions

Answer to Q3:

Not in the student case:

Q1. What is your final diagnosis?

- *Liver cirrhosis.*
- *Portal hypertension (ascites + caput medosa + bledding from dilated oesophageal veins (oesophageal varices) + splenomegaly + pitting oedema)*

Evidence:

History: Jaundice, vomiting blood, increased abdominal girth.

Examination: skin changes suggestive of chronic liver disease (spider naevi, palmar erythema), signs of portal hypertension (ascites, caput medusae, oesophageal varices, splenomegaly, oedema of the lower limbs, evidence of loss of liver function (gynaecomastia, testicular atrophy etc).

Discussion Questions

Answer to Q3:

Not in the student case:

Q2. What would the doctor do at this stage?

- *Correct the haemodynamic changes.*
- *Manage the bleeding (stop the bleeding)*
- *Find out the causes of his problems (complete blood count, liver function tests (LFTs), coagulopathy profile, Ultrasound of the upper abdomen)*
- *Short and long term management plan.*

Progress 1

The doctor in the Accident & Emergency Department inserts two IV cannulas into Saif's median cubital veins, one cannula in each arm. The patient is given intravenous fluids to expand his plasma volume until he receives two blood units from the blood bank. He also sends blood to the laboratory for blood workouts (complete blood count, liver function tests, blood urea, creatinine and electrolytes, serology viral screening tests) and contact a gastroenterologist to review Mr Saif. The gastroenterologist reviews Mr Saif case, checks that Saif has received needed emergency management options, focuses on correcting the circulatory haemodynamics , and prepares Saif for an urgent gastroscopy to stop any further bleeding. The blood test results become available and are shown in the tables below:

Complete Blood Count:

Blood Test	Faisal's results	Normal range
Haemoglobin	8.3	11.5-15.5 g/100ml
White blood cell count	9 x 10^9 /L	4-11 x 10^9/L
Packed cell volume (PCV)	49	37-47%
Mean corpuscular volume (MCV)	98	80-96 fl
Platelet count	89,000	160,000-500,000 mm^3

Progress 1

Liver Function Tests

Test	Saif's Results	Normal Range
Serum bilirubin	83	0-19 µmol/L
Aspartate Aminotransferase (AST)	72	0-40 IU/L
Alanine Aminotransferase (ALT)	59	0-50 IU/L
Alkaline Phosphatase (ALP)	175	0-120 IU/L
Gamma Glutamyltranspeptidase (γ- GT)	109	0-50 IU/L
Serum albumin	28	35-50 g/L
Prothrombin time	20 seconds	10-14 seconds

Serology Screening Tests:

- Hepatitis C virus: positive
- Hepatitis B virus: negative
- Hepatitis A virus: negative

Progress 1

Blood Biochemistry

Blood Test	Saif's Results	Normal Range
Serum Sodium	132	135-146 mmol/L
Serum Potassium	3.9	3.5-5.0 mmol/L
Blood urea	2.1	2.5-6.7 mmol/L
Serum Creatinine	120	79-118 µmol/L
Vitamin B_{12}	360	100-520 pmol/L
Folate- red blood cells	310	160-640 µg/L

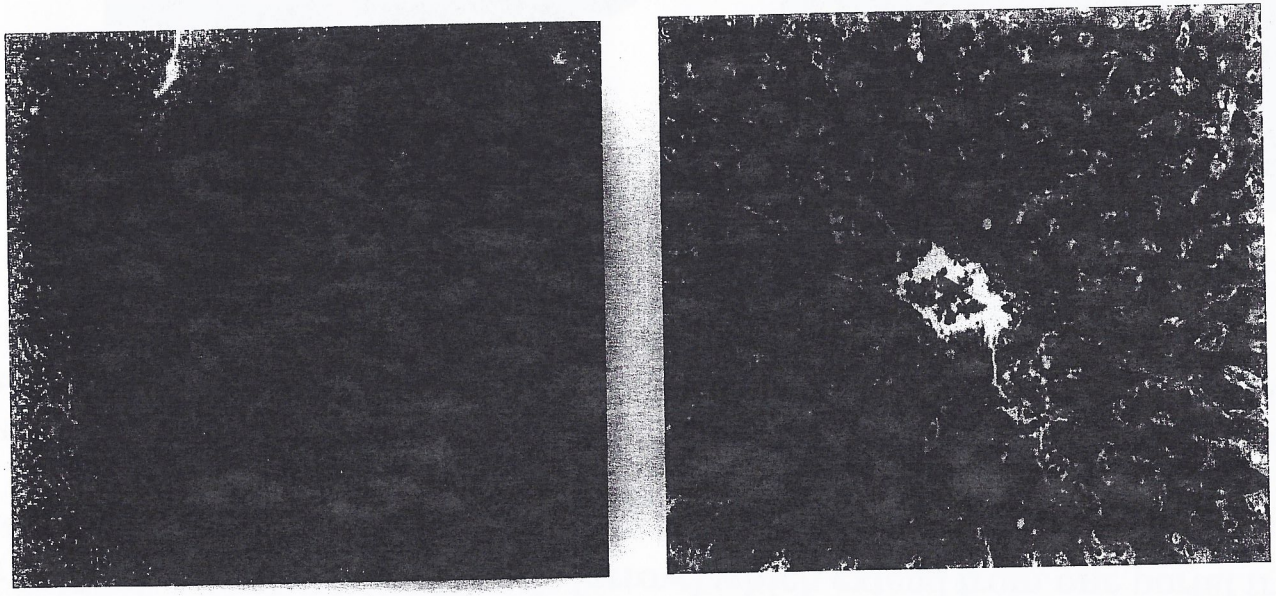
Ultrasound:

- The liver surface is not smooth, it shows nodularity
- No thrombosis in the portal vein or intrahepatic veins.
- No masses suggestive of liver malignancy.
- There is a free fluid in the peritoneal cavity (ascites).

Progress 1

Normally we do not recommend liver biopsy because of his prolonged prothrombin time and bleeding tendency. A liver biopsy is contraindicated in such situations. After correcting his coagulopathy, a liver biopsy was performed under ultrasound guidance. A normal liver histology is shown for comparison.

NORMAL LIVER



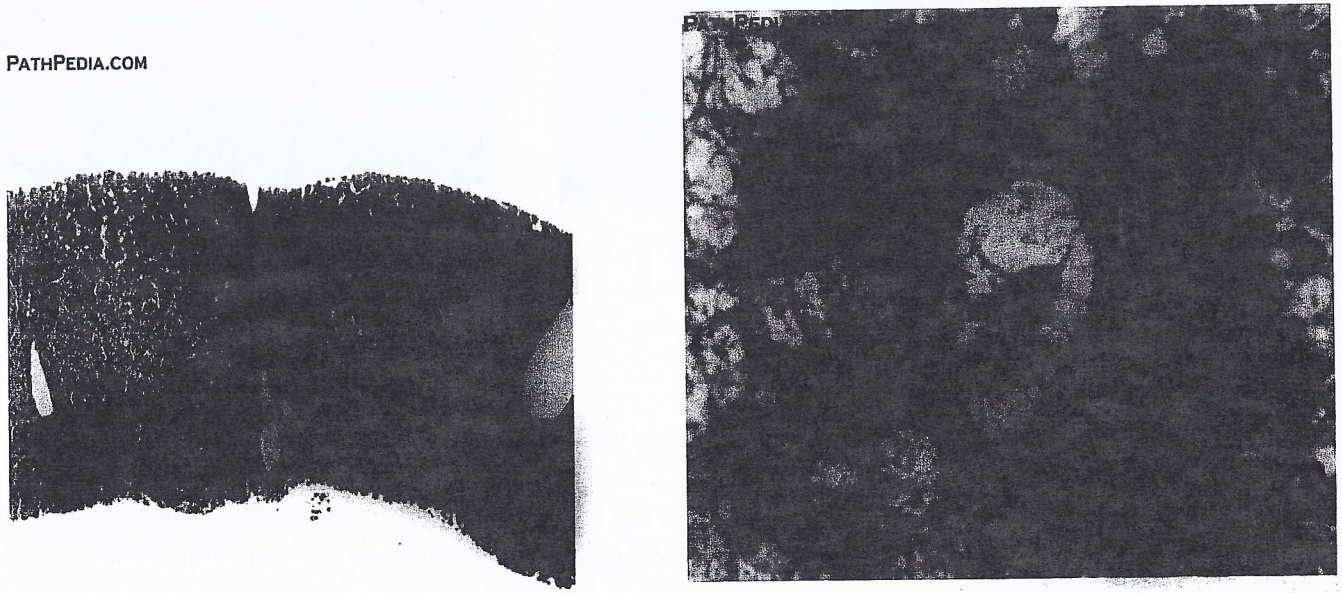
Progress 1

Source: pathpedia.com

Report:

Low power: There is a general liver architectural distortion caused by hepatocellular necrosis with repair in the form of bridging fibrosis (arrow) which extend from one portal tract (number 1) to another portal tract (number 2).

High power: Evidence of inflammatory cellular injury confirmed by ballooning enlargement of hepatocytes (called ballooning degeneration), see black arrow. These changes although non-specific, they are commonly seen in viral hepatitis C infection.



Discussion Questions

- Are there words that you do not understand?
- Summarize key information that you have obtained from this progress.
- On the basis of the new information, what is your final hypothesis?
- Summarise your management goals and your management options?.

Facilitation Questions

What are the underlying mechanisms for his:

- increased serum bilirubin.
- increased PCV
- increased MCV (although his B12 and folate are within normal range)
- changes in his liver enzymes.

What are the mechanisms underlying his decreased serum albumin?

-Decreased synthesis in the liver.
- Increased loss

How would you explain his decreased blood urea (although his blood pressure is low and there is decreased renal perfusion)?

Urea is synthesized in the liver cells from nitrogen. The low serum urea is due to loss of function.

What is Hepatitis C?

Discuss how infection occurs?

Facilitation Questions

What is liver cirrhosis?

Necrosis of liver cells followed by fibrosis and nodule formation.

What are the causes of liver cirrhosis?

- *Hepatitis (B /- D, C)*
- *Alcohol*
- *Biliary cirrhosis.*
- *Autoimmune*
- *Hereditary haemochromatosis.*
- *Wilson's disease.*
- *Alpha-antitrypsin deficiency.*

Facilitation Questions

What are the consequences of liver cirrhosis?

- *Loss of function.*
- *Portal hypertension (ascites, splenomegaly, oesophageal varices)*
- *Nutritional deficiencies*

What is the normal portal pressure?

Portal vein is formed by the union of superior mesenteric and splenic veins. Normal pressure (10-12 mmHg).

What are the consequences of portal hypertension?

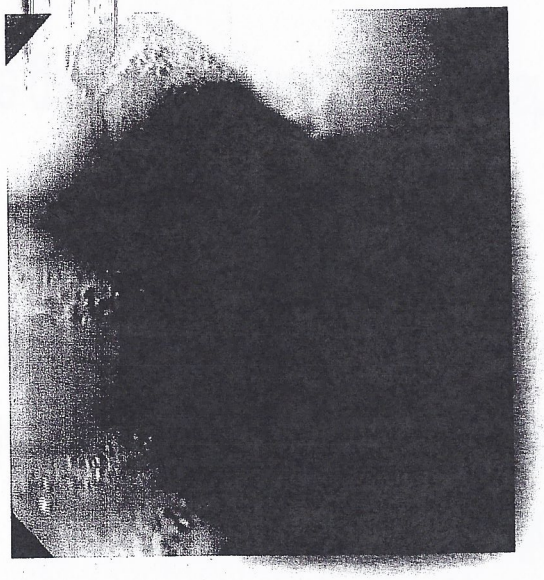
Progress 2

The gastroenterologist examines Mr Saif , and reviews all blood test results. He confirms the diagnosis of liver cirrhosis, and portal hypertension, as evidenced by dilated abdominal veins, splenomegaly, and the presence of ascites. He mentions to Mr Saif that he needs an urgent gastroscopy to stop the blood which is most likely from bleeding dilated veins at the end of the oesophagus (the food pipe). At the mean time, he arranges to give him octreotide to decrease the pressure of the portal vein and the tendency for bleeding.

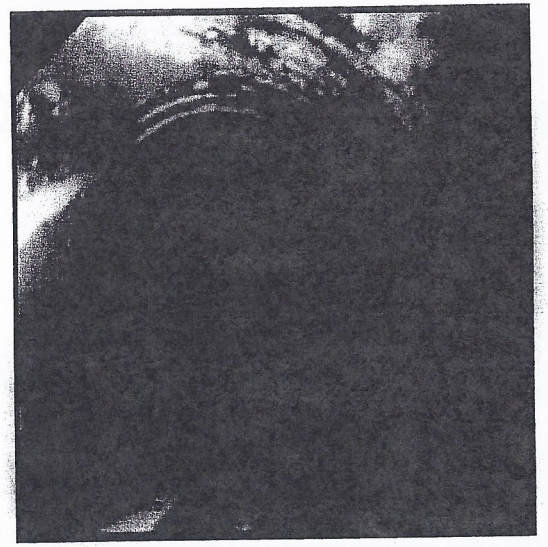
The garstorscopy images below show the lower end of the oesophagus before and after banding.

Progress 2

Before Banding



After Banding



Progress 2

During the gastroscopy procedure, the gastroenterologist identifies the source of bleeding and bands the bleeding oesophageal varices. He ensures that the bleeding has stopped.

SAif is treated in hospital for a few days. Before hospital discharge, the gastroenterologist explains to Mr Saif the nature of his illness and that his liver problem (medically known as liver cirrhosis) is most likely caused by hepatitis C virus infection. This might has happened many years ago and the virus has gradually caused a wide range of changes in the liver causing loss of its cells and hence deterioration of the liver functions. The changes in the liver also resulted in blocking the normal blood circulation in the liver and forced the blood to shift into the systemic circulation via other veins outside the liver, these veins are normally not functioning. This explains the dilated abdominal veins, and the dilated veins at the end of the oesophagus and the bleeding from the oesophageal veins and blood loss.

The gastroenterologist discusses with Saif that he might need a liver transplant ion and arranges for him to review the team at King Faisal Specialised Hospital, Liver Centre . In the mean time, the gastroenterologist commences Saif on diuretics (for ascites), beta blockers (to help in reducing the portal hypertension), and continues him on vitamin K injections (for his prolonged prothrombin time). He also advises him to stick to a low salt diet, decreases proteins in his diet and avoid constipation. Saif reviews the Liver Centre for further assessment.

Discussion Questions

- Are there words that you do not understand?
- Summarize key information that you have obtained from this progress.
- Construct a mechanism summarizing your final hypothesis with regard to the lesion, the mechanisms underlying Saif' s problems. Provide supportive evidence from history, clinical examination and investigation results.

Difficult Words

- Banding.
- Portal hypertension
- Liver transplantation
- Octrotide

Facilitation Questions

- Discuss the pharmacology of drugs used:
  - Octrotide
  - Diuretics.
  - Beta Blockers.
  - Vitamin K

- What are the ethical principles around liver transplantation?