Case Number 7
Beta thalassemia major with pulmonary hypertension

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Case summary:

Demographic details:

Mr. IB, 29
Referred to: A&E

Mr. IB, a 29-year-old gentleman, who is a known case of beta thalassemia major, was referred from the emergency department following an episode of lethargy, cough, exertional dyspnoea and dyspepsia. During his stay, a number of investigations were carried out and the patient was diagnosed with pulmonary hypertension with a mean pulmonary artery pressure of 90-100mmHg – a complication of beta thalassemia.

This is the only reported case in Malta.

Following the diagnosis, the patient was given a number of drugs (see below) to control his symptoms.

Presenting complaint:

Dyspepsia
Exertional dyspnoea
Cough
Lethargy

History of presenting complaint:

The patient was admitted with a presenting complaint of dyspnoea on exertion, lethargy and cough together with dyspepsia. There was no documented history of fever or recent travel.

Past medical history:

Patient was known to suffer from thalassemia major and underwent splenectomy 20 years ago and as a result, the patient is chronically jaundiced. Has a history of blood transfusions as part of treatment for the symptoms of beta thalassemia major.
Beta thalassemia major with iron overload (markedly increased serum ferritin).
Decreased levels of testosterone in setting of low levels of LH and FSH (hypogoandotrophic hypogonadism), a direct effect of iron overload which deposits in the pituitary gland. Bilateral testicular biopsy had shown a reduced number of germinal cells, with an increased number of Sertoli cells. An MRI of pituitary showed rather small pituitary gland, poor enhancement but no lesions and a central pituitary stalk.
Hepatomegaly was confirmed by ultrasound, in which the liver had a hyperechoic homogeneous structure.

Past surgical history

Splenectomy during childhood.

Drug history:

Drug Name	Dosage	Frequency	Type	Reason
Deferasirox (Exjade)	1750mg	Daily	Tablet for oral suspension	Iron chelator to reduce further iron overload
Phenoxymethylpenicillin (Penicillin V)	250mg	QDS	Oral tablet	To prevent infection following splenectomy
Folic acid	5mg	Daily	Oral tablet	For maintenance of normal erythropoiesis, as erythropoiesis increases due to underlying beta thalassemia major

The patient has no known drug allergies (NKDA).

Family history:

The patient has a family history of beta thalassemia. Both parents are known to be carriers of the condition. His sister was also affected and died of the condition.

Social history:

The patient is married and currently unemployed. He tends to binge drink on weekends and smokes a packet of cigarettes a day.

Systemic inquiry:

- General Health: Chronic jaundice and lethargy
- Cardiovascular System: Concentric left ventricular hypertrophy, inferior vena cava dilated, dilated right chambers
- Respiratory System: High raised pulmonary arterial pressure, around 90-100mmHg. Right Ventricular Outflow Tract (RVOT) and Main Pulmonary Artery (MPA) dilated. Exertional dyspnoea, cough.
- Gastrointestinal Tract: Indigestion, dyspepsia
- Genitourinary System: Nil to note
- Central Nervous System: Nil to note
- Musculoskeletal System: Nil to note
- Endocrine System: Iron overload

Discussion of results of general and specific examinations:

On admission to A&E:
Following admission, the following examinations were performed:

Exam	Result
Pulse	110bpm
SpO2	100% on oxygen
Blood pressure	125/76 mmHg
Temperature	Afebrile
CVS sounds	S1 + S2 + 0, raised jugular venous pressure (JVP)
Chest	Clear
Abdomen	Soft and non-tender
ECG	T wave inversion across the anterior leads which was previously present
Chest X-Ray	Cardiomegaly, which was not present on previous chest X-Rays, pericardial effusion with pleural effusion.
Arterial Blood Gases (ABG)	•pO2: 47.9 mmHg •pCO2: 34.6 mmHg
Blood analysis	•Troponin normal •Positive D-dimer levels •Low fibrinogen levels •Lactate: 4.6 •WBC count 140.70x109/L
CT Pulmonary Angiogram (CTPA)	CTPA showed cardiomegaly but excluded pulmonary embolism.

Further specific tests following ward admission:

Exam	Result
Plethysomgraphy	Performed prior to starting treatment for pulmonary hypertension

Chest X-ray revealed a pericardial effusion with pleural effusion. Further examination confirmed free fluid in the abdomen and pelvis together with a few stones in the gall bladder but a normal common bile duct (CBD). Right heart studies were also performed by catheterisation.
Patient also showed persistently increased INR and deranged liver enzymes.

Differential diagnosis:

- Acute haemolytic state, probably secondary to infection, possibly with Disseminated Intravascular Coagulation (DIC).
- Dyspnoea on admission:
    a. Pulmonary embolism – excluded via CTPA.
    b. Chest infection – which was also supported by the high WBC count.
    c. Pulmonary hypertension which was confirmed on investigation.
- Spontaneous increase in INR – probably due to liver dysfunction and possibly DIC secondary to infection.

Diagnostic procedures:

Laboratory Exams:

Test: Arterial Blood Gases (ABG)
Justification for test: To measure the partial pressures of Oxygen (pO2) and Carbon Dioxide (pCO2).
Result: pO2 was 49.7mmHg (75-100mmHg), pCO2 was 34.6mmHg (35-45mmHg)
Conclusion: Low pO2 levels and hence hypoxemia.

Test: Troponin
Justification for test: Troponin used as a marker of heart tissue damage. Beta-thalassemia associated with increased risk of heart tissue damage and cardiovascular diseases.
Result: Normal troponin levels.
Conclusion: Myocardial infarction is excluded.

Test: D-dimer (Fibrin degradation fragment)
Justification for test: Suspected pulmonary embolism; to rule out the presence of a thrombus. Also due to suspected DIC.
Result: Positive D-dimer levels indicative of high levels of fibrin degradation products.
Conclusion: Positive D-dimer levels correspond to possible pulmonary embolism and DIC.

Test: Fibrinogen (Factor I)
Justification for test: Complimentary test to D-Dimer to help with diagnosis of DIC. Test for fibrinogen activity.
Result: Low fibrinogen levels.
Conclusion: Low fibrinogen levels suggestive of increased fibrinogen consumption. Possible DIC.

Instrumental Exam:

Test: Chest X-Ray (CXR)
Justification for test: To identify consolidation, pneumothorax or signs of heart failure.
Result: CXR showed cardiomegaly that was not present on previous CXRs.
Conclusion: Cardiomegaly and query of pericardial effusion.

Test: CT Pulmonary Angiogram (CTPA)
Justification for test: To produce an image of the pulmonary arterial supply using computed tomography and intravenous contrast medium.
Result: CTPA confirmed cardiomegaly but did not show signs of pulmonary embolism.
Conclusion: Pulmonary embolism excluded.

Test: Right Heart Studies/Catheterisation
Justification for test: To determine and assess the function of the heart and the pulmonary arterial pressure.
Result: Right heart studies showed an elevated pulmonary arterial pressure of 90-100mmHg.
Conclusion: Confirmed pulmonary hypertension.

Therapy:

Drugs:

The patient was transfused two units of packed red blood cells (PRC) in view of a low level of haemoglobin (Hb) of 6.6 g/L (13-18 g/L).

Drug	Dosage	Frequency	Formulation	Reason
Meropenem	1mg	Every 8 hours	Infusion	To treat possible infection in lungs (pneumonia)
Deferasirox (Exjade)	1750mg	OD, indefinite	Tablet for oral suspension	To treat the iron overload

Chorionic Gonadotropin (Gonasi®)	5000 I.U.	Three times a week (T.I.W.), indefinite	Subcutaneous injection	To stimulate the Leydig cells in the testes hence stimulating production of testosterone
Bumetanide	1mg	OD for 6 days	Oral tablet	Loop diuretic to treat the heart failure
Phenoxymethylpenicillin (Penicillin V)	500mg	OD, indefinite	Oral tablet	To prevent infection following splenectomy
Co-amoxiclav – following meropenem administration	375mg	TDS for 3 days	Oral tablet	To treat possible pneumonia
Amoxillin – following meropenem administration	250mg	TDS for 3 days	Oral tablet	To treat possible pneumonia

Diagnosis:

Being a known case of beta thalassemia, the presenting complaint of dyspnoea cough and lethargy indicated a complication of the condition. With the D-dimer being positive, the possibility of pulmonary embolism and DIC were considered. With the exclusion of pulmonary embolism using CTPA, it was concluded that the patient was experiencing complications of beta thalassemia leading to pulmonary hypertension, possible pneumonia and DIC. The patient was therefore administered intravenous antibiotics to treat the possible pneumonia and a loop diuretic to control the symptoms of pulmonary hypertension.

Final treatment and follow ups:

Following recovery after treatment for pulmonary hypertension, pneumonia and DIC, the patient was advised to stop smoking, stop binge drinking and reduce exertion. A follow-up appointment for right heart studies was given to the patient. A renal function test (urea, electrolytes, creatinine) to look for adverse effects of bumetanide (low sodium or rise in creatinine) was booked.

Fact Box 7:

Title: Beta Thalassemia Major (with pulmonary hypertension)

Pathophysiology:

Beta Thalassemia is a group of hereditary disorders of the blood which are characterised by aberrant expression of the beta haemoglobin genes, with Beta Thalassemia Major generally involving homozygosity for beta-zero (beta0) or compound heterozygosity for beta-plus (beta+) [1]. As a result of the mutations there is reduced synthesis of the beta chains of haemoglobin which leads to reduced levels of functional haemoglobin in the red blood cells, hence resulting in anaemia due to reduced oxygen carrying capacity of the red blood cells [1]. Because of this, the patient must undergo regular blood transfusions so that correct levels of functional haemoglobin are maintained in the blood. However, repeated blood transfusions lead to iron overload and eventually iron toxicity.

Although pulmonary hypertension (PH) is a complication of thalassemia, the incidence of the condition is not clear, with studies suggesting an incidence rate of 10%-75% in patients with Beta-thalassemia major [2-4]. While the pathophysiology of PH in beta-thalassemia patients is not clearly known, iron overload and deposition in the lungs, liver and heart together with a past history of splenectomy have all been associated with PH [2,5,6]. PH in such patients has been attributed to an increased response to vasoconstrictors as a result of an increased intracellular Ca^{2+} content secondary to potassium channel downregulation and endothelial injury in hypoxic conditions [2,7].

Evidence also suggests that chronic haemolysis plays a key role in the development of pulmonary hypertension in B-thalassemia. The haemoglobin released from the broken down red blood cells somehow scavenges nitric oxide. Hence, the removal of nitric oxide and the lowering of its concentration in the blood reduces its vasodilatory effect on hypoxic pulmonary vasoconstriction. Also, following the breakdown of red blood cells, the enzyme arginase is released. This breaks down arginine – the substrate for the synthesis of nitrogen monoxide. Both of these mechanisms contribute to an overall decrease in NO levels, resulting in a relative increase in endothelin-1 which is a potent vasoconstrictor. Hence this imbalance leads to the development of pulmonary hypertension [8].

Risk factors:

The risk factors which increase the probability that one develops this disease are mainly associated with genetic factors: Family history of thalassemia and certain ancestry.

Symptoms:

Beta Thalassemia Major is generally diagnosed at an early stage in infants of 6 to 24 months who fail to thrive and become pale together with possible enlargement of the liver and the spleen [1]. Beta Thalassemia Major may be attributed to jaundice and pallor, growth retardation, skeletal changes, extramedullary haematopoiesis (with possible mass development), abdominal swelling and hepatosplenomegaly [1].
Cardiac complications which may include cardiomyopathy secondary to iron deposition and myocarditis also increase the morbidity and fatality rate of the condition [8]. A significant contributor to such cardiogenic deaths in patients with Beta Thalassemia Major is the development of pulmonary hypertension, which is another complication of the condition [8].

Prevention:

Being a hereditary condition, the only method (so far) to prevent acquiring Beta Thalassemia is by population screening and genetic counselling.

Complications:

Together with the risks associated with Beta Thalassemia Major itself, the additional pulmonary hypertension may give rise to a number of complications [9]. These include[9]:

- Right-sided heart failure (cor pulmonale)
  Due to increased resistance in the pulmonary circulation, the right ventricle enlarges so as to be able to generate enough force which would allow enough blood to be perfused to the lungs. However, the thickening of the walls and the enlargement of the right ventricular chamber has a limit, beyond which, right-sided heart failure occurs.
- Blood Clots
  The pulmonary hypertension increases the risk that one develops blood clots within the vessels of the lung. These further increase the resistance, and hence contribute to the pulmonary hypertension. Apart from this, another complication which may arise is that these blood clots may dislodge from the pulmonary vessels and end up in the general circulation where they may cause obstruction of other vessels.
- Arrhythmia
  Irregular heartbeats of all chambers of the heart are possible complications of pulmonary hypertension. The arrhythmias may lead to palpitations, dizziness or fainting and can be fatal.
- Bleeding
  This is another fatal complication of pulmonary hypertension, where one starts bleeding into the lungs and eventually coughing up blood – haemoptysis.

Treatment

Management of Beta Thalassemia Major mainly involves regular transfusions for the correction of the anaemia, suppression of erythropoiesis and inhibition of iron absorption from the gastrointestinal system (to decrease iron overload) together with treatment of iron overload which occurs frequently in patients on regular transfusion [1]. The patients may therefore require the use of iron chelators and possible splenectomy while possible delayed puberty, hypogonadism and requirement of assisted reproduction should also be considered [1].

References:

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