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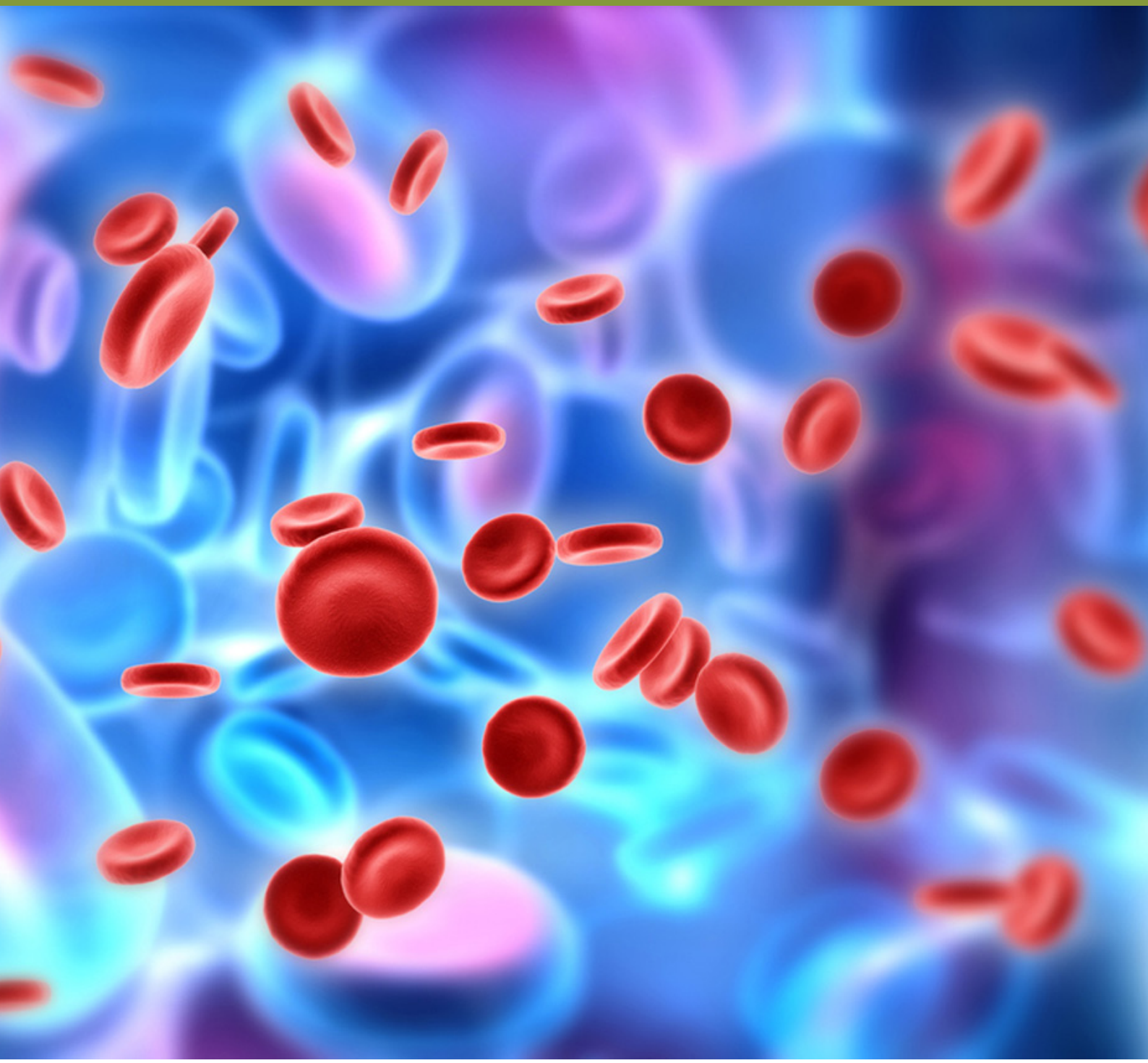

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Volume 11

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A CASE OF ISCHAEMIC COLITIS IN SICKLE CELL DISEASE

E Kumar, F Shah

Abstract

Sickle cell disease (SCD) is an inherited haemoglobinopathy, characterised by a combination of vaso-occlusion and chronic haemolytic anaemia, which give rise to its various acute and chronic clinical manifestations.

We describe a case of a young adult with homozygous sickle cell disease presenting with ischaemic colitis – a rare but recognised complication of the 'girdle syndrome' (abdominal pain secondary to mesenteric vaso-occlusion). This case illustrates the multi-system involvement of SCD, and the approach to the acutely unwell SCD patient. Effective management can prevent associated morbidity and mortality, and should include: early recognition of clinical deterioration, prompt initiation of supportive measures, effective multi-disciplinary working, and appropriate and timely use of blood transfusion. Specialist haematology input should always be sought when managing an unwell SCD patient.

Case Study

An 18 year old lady with homozygous sickle cell disease presented to Accident and Emergency after waking with severe pain in her back, chest, lower abdomen and legs, with a one day history of diarrhoea and sickling pains in both thighs. She was known to have a severe phenotype sickle cell disease, having suffered an ischaemic stroke at the age of three, and was taking long-term oral hydroxyurea.

On arrival she was tachycardic at 117bpm, but normotensive 134/83, afebrile, with oxygen saturations of 99% on air. On examination, she was distressed with pain, her chest was clear to auscultation. Her abdomen was diffusely tender, but soft.

Her initial blood tests (see table 1) showed a neutrophil leucocytosis with unremarkable CRP; her haemoglobin, bilirubin and reticulocyte count were at her baseline. Her chest X-ray showed clear lung fields with no air under the diaphragm, her ECG showed normal sinus rhythm.

	Day 1 of admission	Day 2 of admission
Haemoglobin	94g/L	68g/L
White cell count	29.9 $x10^9$/L	26.5 $x10^9$/L
Neutrophil Count	26.3 $x10^9$/L	23.4 $x10^9$/L
Platelets	664 $x10^9$/L	338 $x10^9$/L
Reticulocyte Percentage	11.99%	-
Reticulocyte count absolute	371.7x10^9/L	-
Creatinine	54 umol/L	70 umol/L
Urea	4.4 mmol/L	6.6 umol/L
Amylase	82 u/L	-
ALT	55 iu/L	33 iu/L
ALP	208 iu/L	135 iu/L
Bilirubin	55 umol/L	128 umol/L
CRP	10 mg/L	143 mg/L

Table 1: Bloods results from day 1 and 2 of the admission.

She was admitted and treated for a painful crisis with intravenous fluids and patient controlled analgesia (PCA) with intravenous morphine sulphate.

During the first 24 hours she reported worsening diffuse abdominal pain which was different from her usual sickling pain, not responding to escalating doses of analgesia via the PCA, and accompanied by two episodes of diarrhoea mixed with altered blood.

On the day following admission, her pulse had risen to 140bpm, with preserved BP 135/80mmHg; oxygen saturation had fallen to 92% on air; she had guarding of the lower abdomen. A venous blood gas showed a lactic acidosis with lactate of 4.8mmol/L, pH 7.28. Repeat blood tests showed haemoglobin had dropped to 64g/L, with CRP 143mg/L, bilirubin 128umol/L, creatinine 70umol/L.

She was reviewed by haematology and general surgical teams: a diagnosis of girdle syndrome (ischaemia due to sickling in the mesenteric vasculature) was suspected, and arrangements made for an emergency manual red cell exchange: a femoral line was inserted (due to her poor peripheral venous access), and seven units of red cells cross-matched.

CT abdomen with angiography showed features of colitis with marked thickening of the ascending colon and proximal transverse colon, mild thickening of the sigmoid colon, and surrounding inflammatory fat stranding. Angiography revealed no large vessel occlusion.

She underwent a seven unit red cell exchange transfusion, bringing the proportion of sickle haemoglobin or "Hb S" from 85% down to 20%. As well as supportive measures including oxygen, intravenous fluids, and PCA analgesia, she was treated with broad spectrum intravenous antibiotics with enteric cover (intravenous ceftriaxone and metronidazole with oral vancomycin), and a therapeutic heparin infusion.

On day 1 post-exchange, her pain remained severe, but lactate stable at 3.2-3.8mmol/L. She was reviewed closely by general surgeons but managed conservatively. By day 2 post-exchange, her pain started to improve, and lactate fell to 1.6mmol/L. Stool cultures and Clostridium difficile testing were negative, supporting a diagnosis of ischaemic colitis secondary to small vessel mesenteric vaso-occlusion. Her pain and diarrhoea continued to settle and she was discharged 15 days post-red cell exchange.

A CASE OF ISCHAEMIC COLITIS IN SICKLE CELL DISEASE

E Kumar, F Shah

Learning Point 1 - Management of the unwell patient with sickle cell disease.

This case illustrates that the patient with SCD can deteriorate rapidly, and sometimes unpredictably. Close observation, regular clinical review and specialist haematology input are crucial in the acute setting. A multi-disciplinary approach is key to the successful management of the unwell SCD patient, and may include input from a variety of disciplines including intensive care, general surgeons, acute pain team, respiratory physiotherapy, and the transfusion lab.

Early intervention with simple measures should include:

- *Oxygen therapy (e.g. to maintain oxygen saturations => 95% or within 3% of patient's baseline)*

- *Intravenous fluids: to re-hydrate and compensate for decreased oral intake while unwell/in pain, with caution not to fluid overload*

- *Analgesia: NICE guidelines(1) advise appropriate analgesia within 30 minutes of attendance to hospital with sickle cell crisis. Timely and adequate analgesia is critical for a positive patient experience, and will also reduce risk of progression to acute chest syndrome, particularly where the patient presents with chest and/or abdominal pain. Care should be taken to avoid hypoventilation due to excess opiate analgesia.*

- *Antibiotics: An infective aetiology is often difficult to exclude in the acute sickle cell presentation. Broad spectrum or targeted antibiotic therapy should always be considered in the unwell patient with sickle cell disease.*

- *Incentive spirometry may reduce progression of painful crisis to acute chest syndrome (Figure 1).*

- *Thromboprophylaxis: SCD is an independent risk factor for venous thromboembolism.*

Emergency red cell transfusion (simple 'top up' or exchange) may be required, for example in acute chest syndrome, acute stroke, or girdle syndrome(2). This should always be instituted with specialist haematology input. Initiated in a timely manner, transfusion can limit morbidity, and be life-saving as in this case.

Figure 1: A bedside incentive spirometer. Regular inspirations from the mouthpiece of the incentive spirometer (e.g. 10 maximum inspirations every 2 hours) (3) help to overcome atelectasis and diaphragmatic splinting in patients presenting with thoracic bone pain(4), and reduces risk of progression to acute chest syndrome. It is best delivered with input from chest physiotherapists, and can also be used to optimise oxygenation in established acute chest syndrome.

Learning point 2: Girdle Syndrome

Abdominal pain is a common presenting symptom. The differential is broad, and includes causes more prevalent in SCD patients, as well as those relevant to all patient groups (see table 2).

Gastritis / Duodenitis and Peptic Ulceration: *Secondary to non-steroidal anti-inflammatory drugs*
Constipation: *Secondary to opiate analgesia*
Gallstone disease: Cholecystitis / Cholangitis / Biliary Colic / Gallstone pancreatitis
Girdle (or mesenteric) Syndrome
Splenic sequestration: *Predominantly seen in paediatric patients - pain, splenomegaly, shock, acute anaemia*
Hepatic sequestration: *Analogous to splenic sequestration, though less common*
Other general causes of abdominal pain: Gastroenteritis, appendicitis, pyelonephritis, ectopic pregnancy etc.

Table 2: Causes of abdominal pain in Sickle cell disease

A CASE OF ISCHAEMIC COLITIS IN SICKLE CELL DISEASE

E Kumar, F Shah

Girdle syndrome is thought to result from sickle-mediated vaso-occlusion in the mesenteric vasculature, and is more common in the paediatric population. So-called because of the typical girdle-like distribution of pain, it is characterised by abdominal pain, and an ileus with vomiting, abdominal distension and absent bowel sounds. Abdominal X-Ray typically shows distended bowel loops and fluid levels.

Initial management includes intravenous fluids and analgesia. If there are prominent ileus features, the patient may need to be kept nil by mouth, with nasogastric tube insertion. If the patient is febrile/unwell, antibiotics should be given with enteric cover.

While symptoms may settle with conservative measures, close observation and specialist haematology and surgical input are crucial: where there are persistent symptoms or clinical deterioration, exchange transfusion may be required.

Ischaemic colitis is a rare but reported complication of girdle syndrome(5): worsening pain, bloody diarrhoea, rising lactate, and features of colitis on CT may be seen. Red cell exchange transfusion is the mainstay of treatment and may avoid colectomy and/or death.

Learning point 3: How are complications of sickle cell disease prevented?

The two current mainstays of disease-modifying treatment of SCD are blood transfusion and the oral drug hydroxyurea. Following her stroke aged 3, our patient had commenced on regular transfusions: these decrease the proportion of a patient's red cells containing sickle haemoglobin, or 'Hb S', by either diluting (with simple or 'top-up' transfusion) or replacing (with exchange transfusion) the patient's blood, with donor red cells containing Haemoglobin A. Regular transfusions reduce the rate of serious complications of SCD including stroke and acute chest syndrome.

At the age of 17, as a result of increasing difficulties with venous access, she discontinued transfusions, and started taking oral hydroxyurea. Hydroxyurea works in SCD by increasing the production of foetal haemoglobin (Hb F), which is usually produced at very low levels in adults. It therefore decreases the proportion of circulating Hb S (though typically by a much lesser degree than regular transfusion). Hydroxyurea also acts to reduce vaso-occlusive events by modifying the interaction between red cells and the vascular endothelium, and by reducing leucocyte and platelet production.

Long-term outcomes remain suboptimal for a number of patients, and the morbidity associated with long-term transfusion may be significant, including: iron overload, red cell alloimmunisation, complications relating to venous access, and the quality of life burden of frequent hospital attendance. This calls for novel approaches to treating SCD: in future, the emerging use of allogeneic stem cell transplantation(6), and the advent of gene therapy(7) may provide additional options for these high risk patients.

MCQs

1. A 24 year old male with sickle cell anaemia presents with an eight hour history of severe pain in his lower back, legs and rib cage. He is afebrile, his oxygen saturation is 98% on air, his initial blood tests are unremarkable. He is commenced on intravenous fluids and regular injections of subcutaneous diamorphine as per the local protocol.

Six hours later, his pain remains severe, and the nurses inform you that his oxygen saturation has dropped to 85% on air. His respiratory rate is 16/minute, his GCS is 15/15 with mid-sized reactive pupils, and chest X ray reveals bilateral infiltrates. The most likely diagnosis is:

1) Community acquired pneumonia

2) Acute chest syndrome

3) Pulmonary embolus

4) Opiate toxicity

5) Fluid overload

2. Which of the following is NOT an appropriate aspect of acute management of the Acute Chest Syndrome?

1) Oxygen

2) Opiate analgesia

3) Hydroxyurea

4) Red cell transfusion

5) Intra-venous fluids

A CASE OF ISCHAEMIC COLITIS IN SICKLE CELL DISEASE

E Kumar, F Shah

Answers

1. Answer = 2) Acute Chest Syndrome

The sickle cell acute chest syndrome is a medical emergency, and a leading cause of premature mortality in SCD patients. It is characterised by fever and/or respiratory symptoms, hypoxia, and new pulmonary infiltrates on chest X ray. It may be the presenting issue, but commonly complicates other acute sickle cell presentations, most frequently the painful vaso-occlusive crisis. Progression may be rapid over hours and early identification is crucial.

All of the answers above are potential causes of hypoxia in a patient with sickle cell disease (and may co-exist). However, in this scenario, the presentation with pain and normal oxygen saturations, followed by acute hypoxia developing over hours without signs of opiate toxicity, is classic.

2. Answer = 3) Hydroxyurea

Initial management includes oxygen, analgesia, intravenous fluids, antibiotics (to include cover for atypical organisms, particularly Mycoplasma), incentive spirometry and chest physiotherapy. Consideration should be given to transfusion (top-up or exchange) in the hypoxic patient after discussion with haematology, and may be life-saving. Hydroxyurea can have an important role in the prevention of acute chest syndrome, but not in its acute management.

Author

Dr Emil Kumar
Whittington hospital
Magdala Avenue
London
N19 5NF

Dr Farrukh Shah
Whittington hospital
Magdala Avenue
London
N19 5NF
farrukh.shah@nhs.net

Corresponding Author

Dr Emil Kumar
emil.kumar@nhs.net

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AN INTERESTING CASE OF THROMBOCYTOPENIA

J Boot, J Roy, E Jacob

Abstract

A case study of a 73 year old man diagnosed with immune thrombocytopenic purpura (ITP) after presenting to hospital with a platelet count of 5 × 10^9/L following the development of shingles. Management was complicated by a history of a recent coronary stent insertion. Discussion includes the diagnosis and management of ITP and the investigation and dilemmas in a gentleman with both high bleeding and thrombotic risks.

Case presentation

A 73 year old man was diagnosed with shingles after presenting to his GP with a ten day history of a rash across his abdomen and back. Two days later he noted a new rash on his legs and blood tests performed by the GP showed a platelet count of 5 × 10^9/L (normal range 115 to 155 ×10^9/L). He was referred and admitted to hospital urgently the same day.

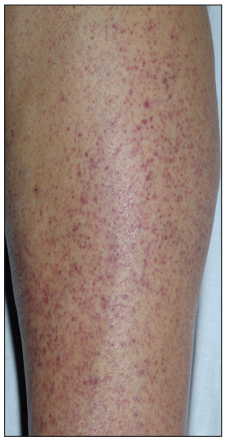
Full Blood Count

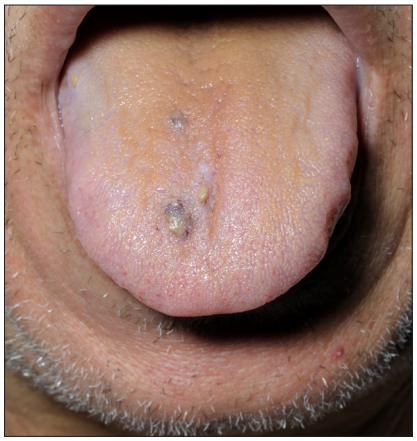
Haemoglobin	*107 g/L (115- 155× 10^9/L)*
White cell count	*7.04 × 109/L (3 -10× 10^9/L*
Platelets	*5 × 109/L (150-400× 10^9/L)*

Learning point

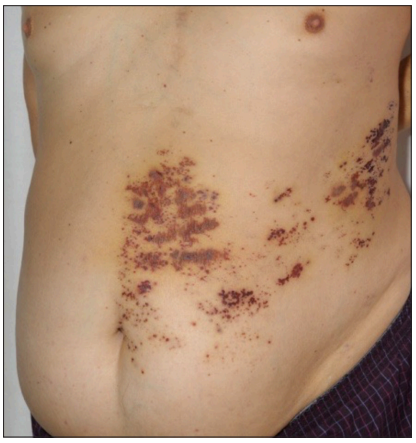
- *Platelets are small cells that stain as pale blue/purple on a blood film. They are 2-3 micrometres in diameter.*
- *Platelets originate from the bone marrow, from a much larger cell called the megakaryocyte.*

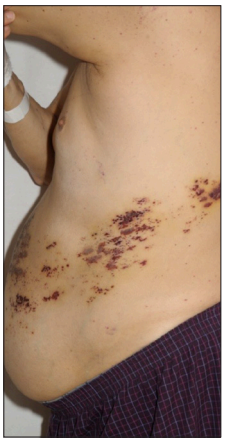
On admission to hospital he reported an additional history of mild epistaxis and bleeding in his mouth. He did not report fevers or other symptoms suggestive of a haematological malignancy. Clinical examination revealed ecchymoses on his head, haemorrhagic vesicles on his tongue and a petechial rash over his legs (images 1 and 2). An extensive vesicular rash with bruising was present across his abdomen and back in a dermatomal distribution in keeping with the diagnosis of shingles (images 3 and 4). There were no palpable lymph nodes or organomegaly.





Images 1 & 2: Petechial rash and haemorrhagic vesicles.





Images 3 & 4: Shingles rash.

He had an extensive history of ischaemic heart disease undergoing coronary artery bypass graft surgery four years earlier and insertion of a drug-eluting stent to his left circumflex coronary artery four months prior to his presentation. He was subsequently started on dual antiplatelet therapy (aspirin 75mg OD and clopidogrel 75mg OD). His other past medical history included a recent duodenal ulcer, beta thalassemia trait, diet controlled diabetes mellitus, hypertension and hypercholesterolaemia.

Immediate management included commencement on prednisone 1mg/kg (80mg in total) and stopping his aspirin and clopidogrel. Thromboembolic disease (TED) stockings were prescribed for venous thromboembolic (VTE) prophylaxis, as low molecular weight heparin was contraindicated due to his thrombocytopenia. After discussion with Cardiology colleagues the following morning, aspirin was restarted due to the high risk of development of stent stenosis and they recommended this to be continued long term. Clopidogrel was not restarted due to the high bleeding risk of dual anti-platelet therapy exceeding the cardiac benefit.

Learning point

- *Due to ongoing platelet destruction, giving platelets as an infusion will not increase the platelet count, but may be beneficial if a patient is actively bleeding.*

Further initial investigations included a blood film (image 5) which showed true thrombocytopenia with no platelet clumps and no evidence of atypical cells such as blasts. Due to his mild anaemia, haematinics were sent which revealed a low B12 and he was commenced on sub-cutaneous hydroxycobalamin replacement. The intra-muscular route was avoided to reduce the risk of haematoma.

AN INTERESTING CASE OF THROMBOCYTOPENIA

J Boot, J Roy, E Jacob

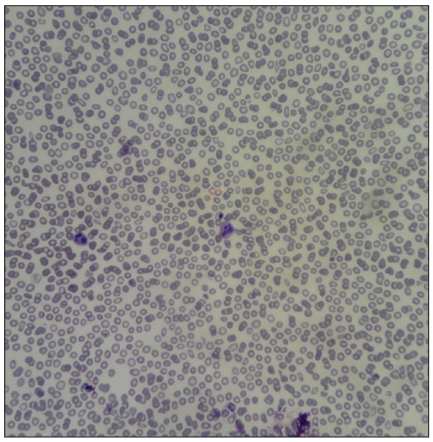


Image 5: Blood film showing true thrombocytopenia.

Due to his concurrent anaemia and age, a bone marrow biopsy was performed. The results showed plentiful megakaryocytes consistent withperipheral platelet destruction. (image 6). No secondary causes of thrombocytopenia were found and a diagnosis of ITP precipitated by shingles (varicella zoster virus) was made.

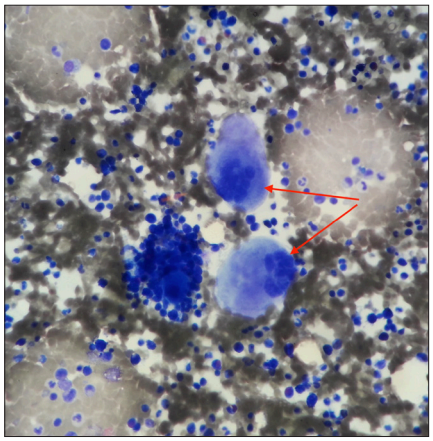


Image 6: Bone marrow aspirate showing megakaryocytes

Following three days of treatment with high dose steroids his platelet count remained 5 x10^9/L. Due to his extensive and complex cardiac history the risk of a thrombotic event following use of intravenous immunoglobulin (IVIG) was deemed to be too high, so he was started on the thrombopoieitin receptor agonist Eltrombopag.

He underwent a CT scan of his chest, abdomen and pelvis to rule out an underlying malignancy. This showed a soft tissue mass over his left gluteal muscle, with no other findings to suggest malignancy. An ultrasound of this soft tissue mass was suggestive of a haematoma.

He continued to have only minor episodes of bleeding and therefore aspirin was continued. After two weeks of steroids and eltrombopag treatment, his platelet count remained below 10 x10^9/L. Due to the prolonged treatment period without response it was deemed necessary to treat him with IVIG at a reduced dose (0.4g/kg total dose). His platelet count increased to 13 x10^9/L and he was discharged home with outpatient follow up.

Discussion

This case highlights some of the important considerations when presented with a new case of thrombocytopenia. One of the principle concerns in the management of a thrombocytopenic patient is the balance between bleeding and thrombotic risks. The potentially grave consequences of coronary stent thrombosis added further complexity to the management of this patient and demonstrates the importance of multi-disciplinary discussion in an attempt to quantify the various risks to the patient.

When a patient initially presents with thrombocytopenia it is important to rule out a secondary cause and most urgently this would be a malignancy. A normal white cell count and haemoglobin can be reassuring but a blood film should be urgently requested (1). Other important secondary causes are HIV and hepatitis B and C infection, they should be tested for in all new cases (1). In this patient these tests were all negative.

Other important differential diagnoses to consider are disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP) and myelodysplasia (MDS) or acute myeloid leukaemia (AML). A coagulation screen would show prolongation of the prothrombin time and activated partial thromboplastin time with low fibrinogen levels in DIC.

In TTP the coagulation screen is usually normal with a high lactate dehydrogenase and normal or elevated white cell count. In MDS or AML there may be other cytopaenias and a blood film may show abnormal blast cells. A stool sample for Helicobacter pylori antigen testing should be considered during investigation, as treatment can sometimes improve ITP (2).

Initial management will be dependent on patient factors. Bleeding and co-morbidities must be taken into account. Due to this gentleman's history of ischaemic heart disease and recent cardiac stenting, continuation of a form of antiplatelet therapy was important. He had only minor bleeding symptoms and it was felt that his bleeding risk was lower than his thrombotic risk.

In order to further reduce the risk of haemorrhage it is important to consider gastric protection when starting high dose steroids. This was particularly pertinent in this gentleman who had a recent duodenal ulcer. He was also a diabetic controlled by diet and steroids would be likely to increase his blood sugars. Therefore, regular monitoring was essential.

AN INTERESTING CASE OF THROMBOCYTOPENIA

J Boot, J Roy, E Jacob

What is ITP?

ITP is an acquired immune mediated condition with an isolated thrombocytopenia (platelet count less than 100x109/L) in the absence of any obvious underlying cause of thrombocytopenia (1). Current theories of the mechanism of thrombocytopenia in ITP involve both impaired platelet production and T cell mediated destruction.

Learning point

- *Platelets not only help stop bleeding. They have many functions, such as interacting with each other to localise and generate clot formation, promote vasoconstriction and help with vessel repair.*

Treatment options in ITP

Corticosteroids are a first line treatment option in ITP (1) they are easily accessible and relatively inexpensive. IVIG can also be given as a first line treatment and is potentially more efficient at increasing the platelet count rapidly (3). IVIG increases plasma viscosity and therefore increases the risk of stroke and cardiac events (3). This risk was potentially even greater in this patient due to his extensive cardiac history. Therefore, IVIG was not given initially.

Eltrombopag is increasingly being used as a second line agent in the treatment of ITP. Eltrombopag works by binding to the thrombopoietin (TPO) receptor. TPO is involved in platelet production via a complex mechanism. By binding to its receptor, production of platelets is increased (4). Eltrombopag absorption is reduced with the addition of antacids and should be taken 4 hours apart from ingestion of calcium rich foods (4). This is an important consideration when prescribing and when discharging patients home on such a medication. Patients should be advised to have a yearly eye check as studies have shown a small risk of cataract.

Learning point

- *The primary signal for development of a megakaryocyte is via thrombopoietin.*

Platelet counts can rapidly increase following treatment, which could further increase the thrombotic risk. Regular monitoring of the platelet count during treatment (3) and appropriate dosage of medication is crucial.

ITP and concurrent antiplatelet treatment

This is a complex issue and management will depend upon the clinical presentation. In patients with no bleeding, antiplatelet therapy can continue if necessary and conversely in catastrophic bleeding, there is often no alternative but to stop antiplatelet therapy. ITP does not protect patients against thromboembolic disease such as myocardial infarction, even though they are thrombocytopenic. In fact, ITP patients can be pro-thrombotic (6). Case reports are available following percutaneous coronary intervention in patients with ITP and conclude it can performed without significant risks, but treatment should be individualised (5).

Conclusion

ITP is a complex condition and this case report highlights the challenges presented that can complicate ITP and its treatment. As a junior doctor, when presented with this case overnight it is important to consider the risks to the patient in the acute setting. Bleeding and thrombotic risks need to be balanced when deciding to withhold medication. It is important to escalate this complex decision-making to your registrar/consultant.

Questions

1. You are the medical SHO on call. A 45 year old man is referred to you with a two day history of bruising on his arms. He has been otherwise well. Observations: Temperature (T) 36.8, heart rate (HR) 72, blood pressure (BP) 135/82, oxygen saturations (O2 sats) 99% on air, respiratory rate (RR) 12/min. Initial Full Blood Count: Hb 145, WCC 10.7, Plts 16. What is the next most appropriate management step?

A. Venous thromboembolic prophylaxis with LMWH

B. Transfuse one pool of platelets

C. Bone marrow aspirate

D. Blood film

E. Discharge home with outpatient haematology follow up

2. You are called to see a 54 year old man on the haematology day unit. He was recently diagnosed with ITP and is receiving the first dose of intravenous immunoglobulin. 30 minutes in to the infusion he reports a new onset headache.

T 36.2, HR 104, BP 130/85, RR 12/min, O2 sats 97% air, BM 6.2

Hb 150, WCC 8.4, Plts 8

What is the next most appropriate step in the management of this patient?

A. Prescribe paracetamol for the headache

B. Ask the nurses to stop the infusion

C. Ask the nurses to continue the infusion at half the rate

D. Ask the nurses to check neurological observations for the duration of the infusion

E. Request an urgent non contrast CT scan of the head

AN INTERESTING CASE OF THROMBOCYTOPENIA

J Boot, J Roy, E Jacob

3. A 29 year old female presents to hospital. She is 37 weeks pregnant (gravida 2, para 1), and her pregnancy has thus far been uncomplicated. She thinks her fingers have become swollen and had difficulty putting her shoes on this morning. Her partner mentions there were problems during the first pregnancy, but cannot recall exact details. Her pregnancy booking blood tests were normal.

T 37.0, HR 72, BP 174/105, O2 sats 99% air

Hb 135, WCC 14.3, neutrophils 7.2, Platelets 45

Urea 15.4, Creatinine 128

PT 12.5, APTT 31, Fibrinogen 4.5

Bilirubin 40, ALP 159, AST 10, ALT 21, LDH 310

The blood film report states 'occasional fragments with true thrombocytopaenia'

What is the most likely diagnosis?

A. Gestational thrombocytopaenia (GT)

B. Budd Chiari syndrome

C. Pre-Eclampsia

D. Thrombotic thrombocytopaenic purpura (TTP)

E. HELLP syndrome

4. A 25 year old man presents to the emergency department with a two day history of sore throat, fevers and easy bruising. He has no past medical history and doesn't take any medications. On examination he is febrile, with widespread bruising and mild bleeding from the gums. There is no palpable lymphadenopathy.

T 39.4, HR 128, BP 97/65, O_2 sats 95% air, RR 22/min
Hb 93, WCC 2.19, neutrophils 0.8, lymphocytes 1.8, Platelets 21
PT 48, APTT 86, Fibrinogen 0.5
The blood film report states 'Bilobed granulocytes containing Auer rods'

What is the most likely diagnosis?

A. Streptococcal pharyngitis

B. Epstein Barr Virus (EBV)

C. Thrombotic thrombocytopaenic purpura (TTP)

D. Acute Lymphoblastic Leukaemia (ALL)

E. Acute Promyelocytic Leukaemia (APML)

5. You are the haematology SHO oncall. The orthopaedic team call you about a 60 year old female who was admitted two weeks ago with a fractured neck of femur. Her admission full blood count was normal. Post-operatively she developed a painful, swollen right leg. US Doppler scan confirmed a right popliteal deep vein thrombosis and she was commenced on treatment dose low molecular weight heparin (LMWH). 7 days following commencement of LMWH her blood tests become deranged:

Hb 109, WCC 5.6, Platelets 80

What is the next most appropriate management?

A. Give platelets

B. Stop LMWH and start fondaparinux

C. Stop treatment dose LMWH and switch to prophylactic dose

D. Stop LMWH

E. Stop LMWH and start warfarin

Answers

Question 1: Correct answer D

A blood film should be requested and reviewed to check for atypical cells such as blasts in acute leukaemias or red cell fragments in thrombotic thrombocytopaenic purpura. Platelet clumps would suggest that the true platelet count of the patient is higher than the automated analyser is reading.

LMWH should not be prescribed in patients with platelet count <50 as this increases the risk of bleeding. In ITP, a platelet transfusion would only be indicated if the patient was actively bleeding. A bone marrow aspirate would not be the next most appropriate step, but should be considered during investigation. Patients with unexplained thrombocytopaenia at such low levels should be investigated in hospital with haematology input.

Question 2: Correct answer B

Plasma or blood components can cause a variety of reactions in patients. When suspecting a reaction, the first step is to stop the infusion. A headache is a recognised side effect of IVI and can be managed with simple analgesia. Slowing the infusion rate should be discussion with seniors. Neurological observations would be important in a patient with a suspected intracranial bleed.

AN INTERESTING CASE OF THROMBOCYTOPENIA

J Boot, J Roy, E Jacob

Question 3: Correct answer C

Pre-eclampsia is the most likely diagnosis. A personal or family history of pre-eclampsia is a risk factor for development in future pregnancies. This patient is hypertensive and has symptoms to suggest oedema. Blood tests confirm thrombocytopaenia and renal failure.

The normal liver enzymes rules out HELLP syndrome. If TTP is high on the differential, ADAMTS13 activity can be tested and plasma-exchange considered. In gestational thrombocytopaenia, which is a diagnosis of exclusion, the platelet count is rarely <50, and the other symptoms and signs would not be expected. Patients with Budd-Chiari usually mention a history of abdominal pain.

Question 4: Correct answer E

This man has an infection with bleeding. His investigations show pancytopaenia which is suggestive of an underlying problem with the bone marrow, and prolonged coagulation studies with hypofibrinogenaemia which are the hallmarks of DIC. The blood film report also mentions Auer rods, which are usually seen in promyelocytic blasts. All the preceding information points towards APML being the most likely diagnosis, and DIC is a hallmark feature of this variant of leukaemia.

Question 5: Correct answer B

This is heparin induced thrombocytopenia (HIT) and therefore it is vital to stop heparin, as this is the precipitating cause. Due to this patient's high risk of thrombosis (DVT and fracture), it's important to start an alternative anticoagulant. The only suitable one in this question would be fondaparinux. HIT typically occurs 5-10days after starting treatment and is immune mediated. The 4T scoring system is a useful tool to determine the likelihood of HIT.

Platelet transfusions should be avoided in HIT as they might increase thrombogenesis. Stopping LMWH is correct, but due to the patient's high risk of thrombosis it would not be safe to leave them without anticoagulation. Warfarin can be used in the long term but warfarin will take a few days to become therapeutic, therefore leaving the patient without anticoagulation. Further to acting on Factors II, VII, IX and X, warfarin also has action on the naturally occurring anticoagulants Protein C & Protein S, and thus can be initially pro-thrombotic until therapeutic levels are achieved.

Author

Dr Jesca Boot
CMT1, North Middlesex Hospital
Sterling Way, London, N18 1QX
jesca.boot@nhs.net

Dr Joydeep Roy
Haematology Clinical Fellow
North Middlesex Hospital
Sterling Way, London, N18 1QX
joydeep.roy@nhs.net

Dr Elizabeth Jacob
Haematology Consultant
North Middlesex Hospital
Sterling Way, London, N18 1QX

Corresponding Author

Dr Elizabeth Jacob
elizabeth.jacob1@nhs.net

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AN UNUSUAL CASE OF INTRAVASCULAR HAEMOLYSIS

O Lomas, C Hildyard, W Atoyebi

Abstract

Septicaemia due to Clostridium perfringens is an uncommon but serious cause of intravascular haemolysis that is usually fatal without early identification and treatment. We present a case of a previously fit-and-well 71-year-old woman who presented to hospital with vomiting, right-upper quadrant pain and fever. She subsequently developed rapidly progressive and fatal intravascular haemolysis. The case serves as an illustration of how to approach haemolysis in a rapidly deteriorating patient. Although rare, Clostridium perfringens septicaemia should form part of an appropriate differential diagnosis because early identification and treatment can improve survival.

Case History

A 71-year-old woman whose only significant past medical history was osteoporosis, presented to the Emergency Department of a district general hospital with abdominal pain, fever and three episodes of vomiting over the past twelve hours. During this period, she had noticed a productive cough and lost her appetite. A retired civil servant, she had recently returned from a holiday with her husband in the south of France where she, and her close contacts, had been well. Her only medications were oral calcium and Vitamin D supplements and she did not have any known drug allergies.

Initial examination revealed right-upper quadrant tenderness on deep inspiration (positive Murphy's sign), which was associated with mild scleral icterus. Examination of the respiratory, cardiovascular and neurological systems was unremarkable. Initial bedside observations were as follows : heart rate 103 beats per minute (regular); blood pressure 142/80 mmHg; temperature 36.2°C and peripheral O_2 saturations 93% on room air. An initial diagnosis of ascending cholangitis was made due to the presence of fever, jaundice and right-upper quadrant pain (Charcot's Triad). Broad-spectrum antibiotics and fluids were commenced. Urinary catheterisation revealed dark-coloured urine, consistent with haemoglobinuria.

Baseline blood tests were as follows : Haemoglobin 106 g/L, MCV 91 fL, WCC 26.60 x109/L (90% Neutrophils); Na+ 135 mM, K+ 5.5 mM, Urea 9.9 mM, Creatinine 67 µM, Bilirubin 70 µM. The initial results were accompanied by the statement 'Sample grossly haemolysed' from the laboratory. The Direct Antiglobulin Test (DAT) was negative. A sample photograph from the initial blood film is shown in Figure 1.

The smear shows wide variation in the size and shape of red cell, or erythrocyte, morphology. Ghost cells (A) represent the lysed remnants of erythrocytes and are pathognomic of intravascular haemolysis. In conjunction with the presence of numerous spherocytes (B) and toxic vacuolated neutrophils (C) and septic causes of intravascular haemolysis is suspected. A reticulocytosis (D) is evidence of bone marrow compensation for the loss of red cells.

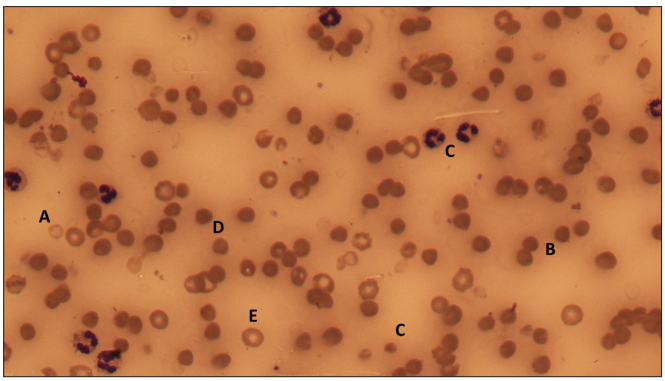

Figure 1: Peripheral blood smear taken from the blood sample taken on presentation to hospital. A = Ghost cell. B = Spherocyte. C = Vacuolated neutrophil. D = Reticulocyte. Note the background red-brown discolouration of the slide due to haemoglobinaemia.

Over the course of the next four hours, the patient deteriorated rapidly. Fulminant septic shock complicated by Acute Respiratory Distress Syndrome (ARDS) ensued, necessitating intubation and ventilation in the Intensive Care Unit. Bedside ultrasound imaging was suggestive of calculous cholecystitis. The progression of the blood counts during the first 12 hours after admission are presented in Table 1.

	Hours since admission			
	0	5	8	12
Hb (g/L)	106	76	56	48
MCV (fL)	91	65	59	*
Platelets (x10^9/L)	144	63	53	42
White Cell Count (x10^9/L)	26.6	26.8	27.5	22.1
Reticulocyte (%)			22	
Na^+ (mM)	135	131	130	*
K^+ (mM)	5.5	5.0	6.4	*
Creatinine (µM)	67	72	213	*
Albumin (g/L)	31	*	24	*
Total Bilirubin (µM)	70	*	92	*
LDH (Units/L)			9,583	
Prothrombin Time (PT) (s) Range : 9-12	*	*	15.2	30
Activated Partial Thromboplastin (APTT) Time (s) Range : 20-30	*	*	73	92

Table 1: Laboratory findings during the first twelve hours of admission.

**denotes unrecordable value – several attempts to obtain laboratory measurements failed because of the gross haemolysis of the samples. For the clotting values (PT and APTT), values were only available as it required manual, rather than automated, assessment.*

AN UNUSUAL CASE OF INTRAVASCULAR HAEMOLYSIS

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The photograph in Figure 2 is taken from the peripheral smear of the sample taken eight hours after the first (Figure 1). The figure depicts some of the processes detailed in Table 1, in particular, the rapid fall in red cell count and the decline in the MCV due to the presence of microspherocytes, a feature common to *Clostridium Perfringens* haemolysis. The prolongation of the Prothrombin Time (PT) and Activated Partial Thromboplastin (APTT), in conjunction with the fall in platelet count would be consistent with Disseminated Intravascular Coagulation (DIC). However, the relative scarcity of fragmented red cells suggests that the primary process of haemolysis is not microangiopathic as would be the case if DIC dominated the clinical picture.

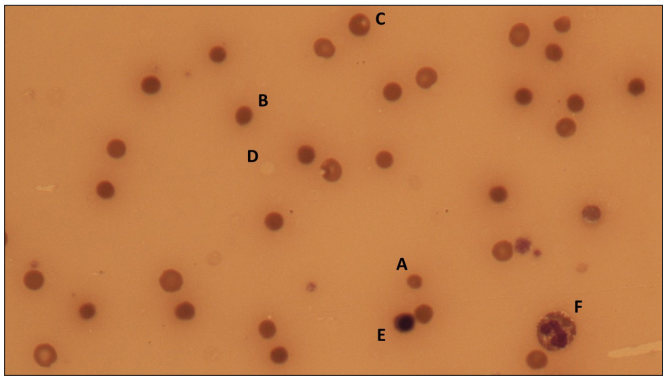

Figure 2: Peripheral blood smear taken from the blood sample taken five hours after admission. Note the decreased number of red cells and the absence of red cell fragments, or schistocytes. A = Microspherocyte. B = Spherocyte. C = Reticulocyte. D = Ghost cell. E = nucleated red cell.

Despite multi-disciplinary support from Critical Care, Infectious Disease and Haematology teams, the patient died twelve hours after admission. The cause of death was attributed to fulminant septic shock secondary to Clostridium Perfringens septicaemia due to calculous cholecystitis. The pathogenic bacterium was only identified from initial blood cultures after the patient had died.

Discussion

Haemolytic Anaemia

Haemolysis describes the shortened life-span of red blood cells. If the destruction of red blood cells occurs at a more rapid rate than they are replenished by the bone marrow, anaemia ensues. The balance between the rate of haemolysis and the rate of production determines the severity of the anaemia.

The causes of haemolysis can be due to two main mechanisms, those intrinsic to the structure of the red cell and those extrinsic to the cell. Intrinsic defects in red blood cell constituents of the haemoglobin molecules; the membrane and cellular enzymes lead to defective red cells with a shortened life-span.

Extrinsic factors also lead to increased red blood cell loss such as immune-mediated destruction, micro-angiopathic mechanical disruption of red cells and infections such as malaria and Clostridium perfringens. Extrinsic factors that cause haemolysis are often characterised by signs of intravascular red cell breakdown. Clinically, the breakdown of red blood cells in the vasculature leads to an elevation in (unconjugated) bilirubin (Table 1) and which may manifest clinically as haemoglobinuria and in the laboratory as remnants of lysed red cells (Ghost cells) on the peripheral blood smear.

Clostridium perfringens septicaemia

Clostridium perfringens is an anaerobic, gram-positive bacillus found in the normal gastrointestinal and genito-urinary tracts, which under certain circumstances such as ischaemia, immune-compromise or direct trauma, may become pathogenic. In the case presented here, cholecystitis appeared to be the precipitant. The Ð-toxin of the bacterium possesses phospholipase C and sphingomyelinase activities which are particularly toxic to the membrane of red cells. Their action causes the red cell to lose its biconcave shape and become more fragile and spherocytic (1).

The combination of spherocytosis, which is normally associated with immune-mediated, extravascular red cell destruction, in the presence of signs of intravascular red cell destruction (haemoglobinuria, haemoglobinaemia, ghost cells) is strongly suggestive of infection by pathogens such as Clostridium perfringens, Plasmodium falciparum or Brucella spp. The other differential to consider would be a cause of intravascular haemolysis in the context of previously undiagnosed hereditary spherocytosis.

The absence of schistocytes, red cell fragments most commonly secondary to Disseminated Intravascular Coagulation (DIC), is an important observation. The negative Direct Antiglobulin Test (DAT) in the context of the spherocytosis helps to discount immune-mediated forms of haemolysis. These key features or 'red flags' are summarised in Table 2.

The toxicity of Clostridium Perfringens coupled with a doubling-time of approximately seven minutes (2) confer a mortality of >70% in 9.7 hours (3). As shown in this case, the organism was only identified in blood cultures after the patient had died. Therefore, rapid identification of suggestive clinical and laboratory features, prompting broad spectrum empirical antibiotics to cover for anaerobic organisms such as C Perfringens is vital for survival.

Diagnosis summary and 'Red flags'
1. Intravascular haemolysis – unconjugated hyperbilirubinaemia and haemoglobinuria
2. Falling Mean Cell Volume with (micro)spherocytes but no schistocytes
3. Negative Direct Antiglobulin Test (DAT)

Table 2: Summary of key diagnostic features in haemolytic Clostridial Sepsis

AN UNUSUAL CASE OF INTRAVASCULAR HAEMOLYSIS

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Conclusion

Clostridium perfringens septicaemia is often fatal without early identification, source control and appropriate antibiotics. The florid nature of the condition means involving numerous specialities simultaneously such as haematology, infectious diseases and critical care medicine. Therefore, medical professionals who are first in contact with the patient, such as Foundation doctors, are vital in raising early clinical suspicion of the condition. We hope this case history and discussion improves awareness of this devastating illness and how junior medical staff can initiate life-saving care.

Multiple Choice Questions – Best Of Five

1. Which of the following is NOT a cause of intravascular haemolysis?

a) ABO-incompatible blood transfusion reaction

b) Micro-angiopathic haemolytic anaemia

c) Red cell enzyme disorders such as Glucose-6-phosphate Dehydrogenase deficiency

d) Auto-immune haemolytic anaemia – CORRECT ANSWER

e) Infections such as Falciparum malaria and Clostridium perfringens

2. Which of the following groups of laboratory findings from a full blood count and smear are consistent with Clostridium Perfringens septicaemia causing haemolysis?

a) Anaemia, DAT positive, spherocytosis, reticulocytosis

b) Anaemia, hyperbilirubinaemia (unconjugated), elevated LDH, Ghost cells – CORRECT

c) Anaemia, schistocytes, prolonged Prothrombin Time (PT)

d) Anaemia, normal reticulocyte count, raised mean cell volume (MCV)

e) Anaemia, hyperbilirubinaemia (conjugated), elevated LDH

Author

Dr Oliver Lomas
Specialist Registrar
Department of Haematology
Churchill Hospital, Oxford, OX3 7LE
oliver.lomas@ouh.nhs.uk

Dr Catherine Hildyard
Specialist Registrar
Department of Haematology
Churchill Hospital, Oxford, OX3 7LE
catherine.hilyard@ouh.nhs.uk

Dr Wale Atoyebi
Consultant Haematologist
Department of Haematology
Churchill Hospital, Oxford, OX3 7LE

Corresponding Author

Dr Wale Atoyebi
wale.atoyebi@ouh.nhs.uk

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BLEEDING ON DIRECT ORAL ANTICOAGULANTS (DOACS); A PRACTICAL GUIDE

A Langridge, L Winn, D Plews

Abstract

An elderly gentleman presents to acute services with symptoms of an upper gastrointestinal bleed while on dabigatran therapy for atrial fibrillation He is initially stable but deteriorates and needs reversal of his dabigatran. This case prompts discussion of management of direct oral anticoagulants (DOACs) during bleeding, an increasingly common presentation to acute medicine. The discussion gives clinically relevant information about the metabolism and monitoring of DOACs and how to approach patients with bleeding.

Case History

An 81-year old gentleman with a history of atrial fibrillation, managed with bisoprolol and dabigatran, presents to accident and emergency after GP review with black, tarry stools. He presents 4 hours after taking his morning medications. On presentation he is stable, with a mild tachycardia (HR 94 but normotensive with blood pressure 119/74 mmHg). Clinically he looks well, is conversational and has no pallor or obvious discomfort.

He describes 3-4 episodes overnight of urgency to pass black, tarry stools that are offensive-smelling. He has not had any obvious trigger for this episode, has no history of possible trigger for infective diarrhoea and is on no new medications. His current medications include treatment for his transient ischaemic attack 2 years previously (atorvastatin and dabigatran), hypertension (amlodipine) and type 2 diabetes mellitus (metformin). He lives at home with his wife whom he helps to care for.

His initial management was observation, with consideration of an urgent but non-emergency oesophago-gastroduodenoscopy (OGD) as although the clinical history was convincing, no stools had been passed in the department and observations where stable.

He is transferred to the medical admission unit where he starts to feel more unwell. He becomes pale and clammy and when observations are performed he is noted to have dropped his blood pressure to 83/64 and his heart rate has risen to 112. His capillary refill time is slowed to 4 seconds and although he is still conversational he obviously does not feel well. He is incontinent of melaena on the bed. Blood results are now available and show.

Haemoglobin (130-180g/L)	69
Mean cell volume (80-96x10^9/L)	94
White cell count (4-11x10^9/L)	15.1
Platelet count (150-400x10^9/L)	442
Urea (2.5-7.8 mmol/L)	18.1
Creatinine (133-146 micromol/L)	105
eGFR (>60 ml/min)	45
CRP (<5 mg/L)	7
PT (12.7-15 s)	17.4
APTT (29-44 s)	45.0
Clauss fibrinogen (1.9-8.0 g/L)	3.6

Principles of Management

The patient needs an urgent ABCDE assessment. Management will include IV fluid boluses to maintain blood pressure and urine output, request for blood transfusion, provisionally 2 units, and involvement of the ward registrar for support and further management. Handover to the registrar should explain that the patient is unwell with cardiovascular compromise due to suspected Upper Gastrointestinal (UGI) haemorrhage on a direct oral anticoagulant (DOAC), and that management so far has been fluid resuscitation and a plan for blood products.

Further review should include an urgent review by gastroenterology for consideration of OGD, and consider critical care outreach if blood pressure support is still needed after initial ABCDE management. There is always haematology cover available, either consultant or registrar, and they should be contacted regarding management of the bleeding on dabigatran.

In this situation since the patient is unstable with suspected significant upper gastrointestinal (UGI) haemorrhage, the priority is urgent dabigatran reversal and immediate correction of the bleeding point. In this case haematology would most likely advise the use of idarucizumab, a specific antidote for dabigatran which instantly reverses the effect of dabigatran, followed by an urgent OGD when the patient has stabilised to ensure the source of bleeding is stopped.

He undergoes an OGD where a bleeding duodenal ulcer is found, cauterised and bleeding appears to stop. Over the next 2-3 hours his observations improve and clinically he starts to look better. He is started on BD injections of omeprazole. Over the coming dys he improves clinically and is discharged after restarting dabigatran as although there is an increased incidence of GI bleeding on dabigatran than rivaroxaban or apixaban, there is an antidote available.

Discussion

This case is a presentation to acute services of suspected bleeding on dabigatran, a DOAC. This is increasingly common as DOAC use increases in the management of venous thromboembolism (VTE) and atrial fibrillation (AF).

The priority of management in these patients is always a thorough ABCDE (Airway Breathing, Circulation, Disability, Exposure) assessment to ensure patient safety by identifying haemodynamically unstable patients promptly, and involving seniors early for support in management in these cases. Thorough medication review is important as this patient was on a beta blocker which is likely to have prevented him mounting a significant reflex tachycardia, masking the severity of his clinical condition.

BLEEDING ON DIRECT ORAL ANTICOAGULANTS (DOACS); A PRACTICAL GUIDE

A Langridge, L Winn, D Plews

He was also on an anti-hypertensive which should be suspended during the acute management of the bleed as it may increase the chance of cardiovascular compromise if bleeding continues. Transfusion should also be cautious as older patients, especially those with a history of vascular disease will have a higher risk of heart disease and possibly heart failure, therefore liberal transfusions may cause morbidity (1). A target range for haemoglobin of 70-90g/L for unwell patients is recommended (1) with regular repeat full blood count if ongoing bleeding is suspected.

Bleeding risk

When assessing a bleeding patient it is important to thoroughly assess the whole bleeding risk to this patient. For this patient;

- *The bleeding source- likely from the UGI tract, which would be expected to require an OGD for definitive management.*
- *He is also on aspirin which will impair platelet function.*
- *He is on dabigatran. This inhibits thrombin and this affects the common. pathway in the coagulation cascade.*

Reviewing blood results; his platelet count is normal. Coagulation tests with DOAC use are notoriously unreliable in reproducibility as PT and APTT can be normal in the presence of a therapeutic level of rivaroxaban (2). This is due to a variable effect between drugs on different tests and between laboratories and analysers (2). See below for summary;

	Dabigatran	Rivaroxaban/Apixaban
PT and APTT	**Cannot be used to safely assess anticoagulation**	**Cannot be used to safely assess anticoagulation**
Thrombin time (TT)	A normal TT indicates little/no active anticoagulation from dabigatran therefore can be used as a sensitive measure – if TT normal, reversal agent not needed	**Cannot be used to safely assess anticoagulation**
Hemoclot (a test specifically for dabigatran/thrombin inhibitor levels)	Specific test for dabigatran levels	**Cannot be used to safely assess anticoagulation**
Anti-Xa calibrated to DOAC	**Cannot be used to safely assess anticoagulation**	Can be used to measure levels of DOAC effect (takes 1-2 hours)

Modified from (2)

In our case the patient had a prolonged prothrombin time (PT), which could be related to dabigatran but also may be related to vitamin K deficiency or clotting factor consumption from the acute bleed. APTT was also slightly prolonged which may be related to dabigatran use or consumption from the bleed.

Managing a GI bleed on DOAC

The questions to ask when a patient presents with bleeding on a DOAC are;

1. *Is the patient unstable? If so complete ABCDE assessment and promptly answer subsequent questions then contact on-call haematology*
2. *Which DOAC do they take?*
3. *What dose and is it once or twice daily?*
4. *When was their last dose?*
5. *Do they have renal impairment?*
6. *How recent was their VTE (if VTE was the indication for anticoagulation?)*

These questions will allow you to work out the likelihood of DOAC still being present in circulation, as in a patient with normal renal function (especially relevant for dabigatran) the majority of the drug should be eliminated within 24 hours of ingestion (see table below).

If the time of ingestion is significantly less than 24 hours, or if there is renal impairment, then the two management options would be to wait for a blood DOAC level which takes roughly 1 hour or, if the patient is unstable, consider the need for urgent cessation of the bleeding source and reversal therapy for the DOAC (or consider dialysis for dabigatran).

Tranexamic acid may also be recommended as data suggests that administration decreases mortality in GI bleeding (the results of a randomised double-blind trial (HALT-IT trial) are awaited in the next year). Tranexamic acid is absolutely contraindicated however in urinary tract bleeding however due to the risk of urinary tract clot retention.

Below is a summary of the metabolic features of each DOAC to aid bleeding risk assessment.

	Dabigatran	Rivaroxaban	Apixaban
Renal Impairment	6 fold higher exposure when CrCL 10–30 ml/min	1.6 fold higher exposure when CrCL 15-29	1.44 fold higher exposure when CrCL 15-29
Age	Age > 75 = 30% increase in trough concentrations	Mean AUC 1.5 fold higher in age > 65	Mean AUC 1.3 fold higher in age > 65
Hepatic Impairment	N/A	2.3 fold increase exposure in Child-Pugh B	N/A
Drug-drug interactions	Avoid strong inhibitors (e.g clarithromycin, erythromycin, lansoprazole) or inducers of p-glycoprotein (e.g rifampicin)	Avoid strong inhibitors of p-glycoprotein and CYP 3A4 (e.g itraconazole, amiodarone, clarithromycin)	Avoid strong inhibitors of p-glycoprotein and CYP 3A4
Half-life (normal CrCl)	13 hours	9 hours	8 hours

Adapted from (3)

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Reversal agents

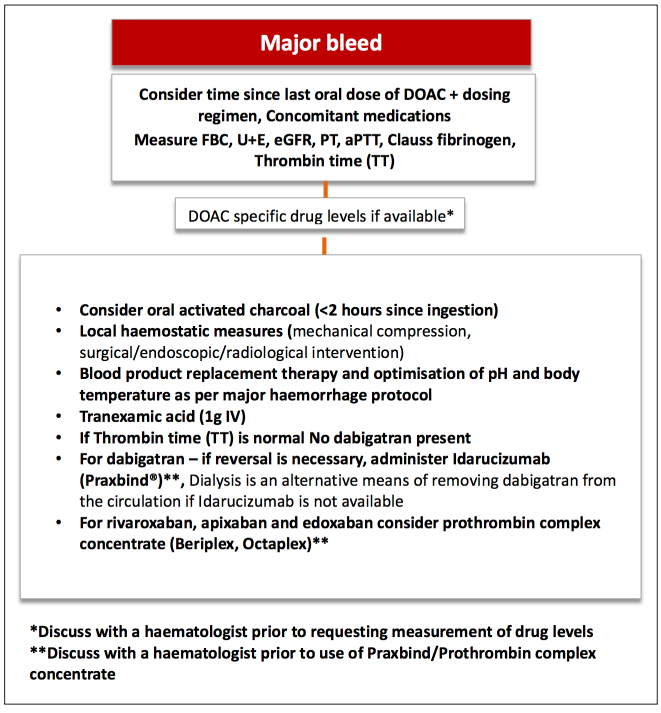
Dabigatran

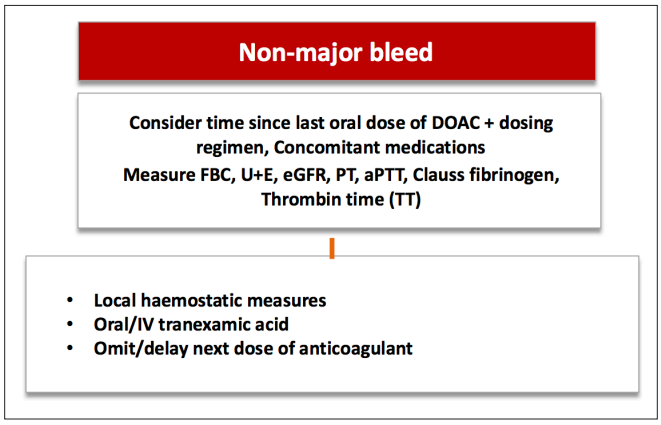
Praxbind (Idarucizumab) is a specific reversal agent for dabigatran. It is indicated in adult patients treated with dabigatran when rapid reversal of its anticoagulant effects is required such as for emergency surgery/ urgent procedures and in life-threatening or uncontrolled bleeding. It is a monoclonal antibody fragment, which works by binding dabigatran and neutralising its activity (4). The recommended dose of praxbind is 5g given as two intravenous boluses of 2.5g within 15 minutes of each other.

Rivaroxaban, apixaban and edoxaban

There is currently no licensed specific reversal agent for the direct Factor Xa inhibitors. In clinical trials, Andexanet Alfa - a recombinant modified human factor Xa decoy protein, has been shown to reverse the anticoagulant activity of apixaban and rivaroxaban (5). This drug is awaiting approval by the US Federal Drug Administration (FDA). In the absence of a specific reversal agent, treatment is largely supportive while waiting for the drug to be cleared.

Prothrombin complex concentrates (PCCs) such as Beriplex and Octaplex are thought to be at least partially effective in reversing the anticoagulant effect of the direct Factor Xa inhibitors (6) and haematology may advise the use of these in patients with life, limb or sight-threatening bleeding, acknowledging the increase risk of thromboembolism with PCCs. Tranexamic acid is also likely to reduce bleeding and should be given (note not in any bleeding from the urinary tract- see 'Managing a Bleed' section.)





Adapted from [7]

For advice regarding peri-operative management of DOACs see the British Society for Haematology guidance (8)

Questions

1. Which of the following is not a direct Factor-Xa inhibitor

a. Rivaroxaban
b. Apixaban
c. Dabigatran
d. Edoxaban
e. Betrixaban

2. Which of the following statements is false

a. The anti-Xa assay is used to measure the anticoagulant effect of LMWH
b. A normal PT and APTT in apixaban-treated patients indicates the absence of apixaban
c. The INR is used to measure the anticoagulant effect of warfarin
d. Rivaroxaban has no effect on the thrombin time
e. A normal TT in dabigatran-treated patients indicates the absence of dabigatran

3. In the presence of normal renal function which anticoagulant has the longest half-life

a. Dabigatran
b. Apixaban
c. Rivaroxaban
d. Warfarin
e. Edoxaban

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4. The excretion of which anticoagulant is most affected by impaired renal function

a. Dabigatran
b. Apixaban
c. Rivaroxaban
d. Warfarin
e. Edoxaban

5. Which of the following is a specific reversal agent for Dabigatran

a. Fresh frozen plasma
b. Cryoprecipitate
c. Prothrombin complex concentrate
d. Tranexamic acid
e. Idarucizumab

Answers

1. Answer c. Dabigatran
Dabigatran is a direct oral thrombin inhibitor. The other four drugs are direct oral Factor-Xa inhibitors.

2. Answer b. A normal PT and APTT in apixaban-treated patients indicates the absence of apixaban
The DOACs have different effects on global tests of coagulation, such as the prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT). Apixaban has little effect on the PT or APTT and the effect of other DOACs are hugely variable; therefore normal test results do not exclude a significant drug effect.

3. Answer d. Warfarin
The elimination half-life of warfarin is 4-5 days, dabigatran 12-17 hours, rivaroxaban 9 hours, apixaban 8 hours, edoxaban 10-14 hours.

4. Answer a. Dabigatran
80% of Dabigatran is eliminated by the kidneys. Warfarin is metabolised in the liver. About 25-35% of Rivaroxaban, Apixaban and Edoxaban is excreted by the kidneys.

5. Answer e. Idarucizumab
Idarucizumab (trade name; Praxbind) is a monoclonal antibody fragment which binds dabigatran and neutralises its activity. Prothrombin complex concentrates such as Beriplex and Octaplex are specific reversal agents for warfarin. They are thought to be at least partially effective in reversing the anticoagulant effect of the direct Factor Xa inhibitors. Tranexamic acid is an anti-fibrinolytic agent which can help reduce DOAC-related bleeding.

Author

Dr Dianne Plews
Haematology Consultant, James Cook University Hospital
Marton Road, Middlesbrough, TS4 3BW
diane.plews@stees.nhs.uk

Dr Luke Yan-Naing Winn
Haematology Registrar, James Cook University Hospital
Marton Road, Middlesbrough, TS4 3BW
lukeywinn@gmail.com

Dr Alexander Langridge
Haematology Registrar, James Cook University Hospital
Marton Road, Middlesbrough, TS4 3BW

Corresponding Author

Dr Alexander Langridge
alexander.langridge@nhs.net

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DEEP VEIN THROMBOSIS IN A 19 YEAR OLD WITH CONGENITAL HIV & CEREBRAL PALSY - A HERALD OF UNDERLYING BURKITT LYMPHOMA

CH Roberts, C Rowntree

Abstract

This case based discussion focuses on a 19 year old male with a background history of congenital human immunodeficiency virus (HIV) and cerebral palsy who presented with pain and swelling of the right leg. An ultrasound scan Doppler examination confirmed a right proximal lower limb deep vein thrombosis (DVT). Five weeks later, whilst still anticoagulated, the patient re-presented with worsening leg swelling and abdominal distension. At this stage an underlying malignant process was suspected. A large intra-abdominal mass, causing inferior vena cava (IVC) compression and hydronephrosis was found and this was confirmed to be Burkitt lymphoma.

This complex case explores the difficulties in assessing patients presenting with unprovoked venous-thromboembolism and discusses the significant link with malignancy. We will highlight the importance of an integrated multidisciplinary approach in investigating VTE. In this case the teams involved included Haematologists, Radiologists, Histopathologists and the Infectious Diseases team.

Case History

A 19 year old male with a background history of congenital HIV and cerebral palsy presented to the Accident and Emergency department with pain and swelling of the right leg. A clinical diagnosis of DVT was made and treatment dose low molecular weight heparin (LMWH) was initiated. The following day he was seen at the DVT clinic where a Doppler ultra sound scan (USS) of the leg was arranged. He attended using a wheelchair. The scan demonstrated acute thrombus in the right distal common femoral vein (CFV).

Baseline investigations: full blood count, renal function, liver function, bone profile, coagulation screen, urine dip and plain x-ray of the chest (CXR), were all within normal limits. The patient had no personal or family history of venous thromboembolism (VTE). A thorough clinical examination was not performed but observations were normal and there were no 'red flag' symptoms from the history; relative immobility due to the cerebral palsy was considered a likely provoking factor.

He was on highly active anti retroviral therapy (HAART) with good compliance and an undetectable viral load. Oral anticoagulation in the form of Rivaroxaban was started. Three weeks later he was reviewed for his dose change and he had no new complaints (dose of Rivaroxaban for acute VTE: 15mg BD for 21 days then 20mg OD for the remaining treatment period).

Five weeks following the initial presentation and whilst on ongoing anticoagulation, he attended his routine review with the Infectious Diseases team, where he complained of increasing pain in his right thigh and also abdominal distension and discomfort.

What could explain his current symptoms?

Here are some suggestions:

- *Underlying malignancy?*
- *Clot propagation?*
- *Intramuscular haematoma - on anticoagulation?*
- *Post thrombotic pain?*

On repeat Doppler USS there was no sign of propagation of the thrombus, however there were now multiple large lymph nodes in the right inguinal region. His blood results demonstrated evidence of an acute kidney injury (AKI) with a creatinine of 122 µmol/L from a baseline of 56 µmol/L. An urgent abdominal USS scan was performed.

The USS abdomen demonstrated bilateral hydronephrosis. Within the pelvis, there was a large mass measuring 12 x 14 cm which was displacing the bladder. Given the likelihood of malignancy and the AKI, Rivaroxaban was converted back to LMWH with guidance from the Haematology team.

Given the USS findings, suggest some tests and investigations that you would request next?

- *Computed tomography(CT) of the thorax, abdomen and pelvis (TAP) – this is to look for other sites of involvement. The Radiologists must be made aware of the creatinine clearance as contrast for the CT could worsen the renal function.*
- *Lactate Dehydrogenase (LDH). Lymphoma is the commonest cancer found in young people (1) and is more common in people with HIV. In high grade lymphoma, LDH (an enzyme that if found in almost all living cells) is usually raised indicating high cell turnover.*

An urgent CT TAP was requested and is shown below in Figure 1.

The CT scan confirmed the large mass arising from the right pelvic wall involving the right bladder wall and obstructing the right ureter. There was associated bilateral hydronephrosis. Also noted were multiple right iliac and inguinal pathological lymph nodes, there was no hepato-splenomegaly or pathological lymphadenopathy in the thorax.

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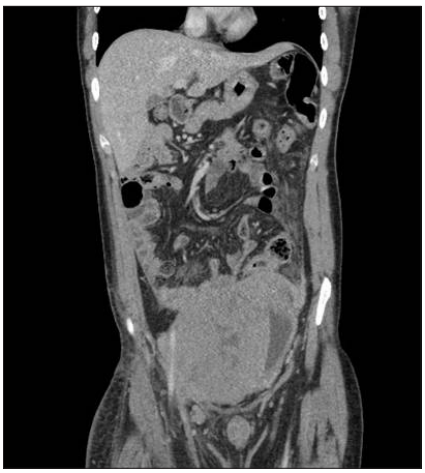

Figure 1: a

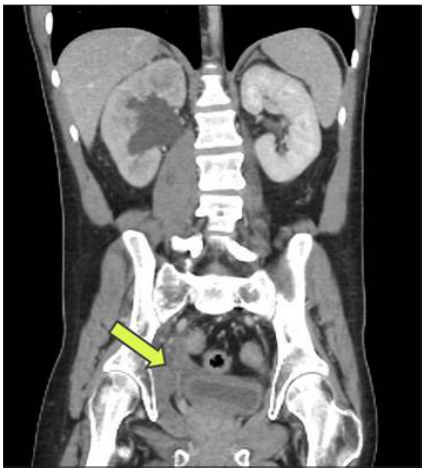

Figure 1: b

Figure 1: Coronal sections of the CT abdomen and pelvis demonstrating a) the tumour mass and b) involvement of the right side of the bladder (yellow arrow) causing bilateral hydronephrosis with a markedly swollen ureter

What would be your next course of action?

1. Arrange an urgent biopsy of the mass

2. Seek Haematology advice regarding managing the anticoagulation to facilitate biopsy.

3. Discussion with Urology and Radiology teams to address the hydronephrosis

4. Inform Haematologists of likely new case of high grade lymphoma

An urgent USS guided biopsy of the mass was arranged. The Radiologists placed bilateral external ureteric stents which relieved the hydronephrosis improving the renal function.

Within 48 hours of the biopsy, the histopathologists confirmed a diagnosis of Burkitt lymphoma (Figure 2) and the patient was initiated on chemotherapy. He continued on LMWH for the treatment of the thrombosis, with dose adjustments allowing for chemotherapy induced thrombocytopenia. He responded well to the chemotherapy and achieved a clinical remission.

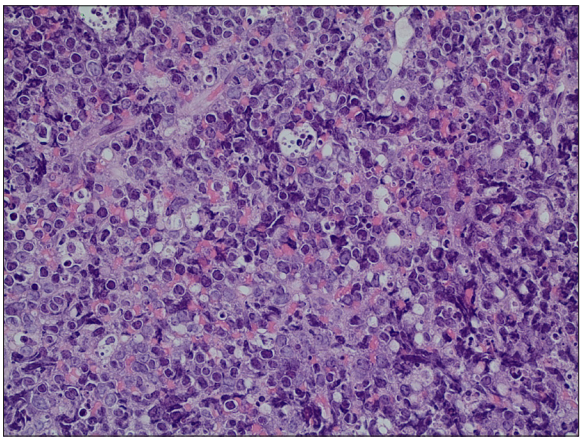

Figure 2: Classically, the histology of Burkitt lymphoma has been described as that of a 'starry sky'. The 'stars' are macrophages that phagocytose apoptotic and necrotic cells resulting from the very rapid turnover from tumour growth. This is set against a background of darkly staining lymphoid (tumour) cells which represents the 'sky'.

Learning Points

This case clearly demonstrates the importance of thorough clinical history taking and examination in patients presenting with an unprovoked VTE. When approaching such a patient one should ask specifically about red flag symptoms such as weight loss, change of bowel habit and night sweats. All patients should be examined thoroughly and breast and rectal examinations performed as appropriate for age, sex and risk factors. Additional tests and investigations such as prostate specific antigen (PSA), lactate dehydrogenase (LDH) or mammography should be considered.

Screening for Occult Malignancy in patients presenting with Venous Thromboembolism

Underlying cancer should always be considered when assessing a patient with VTE. A proportion of patients with unprovoked VTE and no obvious sign of cancer may have an occult cancer. It is estimated that the prevalence of undiagnosed cancer in patients with unprovoked VTE is around 6 % at presentation, increasing to 10 % at 12 months. (1)

In the SOMIT (Screening for Occult Malignancy in Patients with Symptomatic Idiopathic VTE) study, 99 patients were randomised to extensive screening for occult cancer and 102 to no further testing. Patients had a 2-year follow-up period. Cancers were picked up earlier in the extensive screening group but cancer associated mortality was the same in both groups. Also many patients in the extensive screening group underwent unnecessary scans and further testing such as endoscopies. (2)

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This small randomised controlled trial led NICE to recommend the following: 'consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or pulmonary embolism (PE) who do not have signs or symptoms of cancer based on initial investigation.'(3)

More recently, a larger randomised trial of 854 patients with first time unprovoked VTE compared limited and extensive cancer screening strategies (SOME TRIAL). The results demonstrated that extensive investigations (beyond routine laboratory tests and age/gender-appropriate routine screening) for cancer in patients with a first unprovoked VTE are not routinely indicated, because they have not been shown to improve prognosis or mortality. (4)

Following a thorough clinical history, examination and interpretation of the recommended laboratory tests and CXR; any patient presenting with:

• *bilateral -DVTs*

• *clot propagation on anticoagulation, or - early recurrence of VTE should increase the index of suspicion of underlying malignancy and prompt further investigation. (5)*

Predicting thromboembolic risk in cancer patients

Tools have been developed in an attempt to predict the risk of development of thromboembolism in patients diagnosed with cancer (Table 1).

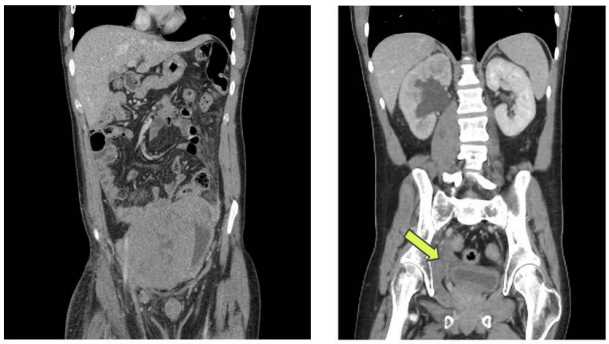

Figure 1a) 1b)

Table 1: Patient characteristics that are predictive of venous thromboembolism in cancer patients with an associated risk score. (6)

While the value of this scoring system is debated (7), there is undoubtedly an increased risk of VTE associated with the malignancies listed in table 1. (6) Chemotherapy also increases the risk of thrombosis, as do the presence of indwelling central venous catheters that are commonly placed to administer chemotherapy and are often complicated by thrombosis. (6)

Figures vary, but it is helpful to remember that '10% of first unprovoked VTEs will be due to an underlying cancer and 10% of patients with cancer will develop a VTE.' (1,5)

Management

Patients with cancer associated thrombosis have a much higher risk of VTE recurrence on anticoagulation than those without cancer. Treatment dose LMWH is the preferred choice of anticoagulation because it results in a significantly lower recurrence rate at 6 months than conventional treatment with Warfarin. (9)

The duration of anticoagulation recommended in cancer associated thrombosis (CAT) is six months. However, if the cancer or treatment is ongoing i.e. the provoking factor has not been removed, then ongoing anticoagulation must be considered.

The highest thrombotic risk is within the first 12 weeks post diagnosis of thrombosis. (5) When considering CAT – this high thrombotic risk period commonly will coincide with chemotherapy treatment. Chemotherapy often causes a low platelet count (thrombocytopenia) and so an increased bleeding risk. The presence of thrombocytopenia demands reassessment of the risk-benefit balance of anticoagulation often with advice from the Haematology team. (10)

Summary

This case demonstrates how assumptions and a lack of thorough history and examination may have led to a delayed diagnosis of cancer in a young man. It was assumed that, due to his cerebral palsy, the patient normally used a wheelchair and that immobility was the provoking factor for DVT development. This was not the case; the wheelchair use was a result of the pain related to the acute DVT.

A thorough examination at presentation may have resulted in palpation of the abdominal mass or inguinal lymphadenopathy prompting earlier diagnosis. There was a lack of consideration that people with HIV are at considerably higher risk of cancer as compared with HIV negative counterparts. (11) Burkitt lymphoma is well associated with HIV.

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Our patient was very compliant with his antiretroviral therapy and although there has been a marked reduction in certain HIV-related malignancies since the introduction of HAART, the rates of some malignancies – Burkitt lymphoma cases amongst others, continue to rise within the HIV positive population. (12)

The Department of Health's National Cancer Patient Experience survey shows that young people with cancer (16 to 24 year olds) are twice as likely as older adults with cancer to have three or more consultations with their GP prior to hospital referral. (13) Underlying malignancy should always be considered whatever the age of the patient.

In patients with first time unprovoked VTE, additional to thorough history and examination, basic investigations should include blood tests, urine dip and a CXR. Collectively these should support any decision to request further investigations if there is a suspicion of cancer. Early recurrence or propagation of the clot or new clot formation on anticoagulation should also prompt further investigation to exclude malignancy.

Young people get cancer too and suspicious circumstances should be investigated irrespective of age. However, a dogmatic approach may lead to over-investigation whilst extensive screening, and even disucssing the possibility of cancer with some patients, may cause considerable anxiety for patients.

Approximately 20% of all cases of VTE occur in the setting of cancer. Thrombosis can further complicate cancer patients receiving chemotherapy and/or with indwelling venous lines making cancer patients 4-7-times more likely to develop venous thrombotic events compared with patients without cancer. (14)

It is crucial that when faced with an unprovoked VTE, the clinician asks the question – 'could this be a herald to an occult malignancy?' but at the same time, good acumen is required to avoid over-screening for cancer in these patients', as this is detrimental from a health economics and patient perspective. And when a cancer associated thrombosis occurs, another balance needs to be struck – between adequate anticoagulation and bleeding risk.

Self-assessment questions

1. Of the following malignancies, select the one with the highest associated thrombotic risk:

a. Prostate

b. Pancreatic

c. High grade lymphoma

d. Renal

e. Lung

2. A 39 year old male is diagnosed with a left common femoral vein thrombosis, he has a history of night sweats and weight loss and examination reveals left inguinal lymphadenopathy. A biopsy confirms a high grade B cell lymphoma – diffuse large B cell lymphoma. He has normal renal function. How would you manage his anticoagulation?

a. Warfarin with regular INR monitoring – for 3 months

b. Rivaroxaban, until treatment for DLBCL is completed

c. Treatment dose low molecular weight heparin (LMWH) with close monitoring of the platelet count whilst on chemotherapy

d. Start chemotherapy and only start anticoagulation if symptoms of the deep vein thrombosis (DVT) worsen despite anticoagulation

e. Inferior vena cava (IVC) filter and prophylactic LMWH

Answers

Q1. Answer b.

Pancreatic cancer is associated with a very high risk of VTE, but all malignancies (bar non-melanoma skin cancers) increase the risk of developing a VTE. (6) The treatments for cancer and any indwelling venous catheters (placed to administer treatment) also increase the thrombosis risk. (5) The spectrum of cancer varies with age, sex and risk factors, this must be considered when assessing and investigating a patient.

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Q2. Answer c.

Anticoagulation with LMWH is recommended in these patients and requires close monitoring of the platelet count, if the patient is receiving chemotherapy, (9) and renal function (with dose reduction and anti-Xa monitoring if the patients' creatinine clearance is <30 ml/min). (5) The use of the direct oral anticoagulants (DOACs) in CAT is not routinely recommended at present.

It would be inexcusable not to anticoagulate a patient with an acute DVT, the risk of a pulmonary embolism (PE) is real and could be fatal. Placement of an IVC filter is indicated in patients with an acute DVT where there is a contraindication to anticoagulation (such as active bleeding), extension of a DVT and/or PE despite adequate anticoagulation. (15)

Author

Dr Catrin Heledd Roberts
Speciality registrar in Haematology
Department of Haematology
University Hospital of Wales
Heath Park
Cardiff
CF14 4XN

Dr Clare Rowntree
Consultant Haematologist
Department of Haematology
University Hospital of Wales
Heath Park
Cardiff
CF14 4XN

Corresponding Author

Dr Clare Rowntree
clare.rowntree@wales.nhs.uk

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FATAL SEPSIS IN A POST ALLOGENEIC HAEMOPOIETIC STEM CELL TRANSPLANT PATIENT WITH ACUTE MYELOID LEUKAEMIA

CSW Tham, JF Apperley

Abstract

A 51-year-old lady with secondary acute myeloid leukaemia who was treated with haplo-identical haemopoietic stem cell transplantation presented on day +196 post-transplant to the haematology outpatient department with cough and coryzal symptoms. She was discharged with supportive treatment but rapidly deteriorated overnight, re-presenting to the emergency department and requiring admission to the intensive care unit (ICU) for inotropic support.

Investigations revealed a right lower zone pneumonia, respiratory syncytial virus infection and *Escherichia coli* (two extended beta-lactamase producing strains) bacteraemia. This was treated with broad-spectrum intravenous antibiotics and ribavirin and the patient made a good recovery. On the day of expected discharge, the patient was found unconscious, hypotensive and tachycardic, requiring readmission to the ICU. The patient continued to deteriorate and passed away later that day.

Case Discussion

A 51-year-old lady with acute myeloid leukaemia secondary to previous myelodysplastic syndrome, who had received a haplo-identical haemopoietic stem cell transplant returned for follow up at the haematology outpatient unit on day +196 post-transplant. This was thirteen days following a 3-month admission with grade 4 acute graft versus host disease (aGvHD) of the gut, cytomegalovirus (CMV) reactivation and bacteraemias with extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli* and multiresistant *Citrobacter*.

At the time of this presentation she was on continuing treatment for her aGvHD of budesonide 3mg TDS, prednisolone 50mg OD and ciclosporin 100mg BD. Her antimicrobial prophylaxis included phenoxymethylpenicillin 250mg BD, co-trimoxazole 480mg BD (3 times a week) and posaconazole 300mg OD. Other regular medications included omeprazole, loperamide, amiloride, amlodipine and gliclazide for pre-existing hypertension and type II diabetes mellitus.

She reported a cough productive of a small amount of clear sputum and coryzal symptoms. She otherwise felt well, was afebrile and not dyspnoeic. Her aGvHD was under control with two soft bowel motions per day. Clinical examination was unremarkable – a peripherally inserted central catheter (PICC) was in situ with no signs of infection. Laboratory results (see table 1) showed nothing of note. Chest radiograph (figure 1A) showed no infective changes. In light of the coryzal symptoms, a nasopharyngeal aspirate was taken for polymerase chain reaction (PCR) for respiratory viruses. Additionally, peripheral and PICC blood cultures were taken. Further follow up for review was arranged in four days.

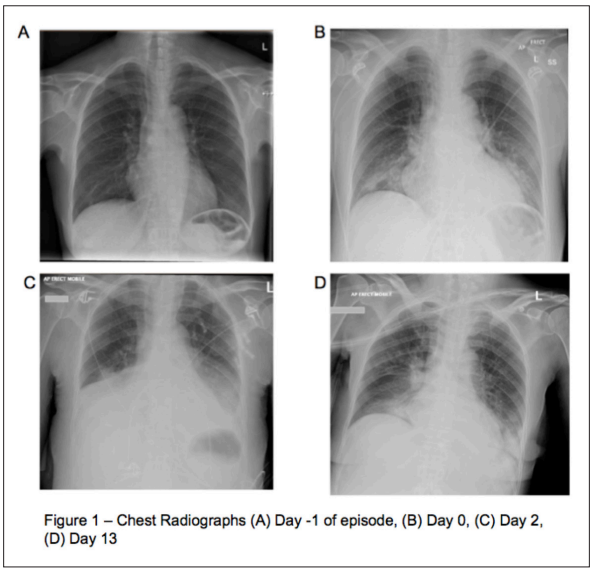

Figure 1 – Chest Radiographs (A) Day -1 of episode, (B) Day 0, (C) Day 2, (D) Day 13

Figure 1

The following day the patient was taken by ambulance to the emergency department after development of fever, and deterioration in her condition. On arrival she was alert and communicative but dyspnoeic requiring 2L/minute supplementary oxygen via nasal cannulae. She was also tachycardic with a heart rate of 150 and hypotensive with a blood pressure of 110/54mmHg. Initial treatment consisted of fluid resuscitation with intravenous crystalloid and prompt administration of intravenous antibiotics – tazocin (piperacillin and tazobactam), amikacin and teicoplanin.

Repeat chest radiograph (figure 1B) showed rapid deterioration since the previous day with new right lower zone consolidation. Arterial blood gas samples showed a type 1 respiratory failure and metabolic acidosis with a lactate concentration of 8mmol/L (see table 1 for full results).

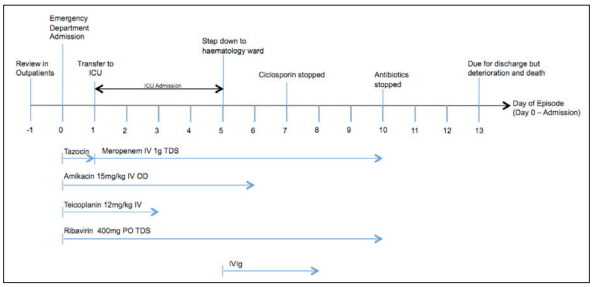

Figure 2

Despite aggressive intravenous fluid resuscitation (6 litres of normal saline), the patient remained hypotensive with a raised blood lactate concentration. This prompted central venous catheter insertion and transfer to the intensive care unit (ICU) for inotropic support with noradrenaline.

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By this time, the nasopharyngeal aspirate from the previous day had detected respiratory syncytial virus (RSV). Treatment with oral ribavirin 400mg TDS and intravenous immunoglobulin (IVIg) was commenced. Blood cultures from admission revealed gram-negative bacilli in both aerobic and anaerobic bottles after less than twenty-four hours. Her PICC was removed (which subsequently showed no microbiological growth) and antibiotic treatment was escalated from tazocin to meropenem for greater gram-negative organism cover. Subsequently, microbiology reported two separate strains of multi-resistant *E. coli*, both ESBL producers sensitive to meropenem. One of these strains was isolated in a concomitant sputum sample, in keeping with her diagnosis of pneumonia.

The patient responded well to antibiotic treatment, was rapidly weaned off inotropic support and stepped down to the haematology ward three days after admission to the ICU, on day 5 (see timeline, figure 2). She continued to recover well, weaning off supplementary oxygen and regaining independence with mobility and other daily activities.

Day of Episode	-1	0	1	2	3	4	5	7	10	11	12	13	13
White Cell Count (4.2-11.2x10^9/L)	3.2	3.3	2.4	4.0	3.2	3.2	2.5	2.9	5.7	5.1	4.4	2.5	0.4
Haemoglobin (114-156 g/L)	98	95	98	79	78	92	107	94	103	98	98	89	64
Platelets (135-400 x 10^9/L)	85	58	68	46	45	37	27	24	22	21	19	16	8
Neutrophils (2.0-7.1 x 10^9/L)	2.1	2.1	2.0	3.1	2.4	2.3	1.8	2.1	4.6	3.6	3.5	2.1	0.2
Sodium (133-146mmol/L)	135	132	138	138	139	136	135	134	128	131	131	133	136
Potassium (3.5-5.3mmol/L)	3.7	3.7	3.4	3.5	3.6	4.0	3.0	3.6	3.8	4.0	4.3	2.7	3.2
Creatinine (60-125μmol/L)	58	62	48	47	42	40	46	46	50	58	54	52	63
C-Reactive Protein (0-5 mg/L)	0.8	50.9	210.3	273.4	155.6	76.6	40.7	26.2	4.1	3.0	2.3	8.1	42.8
Bilirubin(0-21μmol/L)	13						16	19	34	39	33	43	22
Alanine Transaminase (5-40 IU/L)	27						37	71	170	201	181	168	77
Alkaline Phosphatase (30-130 IU/L)	121						306	271	341	355	344	293	148
Lactate Dehydrogenase (125-243 IU/L)	497							838	1322	1303		1060	
FiO_2 (%)		24	30	60	35	28						21	
pH (7.35-7.45)		7.49	7.46	7.48	7.48	7.49						7.48	
pO_2 (10-14kPa)		8	11.2	17.7	10.9	11.2						8.2	
pCO_2 (4.5-6kPa)		3.1	3.6	4	4.1	4						4.1	
Lactate (mmol/L)		8.9	6.1	3.1	4.3	2.8						4.4	
Base Excess (-2 - 2mmol/L)		-5.8	-4.6	-1.2	-0.4	-0.4						-1.2	
HCO3 (22- 26mmol/L)		17.5	19.2	23.1	23.1	22.9						22.3	

Table 1 – Laboratory Results

Table 1

On day 7, routine examination of this patient's blood film showed red cell fragmentation, a rise in LDH and a slight hyperbilirubinaemia suggesting red cell haemolysis. The main differentials were ciclosporin related microangiopathic haemolytic anaemia and oxidative haemolytic anaemia secondary to ribavirin so both drugs were stopped. On day 10 of the admission, meropenem and amikacin were stopped, having completed nine and six day courses of each, respectively.

On day 13 of the admission, the patient was reviewed on the daily ward round and considered fit for discharge. 4 hours later she was found in bed, unresponsive, with a blood pressure of 46/16mmHg, heart rate of 73bpm and SpO_2 88%. She responded to intravenous fluid boluses and intravenous metaraminol, regaining consciousness, but required readmission to ICU for further inotropic support. Treatment with intravenous meropenem, amikacin and teicoplanin was restarted. Despite these interventions, the patient continued to deteriorate and died later that evening.

A CT pulmonary angiography (CTPA) scan shortly after readmission to the ICU revealed no evidence of pulmonary emboli. It did however show severe bilateral multilobar consolidation, reported as "dense consolidation with intrinsic bronchograms throughout the right middle and both lower lobes [and] further dense, patchy consolidation in the posterior segment of the right upper lobe and the posterior aspect of the left upper lobe." A CT scan of the abdomen and pelvis performed at the same time showed progression of gut GvHD with mural oedema throughout the gastrointestinal tract and also in the gallbladder and biliary tree.

Discussion

Haemopoietic stem cell transplant patients are particularly susceptible to severe life threatening infections. Immune reconstitution post-transplant is a slow process, taking months to years for cells of the adaptive immune system to regain full function. This may be compounded by ongoing use of immunosuppressive therapy and is even more problematic in haplo-identical transplants where extra immunosuppresion is required. This means that apparent recovery of the full blood count does not mitigate the risk of infection, hence the ongoing need for prophylactic antimicrobials and prompt initiation of appropriate antimicrobial therapy during active infection.

As mentioned previously, this patient was taking phenoxymethylpenicillin, co-trimoxazole and posaconazole for antimicrobial prophylaxis. Gram-negative bacteria such as E. coli are a major cause of sepsis-related morbidity and mortality in immunosuppressed patients, hence the initial use of intravenous amikacin (in combination with piperacillin and tazobactam) in the above case. Teicoplanin was used to provide broader gram-positive cover in case of line-related sepsis, another complication in those undergoing transplant and receiving cytotoxic medication.

Consequently, ciprofloxacin is typically used as prophylaxis in neutropaenic patients. Once the neutrophil count recovers, this is often changed to phenyoxymethylpenicillin (similar to patients who have undergone splenectomy). This does not, however, cover for gram-negative organisms. It again emphasises that engraftment does not necessarily mean that patients' full immune function has returned.

Co-trimoxazole is used as prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP). It can have myelotoxic effects and is therefore typically stopped during transplant and is only restarted once stable engraftment has occurred. A higher dose is used to treat PCP infection and an intermediate dose can be used to treat *Stenotrophomonas* infection, a gram-negative bacteria that can cause opportunistic infections in immunocompromised patients. Posaconazole provides antifungal prophylaxis.

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Despite initially presenting without alarming clinical features and reassuring investigations, she declined rapidly overnight as described above. This case illustrates the importance of taking appropriate microbiological specimens. The detection of RSV was consistent with the initial clinical presentation of coryzal symptoms and cough. Appropriate treatment for this was given as per British Society for Haematology guidelines (1) – ribavirin and IVIg. Blood cultures also identified a causative organism in the setting of her pneumonia and sepsis.

It is likely that the RSV infection predisposed the patient to secondary bacterial pneumonia and progression to lower respiratory tract infection (LRTI). Using a RSV risk-scoring index (2) this patient fell into a moderate risk category based on her age, previous myeloablative conditioning regimen, GvHD and ongoing use of corticosteroids. Based on this index, she had a 23% risk of progressing to LRTI and a 3% risk of mortality. Perhaps earlier presentation, diagnosis and treatment would have prevented the need for ICU admission.

The detection of multiple resistant strains of *E. coli* in blood cultures further emphasises the need for culture results to guide appropriate antimicrobial therapy. Previous exposure to many lines of broad-spectrum antibiotics puts these patients at risk of infection with resistant organisms. It is likely that these organisms entered the blood stream via translocation through the gut mucosa. Her GvHD of the gut was a key factor here – it has been shown that the gut microbiota is altered leading to a reduction in commensals and a rise in potentially pathogenic bacteria (3).

The patient made a good clinical recovery but had a sudden, unexpected fatal deterioration. From the clinical information gathered at the time, the most likely cause was severe sepsis and shock. This was likely from further bacterial translocation as evidenced by the gut oedema on CT scan of the abdomen. Unfortunately there were few warning signs in the lead up to this, other than an intermittent sinus tachycardia of 100-120 beats per minute recorded on the preceding day. The patient had remained afebrile off antibiotics and was not experiencing any diarrhoea or abdominal pain to suggest recurrence of active gastrointestinal GvHD. However the cessation of ciclosporin on day 7 may be significant in this regard.

This case highlights the vulnerability to severe infection in heavily immunosuppressed individuals such as those who have undergone allogeneic haemopoietic stem cell transplantation, even when not neutropenic. Targeted treatment of causative microorganisms is essential but even despite this these patients can deteriorate suddenly and without warning, as illustrated by two instances in this one case.

Author

Dr Christopher SW Tham
Foundation Year 2 Doctor
Senior House Officer
Department of Haematology
Imperial College London
Hammersmith Hospital
Du Cane Road, London, W12 0NN

Prof Jane F Apperley
Consultant Haematologist
Chair of the Department of Haematology
Imperial College London
Hammersmith Hospital
Du Cane Road, London, W12 0NN
j.apperley@imperial.ac.uk

Corresponding Author

Dr Christopher SW Tham
cswtham@gmail.com

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FATALLY INVASIVE SAPROCHAETE CLAVATA INFECTION IN A PATIENT WITH ACUTE LYMPHOBLASTIC LEUKAEMIA: A UK CASE REPORT & LITERATURE REVIEW

Q Zhou, L Mihailescu, S Bolam

Abstract

Saprochaete Clavata (S. Clavata) is a very rare but emerging and invasive human infection with uncertain source. Limited numbers of previous case reports highlighted its association with severe immunosuppression and generally very poor prognosis. We report a case of invasive S. clavata fungal septicaemia, in a patient with acute lymphoblastic leukaemia (ALL) and neutropenia. Despite of a combined antifungal therapy and recovering neutrophil count, the patient deteriorated rapidly with multi-organ failure, and died at 37th day post methotrexate based induction chemotherapy.

This case report echoed the very poor clinical outcome of previously reported invasive S. clavata infections. However, it uniquely presented the paradoxical trajectory between progression of fungaemia and recovering neutrophil count. It is the first UK case report of S. Clavata in a patient with acute lymphoblastic (ALL) leukaemia, and the patient was the eldest in her age amongst all reported cases.

Keywords

Saprochaete Clavata; Acute lymphoblastic leukaemia; Invasive fungal infection; Amphotericin B and flucytosine.

Background

S. Clavata was previously named Geotrichum Clavata. It is a member of the yeast family, and an emerging causative agent of invasive fungal infections in human. However, they are extremely rare and almost exclusively occurring in patients with prolonged neutropenia during treatment for haematological malignancies (1).

S. Clavata is a type of filamentous fungi, belonging to the genus Geotrichum. The Geotrichum candidum is widely used as adjunct culture in the maturation of cheese, and composed of 18 species. Two species are described in human pathology: S. Clavata and Saprochaete Capitate (S. Capitate) (2). In cultural growth, they produce a frosted-glass appearance. Laboratory diagnosis of S. Clavata can be difficult as it resembles S. Capitate, and misidentification is not uncommon (3).

At present time, the exact niche of S. Clavata remains unknown, and there are no standard recommendations for S. Clavata antifungal prophylaxis and treatment. Prognosis for disseminated S. Clavata is extremely poor with a mortality rate at about 80% (1).

Case presentation

A 75-year old woman was diagnosed with Philadelphia negative ALL in Sep. 2016. She underwent phase 1 induction chemotherapy containing oral mercaptopurine and methotrexate promptly upon diagnosis. She developed neutropenia one week after phase 1 treatment, which was resolved with granulocyte-colony stimulating factor (GCSF) injections. Induction phase 2 chemotherapy (with oral methotrexate and reduced dose of mercaptopurine) was given in Oct. 2016 with a partial response.

Patient was admitted between the 14th and 25th of Nov.2016, with symptoms of diarrhoea, mucositis and neutropenic sepsis, requiring treatment with Tazocin, Metronidazole, Fluconazole and GCSF. She made a good recovery. Discussion was made with her regarding further treatment options upon her discharge. Patient decided to proceed with a 3rd cycle of chemotherapy with reduced dose of methotrexate and mercaptopurin to aim for a complete remission.

She was re-admitted on 20th Dec. 2016 to a haematology ward with high grade fever, diarrhoea and mucositis, two weeks after completion of the 3rd cycle of chemotherapy. She was initially given empirical antibiotics per local guideline (Tazocin, metronidazole and itraconazole), but remained feverish and unwell at 48 hours. A two- week course of Meropenem, Tigecycline and Micafungin was started. Multiples cultures (blood, sputum, urine and stool) were taken during her treatment as she had persistent fever and symptoms of worsening diarrhoea and mouth ulcer. All initial cultural results were negative. A chest computed tomography (CT) scan was performed and found no significant abnormality.

On completion of 14 days of triple antibiotics (day 29 post chemotherapy), her neutrophil count had recovered to 1.7, and temperature was mostly settled (with intermittent low grade fever of 37.9 degree Celsius), despite of a relatively high CRP at 130 and symptoms of extreme lethargy. On day 30 post her 3rd cycle of chemotherapy, S. Clavata was isolated from both Peripherally Inserted Central Catheter (PICC line) and peripheral blood cultures. Patient was given a combined antifungal therapy with liposomal amphotericin B and Flucytocin promptly. In vitro susceptibility test showed an intrinsic resistance to echinocandins. Re-culture from multiple sites were taken. Interestingly, S. Clavata was also grown in urine culture but not in sputum or stool. A galactomannan antigen test was negative.

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Unfortunately, patient deteriorated rapidly despite of a normal neutrophil count. Clinically, she was in multi-organ failure at day 35. Patient and family were opted for palliation after a meeting with the ICU team. Further investigations, such as a total body CT scan to exclude visceral involvement, was deemed inappropriate at this stage. She unfortunately died on day 37 post her 3rd cycle of chemotherapy.

Discussion & conclusion

The largest number of cases with fatal S. Clavata infection were reported in France between 2011 and 2012 (1). A total 30 cases of S. Clavata were observed, with a peak of 18 cases over two months in ten health care facilities located in ten different regions in 2012. S. Clavata was isolated mostly from blood, less so in stools and respiratory samples. 70% of cases were hospitalised for acute myeloid leukaemia (AML), with a median age of 63 years (range from 36 to 69 years). The mortality rate at 60 days was 80% (6 survived out of 30), with death occurring at a median of 7 days after diagnosis of S. Clavata infection (1).

Two years later (in 2014), a case of invasive S. Clavata infection in a 32-year -old with AML was again reported in France. This male patient was treated with therapeutic dose of voriconazole, and was alive at one year after (4). This young man had no significant past medical history, and his AML was cytogenetically classified as inversion 16 with FLT-3 negative indicating a relatively good prognosis at baseline. He developed S. Clavata fungaemia (positive blood, stool and ascitic fluid cultures,) post 2nd course of cytarabine based induction chemotherapy. Despite of prolonged ITU admission with multi-organ failure, he survived with a complete remission of AML (4).

In 2016, a cluster of three cases of Italian patients with haematological malignancies, who developed invasive S. clavata infection (with visceral organ involvement) at three weeks post cytarabine-based chemotherapy (5). Of those three, two patients (21 and 36 years old respectively) were affected by ALL, one patient (50 years old) with mantle cell lymphoma. All of them had positive blood culture for S. Clavata. The 50 years old unfortunately died and the other two younger patients survived, despite of all received prolonged intensive monitor and antifungal therapies with high dose liposomal amphotericin-B (5).

Concurrently, in 2016 there was a young patient (27 years old) in France with aplastic anaemia and severe neutropenia, survived from invasive S. Clavata infection with a combinational treatment of voriconazole, amphotericin B and GCSF. This young man was the only patient who had not been given chemotherapy prior to a diagnosis of S. Clavata fungaemia. Despite of high dose antifungal therapy, blood culture only became negative after a good 4-5 weeks' treatment (6).

From the limited case reports, it is apparent that little information is known about S. Clavata infection in terms of epidemiology, source of contamination, risk factors and the most appropriate treatment regimens. As for today, we have summarised a few important points of S. Clavata infections from the available cases reported. First of all, the majority of cases were affected by AML with neutropenia, and many had received cytarabine-based chemotherapy (4,5) (this is not in our case though).

The fatality rate was extremely high at about 80% (1). The documented age of survivors was very young (21 to 32 years old) (4,5,6). This could be that younger patients had a better baseline performance status and organ functions, such as renal function, which allowed a much higher dose and more intensive antifungal therapy to treat S. Clavata. It seemed that most of those affected had a central venous catheter (CVC) placed and cultures from CVC were proved to be positive at all cases (4,5,6).

Secondly, despite of extensive search for a source of infection, the possibility of fungal transmission through contaminated medical devices or with dairy products has been suspected, none was unequivocally recognised as responsible for this deadly yeast infection (1). Finally, the optimal treatment modalities were not unified. In vitro data indicated that S. Clavata is susceptible to Azoles and Amphotericin B, and resistant to echinocandins (1,4,5,6).

However, some of the literature reported cases developed S. Clavata despite of Azoles given prophylactically such as the case of ours. It may be that the prophylactic dose was inadequate for the treatment of an emerging S. Clavata septicaemia.

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In summary, 35 cases of S. Clavata infection were reported in the current literature. To the best of our knowledge, our report is the first case of S. Clavata disseminated infection in the UK. The patient was the eldest in her age amongst all cases reported. Interestingly, a positive culture was identified at the time when her neutrophil count was recovered, and she was the only one patient who had a positive culture from her urine, indicating a possible visceral involvement of the renal system. These features of our case were not reported in previous literature.

Author

Qiaoling Zhou
Haematology Department
Musgrove Park Hospital NHS trust
Taunton, UK, TA1 5DA

Loredana Mihailescu
Haematology Department
Musgrove Park Hospital NHS trust
Taunton, UK, TA1 5DA

Simon Bolam
Consultant Supervisor
Haematology Department
Musgrove Park Hospital NHS trust
Taunton, UK, TA1 5DA

Corresponding Author

Qiaoling Zhou
qz8028@my.bristol.ac.uk

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NEW DIAGNOSIS OF CHRONIC MYELOID LEUKAEMIA WITH THROMBOTIC COMPLICATIONS

P Dawson, D Radia

Abstract

This article presents a case of a new diagnosis of Chronic Myeloid Leukaemia (CML). We will discuss the presenting features, investigations as well as management of the patient. This case highlights some unusual presenting features of the disease in a patient with complications.

Case Presentation

The patient is a 78 year old male who presented to hospital in Colombia in January 2017. His symptoms were fatigue and weight loss. He was informed in Colombia that he had a diagnosis of 'leukaemia' but declined treatment.

The patient returned to the UK at the beginning of February and represented to hospital with a one day history of rectal bleeding. Past medical history included; atrial flutter, benign prostatic hypertrophy, type 2 diabetes mellitus, haemorrhoids, hypercholesterolaemia and ischaemic heart disease. His only medication was Bisoprolol. He was normally independent, an ex smoker and he rarely consumed alcohol.

On initial examination he had a heart rate of 90/min, blood pressure of 140/80mmhg and saturations of 97% on air. Abdominal examination revealed hepatosplenomegaly and a pulsatile aorta.

Initial investigations demonstrated a white cell count of 320 x 10^9/l, haemoglobin of 71g/l, platelet count of 475 x 10^9/l and an initial blood film consistent with a diagnosis of CML. Biochemistry demonstrated normal calcium but with minimally raised potassium, phosphate and a raised urate level. Chest x-ray was normal. The patient had undergone a CT abdomen to exclude an abdominal aortic aneurysm. There was no evidence of an aneurysm but there was an incidental finding of a right lower lobe pulmonary embolus and extensive luminal thrombus within the aorta and iliac vessels.

What is Chronic Myeloid Leukaemia?

CML is a subtype of myeloproliferative disorder. This condition is characterised by unregulated proliferation of myeloid cells within the bone marrow, with predominantly a granulocytic hyperplasia and associated basophilia. All subtypes of white blood cells can be increased and an underlying mutation causing the Philadelphia chromosome demonstrated in over 80% of cases. CML can present in one of three phases; chronic phase with symptoms evolving over months or years, accelerated phase with symptoms presenting more acutely and difficult to control white cell counts or blast transformation, which can present as an acute leukaemia. (1)

First line investigations (2)

- Full clinical examination including

- Documentation of spleen and liver size in cm below the costal margin

- Where possible documentation of spleen size by USS

- Full blood count with manual differential and blood film

- Routine biochemistry – including U&E, LFTs, albumin, calcium, LDH and urate

- Viral serology

- Bone marrow aspirate and trephine (BMAT)

- Cytogenetics to confirm the Philadelphia chromosome.

- Immunophenotyping

The patient underwent bone marrow aspiration on the evening of admission to expedite anticoagulation with low molecular weight heparin (LMWH) to treat his newly diagnosed thrombosis. He was started on allopurinol prophylaxis and intravenous fluids.

The likely diagnosis of CML in chronic phase was confirmed morphologically (Figure 1). The diagnosis was later confirmed on cytogenetics. SOKAL score was 0.98 (Intermediate risk). This is a hazard ratio used in chronic phase CML to determine overall survival, response to treatment and to guide treatment.

The score is calculated at diagnosis using the following factors; age, spleen size (cm below the costal margin), platelet count, peripheral blast, eosinophil and basophil count (as a percentage of leucocytes) (3). Prognosis in chronic phase CML is excellent with an 8 year overall survival of more than 75%. The patient commenced rasburicase prophylaxis for tumour lysis syndrome (TLS) following a normal G6PD level and commenced cytoreductive therapy with hydroxycarbamide.

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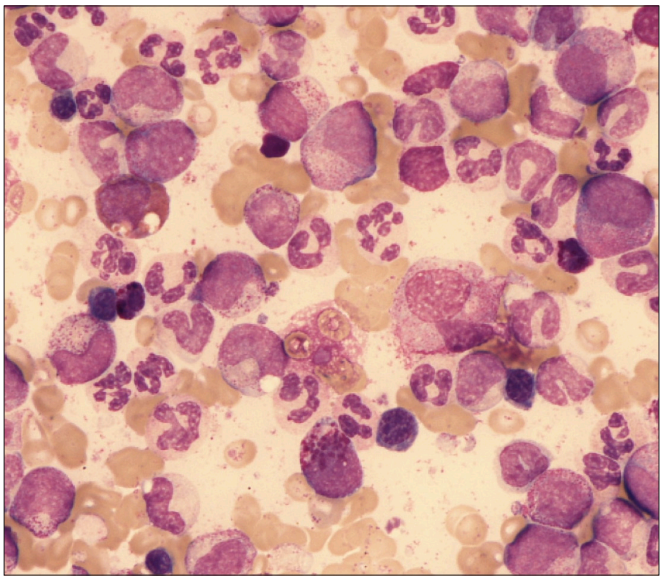

Figure 1: Bone Marrow aspirate of a patient with chronic phase CML. Showing increased myelopoesis, nucleated red cells and basophils. (X60 oil magnification).

Over the next 72 hours the patient was monitored for TLS with bloods twice daily as his white blood cell count declined. There was no evidence of TLS so he was converted to allopurinol once his white cell count had reduced to below 100 x 10^9/L. The patient's full blood count demonstrated a progressive decline in haemoglobin count to 53g/l. This was thought to be due to the combination of initial rectal bleed, hydroxycarbamide therapy and oozing from the biopsy site. Blood transfusion decisions were made at Consultant level with each unit given over four hours with intravenous fluids in order to minimise the risk of hyperviscosity.

The patient was discharged following a two week admission with a white cell count of 33 x 10^9/l and stable haemoglobin. He remained on allopurinol, hydroxycarbamide and LMWH. He was seen in clinic one week later with stable blood counts but a new symptom of nausea, which he attributed to hydroxycarbamide and stopped himself. He commenced imatinib following confirmation of Philadelphia positive CML. He remains monitored in clinic and will be reviewed by the thrombosis team.

Discussion

This article presents a new diagnosis of CML requiring inpatient treatment. The need for urgent treatment was precipitated by the delay in presentation to services in the UK. The incidental finding of pulmonary embolism presented a challenge during the investigation of this patient and a prompt bone marrow biopsy was performed in the emergency department to expedite initiation of anticoagulation as well as facilitating a formal diagnosis.

This patient responded to cytoreductive therapy but his white cell count conferred a significant risk of TLS, necessitating close monitoring of his serum biochemistry. He is now on first line treatment imatinib. At diagnosis he was anaemic but the significant leucocytosis placed him at increased risk of hyperviscosity.

This meant that the administration of blood products must be considered carefully and only if the patient was significantly symptomatic as the anaemia is likely to be due to CML in most cases. As the junior doctor it would be important to recognise that blood transfusion presents an additional risk in this patient group. Early involvement of senior haematologists would be advised prior to administration of blood products.

Multiple choice questions

1. What is the standard length of anticoagulation given to patients with a new diagnosis of DVT or PE who have an active malignancy?

A. Minimum 6 weeks

B. Minimum 3 months

C. Minimum 6 months

D. Following curative treatment of the malignancy

E. Lifelong

2. What is the underlying translocation mutation giving rise to the Philadelphia chromosome?

A. t(15;17)

B. t(8;14)

C. t(11;14)

D. t(14;18)

E. t(9;22)

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3. Which of the following sets of blood results are most consistent with Tumour Lysis Syndrome (TLS)?

A. Potassium 4.1 mmol/L, Calcium 2.73 mmol/L, Urate 0.1 mmol/L, Phosphate 0.8 mmol/L

B. Potassium 6.2 mmol/L, Calcium 2.04 mmol/L, Urate 0.95 mmol/L, Phosphate 1.4 mmol/L

C. Potassium 3.4 mmol/L, Calcium 2.01 mmol/L, Urate 0.8 mmol/L, Phosphate 1.2 mmol/L

D. Potassium 6.5 mmol/L, Calcium 2.55 mmol/L, Urate 0.3 mmol/L, Phosphate 0.85 mmol/L

E. Potassium 5.1 mmol/L, Calcium 2.12 mmol/L, Urate 0.2 mmol/L, Phosphate 0.7 mmol/L

4. What is the reason for checking the patient's G6PD status prior to starting Rasburicase?

A. Methaemoglobinaemia

B. Anaphylaxis

C. Nephrotoxicity

D. Hepatotoxicity

E. Steven Johnson syndrome

5. What is the mechanism of action of Imatinib?

A. Alkylating agent

B. Topoisomerase inhibitor

C. Monoclonal antibody

D. Tyrosine Kinase inhibitor

E. Dihydrofolate Reductase inhibitor

Answers

1. Correct answer C.

Following a suspected diagnosis of VTE NICE advises starting treatment with LMWH or Fondaparinux. Once diagnosis is confirmed patients should commence a vitamin K antagonist with LMWH continued until the INR is within the therapeutic range for two consecutive days. In the case of patients with active malignancy, NICE advises sole treatment with LMWH for a minimum of 6 months. (4)

2. Correct answer E.

The Philadelphia chromosome is present in the majority of patients diagnosed with CML. It is not specific to this disease and can be found in cases of Acute Lymphoblastic Leukaemia (ALL) where is confers a poorer prognosis. The Philadelphia chromosome results from a translocation of the ABL gene on chromosome 9 to the BCR gene on chromosome 22, this results in a fusion gene coding for a tyrosine kinase allowing unregulated cell division. (5)

3. Correct answer B.

TLS is a potentially life threatening medical emergency occurring in haematology and oncology patients following rapid cell break down, usually as a consequence of chemotherapy or corticosteroids but can occur spontaneously. Those at highest risk are patients whose cancer has a high tumour burden. The syndrome is characterised by hyperkalaemia, hyperuricaemia, hyperphosphataemia and hypocalcaemia.

These abnormalities can lead to renal failure and cardiac arrhythmias. Treatment is intravenous hydration, stimulation of diuresis and prevention of hyperuricaemia with allopurinol or rasburicase. (6)

4. Correct answer A.

Rasburicase is a recombinant form of urate oxidase used to prevent hyperuricaemia in TLS. A rare side effect of Rasburicase is methaemoglobinaemia. Methaemoglobin is formed as a result of rasburicase oxidising the ferrous form of iron within erythrocytes to the ferric form. This reduces the ability of haemoglobin to bind to oxygen. (7)

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an inherited X-linked condition predisposing to haemolysis in response to infections, certain foods and drugs. (5) Patients with G6PD deficiency are at higher risk of methaemoglobinaemia and acute haemolysis following rasburicase.

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5. Correct answer D.

Imatinib competes with ATP to bind to the ABL-BCR tyrosine kinase receptor. By preventing the binding of ATP, imatinib prevents downstream signalling from the receptor, which would otherwise cause unregulated white cell proliferation. Unlike hydroxycarbamide, imatinib is able to induce complete haematological response in many patients in the chronic phase of CML and toxicity is low. This has led to imatinib becoming first line therapy in CML (8).

Most patients with CML are treated in clinic with a tyrosine kinase inhibitor (TKI). Imatinib and nilotinib are NICE approved for first line treatment. Drug of choice depends on SOKAL score and comorbidities. Patients are monitored to assess for remission. Patients who have a high tumour burden or complex presentation at diagnosis may be initially cytoreduced using hydroxcarbamide.

Only a minority of patients have primary resistance to imatinib and these patients will not have the expected clinical response within 4-6 weeks of treatment. Bone marrow transplants in patients who are resistant to treatment or fail to achieve molecular milestones offer a curative therapeutic option. (9)

Author

Dr Patrick Dawson MBBS, BSc, MRCP.
Guys and St Thomas NHS trust
Great Maze Pond Road, SE1 7EH

Dr Deepti Radia BSc, MRCPI, FRCPath, MSc Med Ed.
Guys and St Thomas NHS trust
Great Maze Pond Road, SE1 7EH
Deepti.Radi@gstt.nhs.uk

Corresponding Author

Dr Patrick Dawson
Patrickdawson@doctors.org.uk

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POLYCYTHAEMIA VERA MASKED BY IRON DEFICIENCY ANAEMIA

E Booth, Z Rudzki, J Ewing

Abstract

We discuss the case of a 51 year old lady who presented with a 2 year history of abdominal pain. Investigation revealed extensive portal vein thrombosis. Anticoagulation led to significant gastrointestinal variceal bleeding. She was referred to haematology for investigation of her iron deficiency and anticoagulation management. Subsequent investigation with molecular genetic testing and bone marrow trephine revealed a diagnosis of polycythaemia vera (PV).

Although PV is a relatively rare condition with incidence of 1.9 in 100,000 patients per annum, symptomatic patients who are untreated have a median survival of 6 to 18 months from diagnosis, largely due to thrombotic complications (1). It is important to make a timely diagnosis in these patients as current survival of optimally treated patients is improved to 14 years or more (2).

This article will discuss the case itself and an approach to the investigation of erythrocytosis and diagnosis and management of PV.

Erythrocytosis had been previously defined by BCSH criteria as a haematocrit of >48% in women or >52% in men and Hb >165g/l in women or >185g/l in men (3). The diagnostic criteria have been revised in World Health Organisation diagnostic criteria for diagnosis of myeloproliferative neoplasms, WHO 2016, to account for the phenomenon of 'masked' PV so that the diagnosis can now be made with Hb >165g/l or Hct >0.49(male) or >160g/l or Hct > 0.48(female) (4).

A case history of portal vein thrombosis

A 51 year old lady presented to gastroenterology with a 2 year history of abdominal pain and intermittent diarrhoea and vomiting. She underwent abdominal CT scan which showed thrombosis of the portal, superior mesenteric and splenic veins (Figure 1).

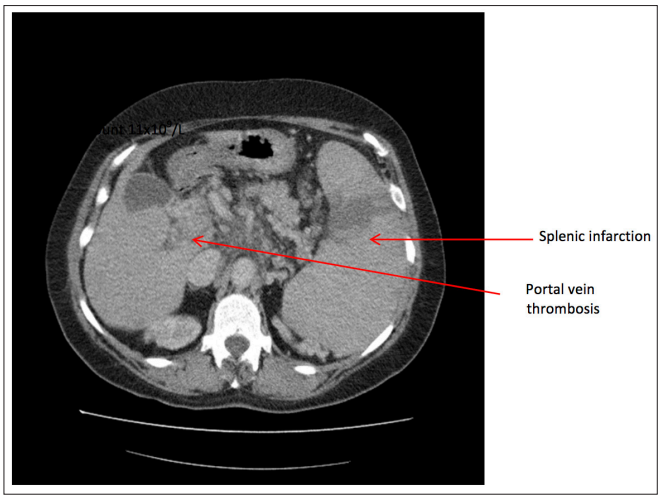

Figure 1: Abdominal CT scan.

Presentation blood results	In haematology clinic (> 3 months later)
Haemoglobin 150 g/L	Haemoglobin 120 g/L
Haematocrit 0.47	Haematocrit 0.36
Platelets 580 x10^9/L	Platelets 350 x10^9/L
Mean cell volume 71 fL	Mean cell volume 70 fL
Ferritin 11ng/mL	
White cell count 12.2 x10^9/l	White cell count 10 x10^9/L

Table 1: Interpretation of blood results.

Her blood results at presentation show a low MCV and low ferritin level consistent with iron deficiency however the haemoglobin value and haematocrit are at the upper end of normal range – these would normally be expected to be low given the degree of iron deficiency.

She was commenced on warfarin and aspirin, however the development of melaena after 10 weeks necessitated that this was stopped. She had upper gastrointestinal endoscopy which showed oesophageal varices and gastric and duodenal erosions. She had variceal banding and was started on propranolol for portal hypertension. She was referred to haematology, at which stage blood test results were as shown in table 1.

Given the previous history of thrombosis and normal haematocrit in the face of iron deficiency a diagnosis of PV was suspected and she was tested for the JAK2 V617F mutation. This was found to be positive (a JAK2 V617F mutation leading to constitutively activated myelopoeisis is seen in over 95% of cases of PV (5)).

She also had a bone marrow trephine performed which was consistent with a diagnosis of PV showing a hyperplastic marrow, with increased numbers of megakaryocytes, erythroid and myeloid activity and normal reticulin staining (Figure 2). Erythropoietin level at this stage was not interpretable due to the acute bleeding history at this time.

POLYCYTHAEMIA VERA MASKED BY IRON DEFICIENCY ANAEMIA

E Booth, Z Rudzki, J Ewing

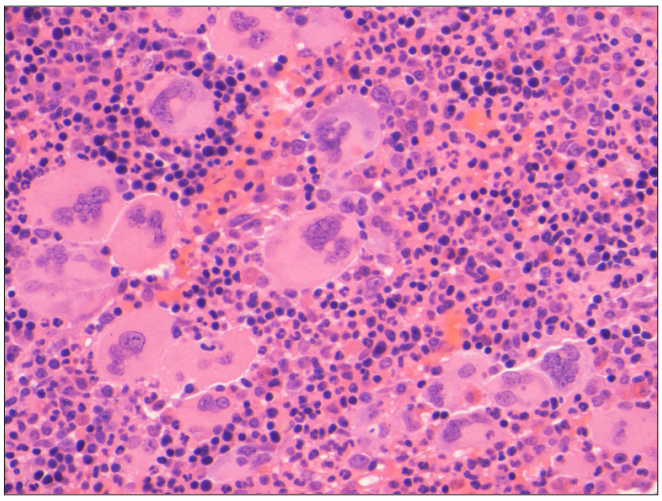

Figure 2: Bone marrow trephine demonstrating hyperplasia of all main haematopoietic lineages: erythroid, myeloid and megakaryocytic with loss of the normal fat spaces seen in bone marrow. The erythropoietic cells which have dark, almost 'black' nuclei, are scattered all over the marrow instead of forming discrete islands.

The myeloid-to-erythroid ratio, which is normally approximately 3:1, is shifted towards the erythropoiesis. Megakaryocytes – which generally retain their regular shapes and nuclear segmentation patterns show abnormal clustering.

Looking at the World Health Organisation (WHO) diagnostic criteria, given in table 2, it can be seen that our case fulfils 2 of the major criteria for PV. The acute bleeding masked the Hct value and meant erythropoietin assessment could not be interpreted.

A diagnosis of PV that had been 'masked' due to iron deficiency was made. She was treated with low dose aspirin, hydroxycarbamide and venesected when her haematocrit was >0.42 in view of the prior portal vein thrombosis. Iron supplements were avoided to prevent the rapid rise in haematocrit that can occur in patients with PV. This case illustrates how the complications of a disease can hide a diagnosis and a careful assessment of a case history can be traced backwards to enable diagnosis. She continues to do well with no further complications.

PV is one of the myeloproliferative neoplasms and is the most common form of acquired primary erythrocytosis (6).

WHO revised diagnostic criteria for PV (2016) (4):

Diagnosis requires the presence of all 3 major criteria or the first two major criteria and the minor criteria.

Major criteria:

(a) Hb>165 or haematocrit>0.49 (men), Hb>160 or haematocrit>0.48 (women) or red cell mass> 25% above normal predicted value

(b) Bone marrow biopsy showing trilineage hypercellularity for age with pleomorphic megakaryocytes

(c) Presence of JAK2V617F or JAK2 exon 12 mutation

Minor criterion:

1. Serum erythropoietin level below the reference range for normal

Table 2

How to assess a patient with erythrocytosis

Erythrocytosis is often an incidental or serendipitous finding, although it may be revealed when one of the complications arises such as thrombosis (as in the case study) or during investigation of generalised symptoms such as sweating or pruritus.

It is important to remember during the investigation of erythrocytosis that erythrocytosis can be either primary or secondary in nature and that secondary causes are much more common in clinical practice (7). There is also a type of erythrocytosis that can occur because of a reduction in plasma volume, although the actual red cell mass is normal, known as 'apparent' erythrocytosis (Table 3).

Primary erythrocytosis occurs when an alteration in the erythroid compartment of the bone marrow leads to increased red cell production and secondary erythrocytosis occurs when there is an external influence causing increased red cell production. The most common cause of secondary acquired erythrocytosis is central hypoxia due to a respiratory cause.

POLYCYTHAEMIA VERA MASKED BY IRON DEFICIENCY ANAEMIA

E Booth, Z Rudzki, J Ewing

Previous blood results can be reviewed to assess the prior trend, and a full blood count can repeated ensuring the patient is well hydrated at time of sampling to rule out a spurious reading.

What to discuss during history taking and examination?

Careful directed history and examination may help elicit the likely cause of the erythrocytosis, especially in the case of apparent and secondary causes.

- *Symptoms such as aquagenic pruritus (itching after bathing or showering) and erythromelalgia (sensation of burning or asthesia in extremities) may give evidence for a primary PV.*
- *Smoking and alcohol are common causes*
- *Sleep apnoea (snoring, night time awakening, daytime somnolence often in patient with obesity or a high BMI) may be explored in the history.*
- *Family history may reveal possibility of a rare inherited cause.*
- *Potential medication causes of apparent erythrocytosis such as diuretic use may be of relevance as well as enquiry around use of other drugs including testosterone and steroids which may be both prescribed and illicit.*
- *Prior venesection history may be of relevance eg regular blood donation may mask PV.*
- *Cardiovascular event or venous thrombosis history should be taken.*
- *Cardiovascular risk factor assessment.*
- *Examination of respiratory tract and for splenomegaly are important.*

Those with severe unexplained polycythaemia, with haematocrit >0.56, should be referred urgently to haematology. Patients with thrombosis or who are acutely symptomatic need urgent treatment. Hyperviscosity symptoms, blurred vision (or symptoms of amaurosis fugax), migraine, slow mentation or a sense of depersonalisation could indicate need for urgent venesection. Patients with unusual site thrombosis such as portal vein thrombosis should be screened with JAK2 mutation analysis.

How further investigations assist in diagnosis

More than 95% of patients with PV carry the JAK2 V617F mutation whilst a further 2-3% carry an exon 12 JAK2 mutation (5) and molecular testing forms a key part of the diagnostic work up. Measurement of erythropoietin is usually a key investigation as this is suppressed in the face of primary polycythaemia vera.

It is important this test is taken before venesection is undertaken as it can rise in response to blood loss. Other diagnostic tests that are used in the haematology clinic are a complete blood count and blood film (to assess features of myeloproliferative disease such as raised platelets and white cell count, changes associated with fibrosis), serum ferritin (due to iron deficiency masking erythrocytosis) and renal and liver function tests. An ultrasound to look for splenomegaly is also often performed, with two thirds of patients with PV being found to have splenomegaly (8).

Apparent erythrocytosis	**True erythrocytosis (defined as a red cell mass of greater than 125% of the predicted value for a persons' sex and body mass)**			
	Primary causes		**Secondary causes**	
Obesity Alcohol excess Smoking Hypertension Diuretics Burns	**Congenital** Erythropoetin (EPO) receptor gene abnormalities (constitutively activating mutations)	**Acquired** Polycythaemia vera	**Congenital** Oxygen-sensing pathway defects eg Von-Hippel Lindau, Proline hydroxylase 2 PHD2 mutations Altered affinity of oxyhaemoglobin	**Acquired** *Appropriately elevated serum EPO* Central hypoxia (eg. sleep apnoea, smoking, chronic obstructive or interstitial lung disease, left to right shunt) *Inappropriately elevated serum EPO* Local hypoxia (eg. renal artery stenosis, post renal transplant) Pathological EPO production (from tumours eg renal cell carcinoma, hepatocellular, haemangioblastoma, uterine fibroma) Exogenous EPO use Exogenous use of testosterone and anabolic steroids

Table 3: Causes of erythrocytosis.

POLYCYTHAEMIA VERA MASKED BY IRON DEFICIENCY ANAEMIA

E Booth, Z Rudzki, J Ewing

Polycythaemia Vera

Management

The British Committee for Standards in Haematology (BCSH) guidelines recommend that patients are individually managed according to their symptoms and risk. The risk of thrombosis in patients with polycythaemia vera is 1.6 times that of the general population, with an incidence of thrombosis at 1.9% per year so much of the treatment is aimed at preventing thrombotic events and all patients are treated with low dose aspirin or clopidogrel where aspirin may be contrindicated.

Treatment is based on stratification of patients into 2 groups based on their individual risk of thrombotic events and underlying cardiovascular risk factors. Individuals at high risk of thrombosis are treated with cytoreductive treatment with additional venesection if required to maintain Hct <0.45. In very high risk cases such as those who have had portal vein thrombosis a more aggressive target is sometimes used of Hct <0.42 as described in our case. Hydroxycarbamide, which is an antimetabolite and controls red cell and other haematopoietic cell production, is the first line treatment for high risk polycythaemia in patients over 60 years of age.

There was some debate as to whether hydroxycarbamide increases risk of transformation to acute myeloid leukaemia, but large studies have shown there is no increased risk from the use of this agent although there is an increased risk for other secondary cancers such as skin cancers (9). In younger patients who are at high risk, interferon alpha (which is not teratogenic or leukaemogenic) may be used.

Patients at low risk, (without active thrombosis and not at risk for thrombosis), have their haematocrit controlled to a level of <0.45 by serial venesections (with an average lowering of 3% in haematocrit per 500ml removed). Maintaining a haematocrit <0.45 has recently (in the CTYO-PV study) been shown to significantly reduce thrombosis risk (10,11).

Optimal control is considered a haematocrit value of <45% (10,11). Venesection will result in relative or absolute iron deficiency as evidenced by low MCV but this should not be treated with iron supplementation as this can give a rapid rise in haematocrit (12).

BCSH Guidelines for Polycythaemia Vera[3]

High risk Definition	High risk Management
• >60 years • Prior thrombosis history • Platelets >1000 x 10^9/l • Diabetes or hypertension requiring pharmacological therapy	• Low dose aspirin (clopidogrel if contraindicated • Aggressive venesection to maintain Hct <0.45 • Cytoreductive therapy:hydroxycarbamide or interferon alpha • Manage cardiovascular risk profile
Low Risk	**Low risk management**
• <60 years • None of the above risk factors	• Low dose aspirin (clopidogrel if contraindicated) • Venesection to achieve Hct < 0.45 • Manage cardiovascular risk profile

Table 4

Complications and malignancy

In PV the most common causes of death are thrombosis, malignancy (both haematological and otherwise), haemorrhage and transformation to myelofibrosis (13). Treatment is aimed at reducing the incidence of these complications. Haemorrhagic complications occur in around 2-8% of patients and are thought to be due to acquired von Willebrand's disease (14) whilst thrombosis occurs in 2.7 per 100 patients per year (15).

Patients with PV need to be followed up under specialist care not only to receive cytoreductive treatment but also to be monitored for signs of progression to the myelofibrotic stage of the disease. Post PV myelofibrosis has an incidence of 15-20% at 15 years (16) and acute leukaemic transformation at 3-5% (17).

Best of 5 MCQ questions

1) An obese gentleman, who has been waking frequently at night and feeling tired during the day is found to have a raised haematocrit of 0.52 and his Hb is 185. His red cell mass is >125% of that expected for his gender and weight. He is given a CPAP machine and parameters show some improvement. What type of erythrocytosis is he likely to have?

(a) Acquired primary erythrocytosis (polycythaemia vera)

(b) Congenital secondary erythrocytosis

(c) Apparent erythrocytosis

(d) Acquired secondary erythrocytosis

(e) Congenital primary erythrocytosis

2) A 55 year old woman is newly diagnosed with polycythaemia vera. She is judged to be at low risk as she does not have any active thromboses, nor any risk factors for thrombosis. Her latest haematocrit is 0.49. What treatment should she be offered?

(a) Cytoreductive agent such as hydroxycarbamide

(b) Venesection to maintain her haematocrit <0.50 and aspirin

(c) Venesection to maintain her haematocrit <0.45 and aspirin

(d) No treatment until she develops an initial thrombosis/thrombotic event

(e) Aspirin alone until she develops an initial thrombosis/thrombotic event

POLYCYTHAEMIA VERA MASKED BY IRON DEFICIENCY ANAEMIA

E Booth, Z Rudzki, J Ewing

3. Which of the following is not a cause of apparent erythrocytosis?

(a) Obesity

(b) Excess

(c) Smoking

(d) Hypertension

(e) Renal artery stenosis

4) Which of the following is not a complication of PV?

(a) Myelofibrosis

(b) Thrombosis

(c) Cardiovascular related death/disease

(d) Acute lymphoblastic leukaemia

(e) Haemorrhage

5) Which of the following is not one of the diagnostic criteria for PV?

(a) Hb>165 or haematocrit>0.49 in men, Hb>160 or haematocrit>0.48 in women or red cell mass> 25% above normal predicted value

(b) Bone marrow biopsy showing trilineage hypercellularity for age and pleomorphic megakaryocytes

(c) Presence of JAK2V617F or JAK2 exon 12 mutation

(d) The presence of hyperviscosity symptoms

(e) Serum erythropoietin level below the reference range for normal

Answers

Q1. (d)

This gentleman has acquired secondary erythrocytosis as a result of his sleep apnoea. Although obesity could cause apparent erythrocytosis, calculating a red cell mass would enable us to differentiate between an apparent and true erythrocytosis. His red cell mass is indicative of a true erthyrocytosis.

Erythrocytosis can be divided into apparent and true primary or secondary causes. Apparent causes are due to a reduction in plasma volume. Secondary acquired erythrocytosis is due to the stimulation of excess blood cell production through either appropriate EPO secretion eg in response to hypoxia or to excess inappropriate production for example by a tumour.

Q2. (c)

Patients with polycythaemia vera are at an increased risk of thrombotic events and all require treatment and specialist follow up. Patients with PV are stratified into 2 treatment groups (low, and high) with the British Haematology Society guidelines recommending specific treatments for those in the low and high risk groups.

For low risk individuals the recommendation is for long term aspirin and serial venesections to maintain haematocrit < 0.45. High risk individuals should be treated with cytoreductive agents, aspirin and venesection if needed in addition to maintain Hct <0.45.

Q3. (e)

Renal artery stenosis causes secondary erythrocytosis due to local (renal) hypoxia leading to an increase in red cell production.

Q4. (d)

Acute lymphoblastic leukaemia. The red cells are part of the myeloid lineage and so the complication is acute myeloid leukaemia rather than lymphoblastic.

Q5. (d)

The presence of hyperviscosity symptoms (although important for treatment stratification and meaning an urgent referral to haematology) is not one of the diagnostic criteria for PV. Symptoms caused by hyperviscosity include chest and abdominal pain, myalgia and weakness, fatigue and blurred vision (or symptoms of amaurosis fugax).

POLYCYTHAEMIA VERA MASKED BY IRON DEFICIENCY ANAEMIA

E Booth, Z Rudzki, J Ewing

Author

Dr Emily Booth
Core Medical Trainee
Birmingham Heartlands Hospital
Bordesley Green East
Birmingham
West Midlands
B9 5SS

Dr Zbigniew Rudzki
Consultant Histopathogist
Birmingham Heartlands Hospital
Bordesley Green East
Birmingham
West Midlands
B9 5SS
Zbigniew.Rudzki@heartofengland.nhs.uk

Dr Joanne Ewing
Consultant Haematologist
Birmingham Heartlands Hospital
Bordesley Green East
Birmingham
West Midlands
B9 5SS
Joanne.ewing@heartofengland.nhs.uk

Corresponding Author

Dr Emily Booth
emilyjane.booth@nhs.net

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SPLANCHNIC VEIN THROMBOSIS - NEW DIAGNOSIS OF MYELOPROLIFERATIVE NEOPLASM & HEPARIN INDUCED THROMBOCYTOPENIA WITH THROMBOSIS (HITT) SYNDROME

AG Bashford, T Everington

Abstract

We describe the case of a 70-year-old woman presenting with abdominal pain. Initial imaging showed an extensive thrombosis of the portal venous system that was treated with anticoagulation. A myeloproliferative neoplasm, confirmed by screening for the V617F JAK2 mutation was found to be the underlying cause of the venous clot.

The patient developed heparin induced thrombocytopenia with thrombosis (HITT) following sequential exposure to low molecular weight and unfractionated heparins.

The myeloproliferative neoplasm (MPN) was occult with a near normal blood count at the time of presentation and the diagnosis of HITT could have been missed as there were additional reasons for subsequent thrombocytopenia. Both conditions require a high index of clinical suspicion.

Case History

A 70-year old woman who was normally well, presented with acute on chronic abdominal pain. The patient described two weeks of vague abdominal pain which had become severe in the right upper quadrant in the 48 hours prior to admission. The pain radiated through to her back and was associated with malaise and vomiting.

She had no history of fevers or night sweats and reported no urinary or bowel symptoms. On examination she was apyrexic with normal vitals (HR 94, BP 130/90). She was obese (BMI 33), not jaundiced and had mild right upper quadrant tenderness without signs of peritonism.

The initial blood work showed a CRP of 214mg/L, Hb of 147g/L with a haematocrit of 0.44, platelets of $476x10^9$/L and WCC of $20.7x10^9$/L with a neutrophilia of $18.1x10^9$/L. Her liver function, amylase and renal function were within normal ranges. She was commenced on ceftriaxone and metronidazole for presumed intra-abdominal sepsis.

An urgent ultrasound scan of the abdomen showed free abdominal fluid and mild splenomegaly (14cm), but no biliary disease. A CT abdomen and pelvis showed an extensive thrombosis of the portal venous system including the entire main portal, splenic and superior mesenteric veins. The patient was started on treatment dose low molecular weight heparin (dalteparin).

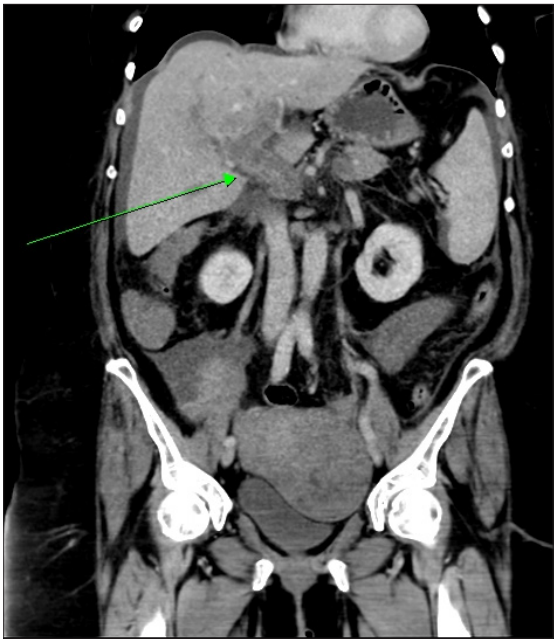

Figure 1: CT images – Thrombosis of main portal vein (White arrow) with coincidental benign uterine lesion.

On day 3 of her admission our patient became acutely unwell with hypotension (BP 80/60) and was desaturating despite high flow oxygen therapy. Her renal function had deteriorated (peak creatinine 380umol/l) and she was switched from dalteparin to an unfractionated heparin infusion and transferred to ITU for inotrope support and subsequent haemofiltration.

Repeat imaging was performed with a CT abdomen and pelvis showing no perforation or evidence of progression of thrombosis and a CTPA that showed small bi-basal effusions, but no pulmonary embolism. The deterioration was likely multifactorial from gastrointestinal ischaemia and sepsis. Over the following days our patient had episodes of small volume altered coffee-ground vomit and high output diarrhoea with altered blood, which was monitored with a faecal management system. She received total parenteral nutrition and continued with IV antibiotics.

After the first few days of her illness her full blood count changed dramatically with her haemoglobin (peak 180g/l, HCT 0.53) and platelet counts (peak 110^9 x 10^9/L) rising steeply from near normal. She was started on hydroxycarbamide empirically for a presumed diagnosis of a myeloproliferative neoplasm (MPN), which was confirmed by molecular screening for the JAK2 Val (6,17).

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The mutation. A full workup had been completed for precipitants of atypical thrombosis. She gave no clinical history of Behçets disease, there were no signs of chronic liver disease and her 24-hour urinary protein was 0.648g/24hours. Screens for antiphospholipid syndrome and paroxysmal nocturnal haemoglobinuria were negative. When she had stabilised, a bone marrow biopsy was performed which was consistent with a diagnosis of MPN, showing increased cellularity with plentiful pleomorphic megakaryocytes and increased granulopoiesis.

Local Causes:

- Cirrhosis* (also pro-thrombotic)
- Intra-abdominal infection
- Inflammation – pancreatitis
- Malignancy
- Trauma or surgery
- Retro-peritoneal fibrosis

Pro-thrombotic Disorders

- Myeloproliferative Neoplasms
- Paroxysmal nocturnal haemoglobinuria (PNH)
- Antiphospholipid syndrome
- Inherited Thrombophilias
- Behcets Disease
- Nephrotic syndrome

Box 1: Aetiology of intra-abdominal vein thrombosis.

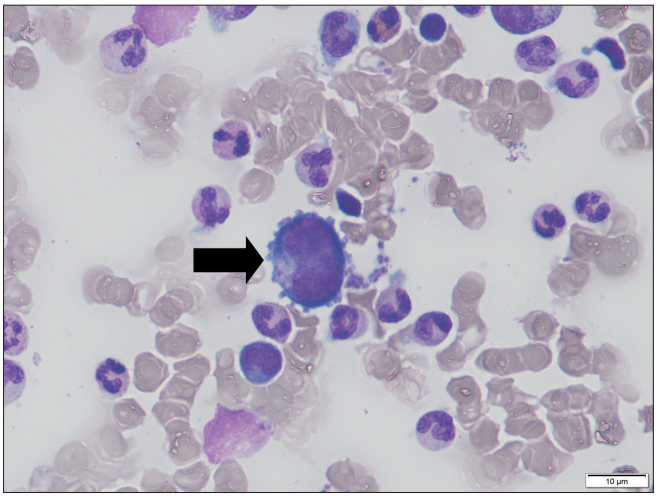

Figure 2: Bone Marrow Aspiration. Abnormal megakaryocyte (Black Arrow).

Our patient stabilised with conservative treatment and was transferred to the gastroenterology ward. Her platelet count had initially been controlled with a titrated dose of hydroxycarbamide, but two weeks after starting unfractionated heparin it dropped to a nadir of 43 x 10^9/l. A diagnosis of heparin induced thrombocytopenia with thrombosis (HITT) was considered and she had an intermediate risk (4 of 8) with the "4T's score"(1).

All heparin was stopped, she was switched to fondaparinux and hydroxycarbamide was withheld. A "HITT screen" (ELISA against anti-platelet factor 4 (PF4) antibodies) was sent and returned as positive with "optical density" of 0.78 units (positive cut off 0.50).

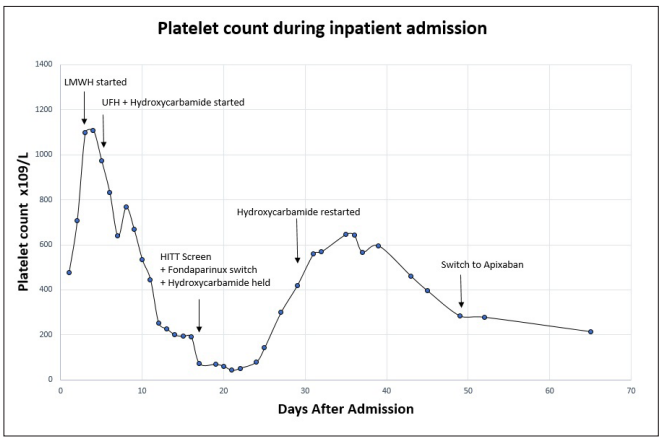

Figure 3: Platelet count and timing of medications during in-patient admission.

Our patient recovered remarkably well from her critical illness with normalization of renal function, but she was greatly debilitated and required a walking frame to mobilize. Aspirin was added to her treatment, but as she subsequently reported infrequent episodes of self-limiting epistaxis (related to an NG tube) and fresh PR blood on the toilet paper, it was discontinued. She was discharged on fondaparinux and returned to the outpatient department for review.

Within 4 weeks of discharge she had returned to normal daily activities using a walking stick for reassurance. She was switched to apixaban for long term anticoagulation and continues on hydroxycarbamide titrated to normalize the platelet count. During admission she lost considerable body weight. She has subsequently embarked on a healthy weight reduction programme.

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Discussion

Portal vein thrombosis (PVT) is a relatively uncommon site for venous thrombosis. The portal vein is formed from the superior mesenteric and splenic veins with the inferior mesenteric vein draining into the latter. Therefore the portal venous systemic drains the majority of the enteric system to the liver for first pass metabolism.

Acute thrombosis can be asymptomatic, but may present with sudden or subacute abdominal pain that may radiate to the back and mimic pancreatitis or biliary disease. GI bleeding may be a feature secondary to portal hypertension especially if there is existing liver disease with varices. If the mesenteric veins are involved, ascites and bowel ischaemia or infarction may result.

Investigations for an underlying cause of thrombosis should always be performed. In the case of decompensated cirrhosis further investigation for pro-thrombotic states may not be warranted, but in its absence those conditions listed in box 1 should be investigated.(2) Management is with early anticoagulation which, in up to a third of patients, allows recanalization of the portal vein.

In patients with splenic vein involvement and ascites more invasive therapy, such as instrumental thrombolysis, should be considered as recanalization rates are significantly lower.(3) Our patient has not had repeat imaging to assess this due to clinical improvement. Despite these severe complications mortality is low if treated before intestinal infarction, with a 1 year mortality of 2%.(4)

Myeloproliferative neoplasms are haematological disorders where cells of the myeloid lineage are produced in excess with terminal differentiation. They include, but are not limited to polycythaemia vera (PV), essential thrombocythaemia (ET), primary myelofibrosis (PMF) and chronic myeloid leukaemia (CML). Mutations of the tyrosine kinase Janus kinase 2 (JAK2) cause increased sensitivity of progenitor cells to growth factors and are associated with nearly all cases of PV, 50-60% cases of ET and PMF, but rarely occur in CML.

Our patient's presenting platelet count and haemoglobin were near normal. There were no historical counts available for comparison. The exaggerated rise in blood counts in response to critical illness was suggestive of an underlying myeloproliferative neoplasm although these features can be seen in normal individuals.

Myeloproliferative neoplasms should always be considered in cases of intra-abdominal vein thrombosis and there is a strong association with positivity for the V617F JAK2 mutation. This mutation has been found in between 35% - 59% of cases PVT without cirrhosis.

It is notable that the positive yield for mutational screening in those presenting with intra-abdominal vein thrombosis is significantly higher than it is for those presenting with VTE at other sites. (5) (6) (7)

Heparin induced thrombocytopenia with thrombosis (HITT) is a life-threatening complication of heparin exposure which can be seen in up to 5% of exposed patients. It is more common with UFH exposure but can also be seen with LMWH. It develops due to the formation of autoantibodies against platelet factor 4 that are complexed with heparin.

The complexes activate platelets causing both thrombocytopenia and paradoxical thrombosis. The platelet count typically drops by over 50% from baseline 5-10 days after exposure with a nadir rarely below 20x109/L. If there has been prior heparin exposure in the last 100 days the pre-formed antibodies can cause a precipitous drop within days of re-exposure.(8)

The 4T's screening tool is useful in aiding the diagnosis of HITT. It considers the degree and timing of thrombocytopenia, whether there is thrombosis and other causes for the thrombocytopenia. It has a high negative predictive value, thus a "low" pre-test probability can be used to rule out HITT.(1) A high index of clinical suspicion is important for a diagnosis of HITT as the absolute platelet count may not be subnormal but the risk of thrombotic complications remains.

This case especially highlights the importance of considering a diagnosis of HITT even when there may be other explanations for the fall in platelet count. In our patient the drop in platelet count could have been attributed to a combination of hydroxycarbamide and sepsis. Failure to recognize HITT may have resulted in further thrombosis and this may well have been catastrophic for our patient.

Multiple Choice Questions

(1) Where is the location of thrombosis in Budd Chiari syndrome?

a) Splenic vein

b) Hepatic vein

c) Inferior vena cava

d) Main portal vein

e) Hepatic artery

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(2) Which of the following is not an indication to start hydroxycarbamide therapy in essential thrombocythaemia?

a) A 68 year old woman with Plt > 600x10^9/L positive for the V617F JAK2 mutation

b) A 40 year old man with previous myocardial infarct and a platelet count of >700x109/L

c) A 60 year old woman who was diagnosed after a DVT but was negative for V617F JAK2

d) A 55 year old man with erythromelalgia (burning hands and feet)
e) A 50 year old man with previous pulmonary embolism

(3) Which of the following is a not an adverse effect of treatment with hydroxycarbamide?

a) Oral ulcers

b) Diarrhoea

c) Pancreatitis

d) Nail dystrophy

e) Hyperpigmentation

(4) Which of the following will not cause heparin induced thrombocytopenia with thrombosis (HITT)?

a) Unfractionated heparin

b) Enoxaparin

c) Dalteparin

d) Tinzaparin

e) Apixaban

(5) When should an increased platelet count raise suspicion of myeloproliferative neoplasm?

a) An 8 year old child with platelets >1000 x 10^9/L following tonsillitis

b) A 15 year old girl with iron deficiency anaemia due to heavy periods

c) A 75 year old woman with hypertension and a haematocrit = 0.47

d) A 50 year old woman with a urinary tract infection

e) A 28 year old man with a ruptured spleen requiring splenectomy after a bike accident

Answers

Question 1 - Answer: B

Budd Chiari syndrome is a thrombosis of the hepatic veins exiting the liver. It causes hepatic vascular congestion and may cause fulminant liver failure, portal hypertension and ascites. Portal vein thrombosis may co-exist. This patient did not have Budd-Chiari syndrome.

Question 2 - Answer: D

Management of essential thrombocythaemia involves risk stratification. Cytoreductive therapy with agents such as hydroxycarbamide is indicated in high risk patients. The high-risk criteria are: age >60 years old, previous thrombosis and a platelet count >1,500x10^9/L. Erythromelalgia and other vasomotor symptoms can be managed with aspirin and are not in themselves an indication for cytoreduction.

Question 3 - Answer: C

Hydroxycarbamide is a chemotherapy agent that inhibits ribonucleotide reductase causing impaired DNA synthesis and apoptosis in the S-phase of the cell cycle. It is well absorbed orally and excreted via the renal system. Its main side effect is dose related myelosuppression which is also its mechanism of action, but it also commonly causes muco-cutaneous side effects. There is no association with pancreatitis.

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Question 4 - Answer: E

Both UFH and LMWH activate antithrombin III to bind to the Factor Xa. UFH also inactivates thrombin due to longer saccharide chains and those over 18 units long can help stabilise a ternary complex. Platelets release platelet factor 4 from their granules which complex with heparin and antibodies are formed against this complex. The larger size of UFH causes greater interaction with PF4 and thus higher rates of HITT type II. The absolute risk of developing HITT is 2.6% with UFH compared to 0.2% with LMWH.. Apixaban is a direct oral anticoagulant (DOAC) active against factor Xa.

Question 5 - Answer: C

Thrombocytosis is a common sequelae of infection or surgery and can be particularly marked in young children. Around 40% women of child bearing potential are iron deficient with or without anaemia which is often associated with a mild thrombocytosis. A raised haematocrit may have a number of causes including dehydration and hypoxia, but the association with a raised platelet count in a patient with hypertension is suspicious for an MPN.

Author

Dr Alexander Guy Bashford
FY2 Haematology
Salisbury District Hospital
Salisbury
SP2 8BJ

Dr T Everington
Consultant Haematologist
Salisbury District Hospital
Salisbury
SP2 8BJ

Corresponding Author

Dr Alexander Guy Bashford
alex.bashford@gmail.com

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UPPER GASTROINTESTINAL BLEEDING IN OLDER PEOPLE

L Attwell, M Vassallo

Abstract

More than 1% of people aged 80 or over will be hospitalized each year due to gastrointestinal bleeding (1), with this number likely to continue to increase with the ageing population and increased use of non-steroidal anti-inflammatory drugs (NSAIDs), anti-platelets and anti-coagulants. Bleeding may be caused by a variety of lesions, similar to those affecting younger patients, including peptic ulcer disease, varices, oesophagitis or malignancy. Older people present with an upper GI bleed differently, and due to co-morbid conditions require prompt assessment and management for favourable outcomes. This article covers a typical case of upper GI bleeding in an older person.

Case history

An 83-year-old gentleman presents to the emergency department at 9pm having been found more confused at home by his carers, who visit twice a day. He reports no symptoms, but his carers have noticed that he has been passing loose, offensive tarry stool over the last couple of days.

He has a past medical history of mild dementia (MMSE 23/30) diagnosed last year, osteoarthritis, ischaemic heart disease and chronic kidney disease stage 3 (creatinine 160, estimated glomerular filtration rate 38). His regular medications include aspirin, donepezil and simvastatin.

On physical examination he is pale and dehydrated with a heart rate of 110 beats per minute and a blood pressure of 95/60mmHg. He is afebrile with oxygen saturations of 96% on room air and a respiratory rate of 18 breaths per minutes. Abdominal examination reveals mild epigastric tenderness but no signs of peritonism. Rectal examination reveals melaena on the glove.

Blood tests show that he is anaemic (Hb 9.2g/dL). He has an acute kidney injury with a urea of 27.3 and a creatinine of 202. Electrolytes are normal, as are his liver function tests and C-reactive protein.

The patient is resuscitated with two litres of intravenous fluid, with improvements in both BP (105/90) and HR (90bpm). He has no witnessed episodes of melaena in the department. He is referred to the medical team as a patient with a probable upper GI bleed.

The medical team discusses the case with the on-call endoscopist who decides, given the improvements in observations and clinical condition, oesophagogastroduodenoscopy (OGD) does not need to be performed overnight. He remains stable. Endoscopy is performed the next morning, which shows a large duodenal ulcer, with signs of recent bleeding. The ulcer is heater probed, injected with adrenaline and clipped, with good result. The patient is transferred to the upper GI bleeder bay on a gastroenterology ward and makes a good recovery. He is discharged 5 days later.

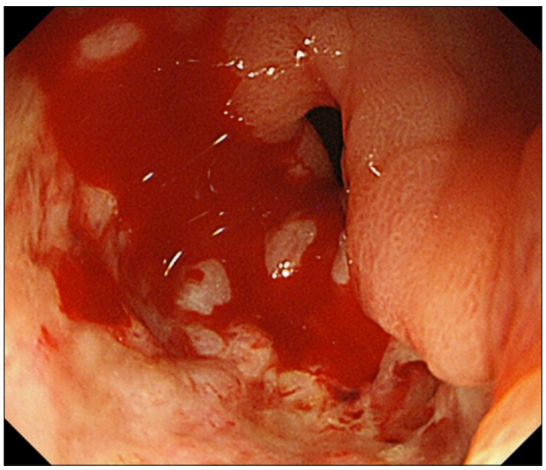

Image 1: Duodenal ulcer with active bleeding on endoscopy.

Discussion

This case describes a presentation of an unwell older person with an acute upper GI bleed.

Upper gastrointestinal bleeding (UGIB) is defined as bleeding originating proximal to the ligament of Treitz. The overall incidence of non-variceal upper GI bleeding has declined over the last 20 years, however there has been a substantial increase in the proportion of older people presenting with a UGIB. Studies have shown that up 65% of patients presenting with an UGIB are over 65 years of age (2, 3), with more than quarter over 80 years of age.

The increase in elderly people presenting with an UGI bleed is thought to be multi-factorial – both due to the ageing population and due to changes in the epidemiology of peptic ulcer disease (the most likely cause of upper-GI bleeding in older people). NSAIDS are known to be an important cause of peptic ulcer formation and bleeding, and increased use of these drugs and anti-platelets puts the elderly at higher risk. The risk of serious side effects from NSAID use is 5.5 times that of controls in older people, whereas in younger patients it is only 1.5 times (4).

Aetiology	Article		
	Segal and Cello [6] (% of patients)	Kaplan *et al.* [7] (% of patients)	Cooper *et al.* [8] (% of patients)
Common			
Peptic ulcer	73	44	42
Oesophagitis or esophageal ulcer	11	7	18
Gastropathy	7	28	13
Oesophageal or gastric varices	11	ND	2
Mallory–Weiss tear	3	4	2
Upper gastrointestinal malignancy	1	4	4
Less common			
Portal hypertensive gastropathy, dieulafoy lesion, Gastric antral vascular ectasia, Haemobilia, *Haemosuccus pancreaticus,* Aortoenteric fistula.			

Table 1: Causes of upper GI bleeding in the elderly (5).

ND = not determined

UPPER GASTROINTESTINAL BLEEDING IN OLDER PEOPLE

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Advanced age has consistently been identified as a risk factor for mortality in patients presenting with UGIB, due to co-morbidity and polypharmacy, with mortality rates between 12 and 35% for people aged 60 or over, and less than 10% for those aged less than 60 9, 10.

Clinical features in older people

There are similarities in the presentation of UGIB in older and younger people including symptoms such as haematemesis (50%), melaena (30%) or both (20%), peptic ulcer disease being the most common aetiology in both patient groups & the safety and efficacy of endoscopic therapy.

Older people can present with upper gastrointestinal bleeding differently to younger patients. They tend to have fewer preceding symptoms such as abdominal pain or dyspepsia. NSAIDs, aspirin and anti-coagulant use is more common as is significant co-morbidity. They have higher rates of hospitalization, re-bleeding and mortality (11). Patients over 80 have up to double the risk of re-bleeding than those less than 60 (5).

Management of upper GI bleeding requires succinct history taking and examination (using an ABC approach) and prompt resuscitation +/- endoscopy.

Important points from the history include:

- *Onset of melaena*
- *Haematemesis*
- *Abdominal pain*
- *Recent significant vomiting (raising possibility of Mallory-Weiss tear)*
- *Dyspepsia*
- *Dysphagia*
- *Change in bowel habit*
- *Weight loss*
- *Previous GI bleeding*
- *Underlying liver disease*
- *Alcohol use*
- *Medications (anti-coagulants, anti-platelets, NSAIDs, steroids, SSRIs)*

Initial investigations include FBC, U&E, LFT, INR/Clotting, Group and Save (including crossmatch if actively bleeding) and blood gases.

What will my registrar want to know?

Haemoglobin
Urea
Haemodynamic status (BP/Pulse)
Has this happened before?
Alcohol (Is this a variceal bleed?)
Co-morbidity
Medication (anti-platelets, anti-coagulants)
Treatment instigated so far

The use of the Blatchford and Rockall scoring systems identify those patients likely to require intervention and at high risk of mortality respectively.

Blatchford Score	
Marker on Admission	**Score**
Urea (mg/dL)	
6.5 to 7.9	2
8.0 to 9.9	3
10.0 to 24.9	4
≥25.0	5
Haemoglobin (g/dL)	
12.0 to 12.9	1
10.0 to 11.9	3
<10.0	6
Systolic BP (mmHg)	
100-109	1
90-99	2
<90	3
Other Parameters	
Pulse >100bpm	1
Melaena	1
Syncope	2
Hepatic disease	2
Cardiac failure	2

Table 2: Blatchford Score. A score of 6 or more equates to a 50% chance of needing an intervention (blood products or endoscopy) (12).

Variable	Score 0	Score 1	Score 2	Score 3
Age	<60	60- 79	>80	
Shock	No shock	Pulse >100, SBP >100	SBP <100	
Co-morbidity	Nil major		CHF, IHD, major co-morbidity	Renal failure, liver failure, metastatic cancer
Diagnosis	Mallory-Weiss	All other diagnoses	GI malignancy	
Evidence of bleeding	None		Blood, adherent clot, visible vessel	

Table 3: Rockall Score. A score of less than 3 carries a good prognosis, more than 8 is associated with a high risk of mortality (13).

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Management

Early management should include fluid resuscitation to keep the patients blood pressure in low-normal range (higher blood pressure can cause increased flow of bleeding in variceal bleeds). Urinary catheter insertion can allow accurate measurement of urine output and hence tissue perfusion. Blood transfusion is required if haemoglobin drops to below 8.0g/dL. Platelets should only be used if the platelet count is below $50x10^9/L$ with active bleeding.

Vitamin K should be given if no active bleeding, whereas fresh frozen plasma (FFP) is used if actively bleeding. If the patient is on warfarin, then prothrombin complex can be used for reversal. Terlipressin should be used for suspected variceal bleeding 14. Proton pump inhibitors should be used for non-variceal upper gastrointestinal bleeding and stigmata of recent haemorrhage shown at endoscopy. No evidence supports their use pre-endoscopy.

Definitive intervention with endoscopy should be arranged once the patient has been stabilized. During endoscopy, testing for Helicobacter Pylori should be undertaken if evidence of inflammation or ulceration (and eradication with triple therapy – two antibiotics and high dose PPI if identified).

If a bleeding lesion is identified, treatment is often a combination of adrenaline injection, heater probe therapy and mechanical methods such as clipping or banding (if variceal in nature). Combination therapy using two of the above methods has been shown to have better outcomes 15. Blood loss and emergency surgery are not well tolerated by older people, therefore successful endoscopic therapy can reduce the need for surgical intervention. Age should not preclude patients from endoscopic intervention.

Best Of Five Questions

1. Which of the following is the most common aetiology of upper gastrointestinal bleeding?

a. Varices

b. Peptic ulcer disease

c. Mallory-Weiss tear

d. Malignancy

e. Gastropathy

2. At what level should platelet transfusion be considered in ongoing upper gastrointestinal bleeding?

a. 25 x $10^9/L$

b. 50 x $10^9/L$

c. 75 x $10^9/L$

d. 100 x $10^9/L$

e. 150 x $10^9/L$

3. Which of the following carries the highest risk of mortality according to the Rockall score?

a. Heart rate of 90 beats per minute

b. Ischaemic heart disease

c. Congestive cardiac failure

d. Renal failure

e. GI malignancy

Answers

1. b

Peptic ulcer disease is the most common aetiology of upper GI bleeding in all age groups

2. b

Patients with platelet counts of less than 50 x $10^9/L$ should have a platelet transfusion

3. d

Renal failure gives 3 points in the Rockall scoring system

UPPER GASTROINTESTINAL BLEEDING IN OLDER PEOPLE

L Attwell, M Vassallo

Author

Luke Attwell
Core Medical Trainee
Royal Bournemouth & Christchurch
Hospitals NHS Foundation Trust Castle Lane East
Bournemouth
BH7 7DW

Michael Vassallo
Consultant Geriatrician
Royal Bournemouth & Christchurch
Hospitals NHS Foundation Trust Castle Lane East
Bournemouth
BH7 7DW
michael.vassallo@rbch.nhs.uk

Corresponding Author

Luke Attwell
attwell.luke@gmail.com

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PATIENTS WHO FALL

L Cook

Abstract

This case based discussion focuses on an independent elderly gentleman presenting acutely to hospital with a fall. The assessment, investigations and initial management are discussed.

Case History

An 85 year old man has been admitted to the medical assessment unit after falling at home. This is the second fall in 3 months. He was unable to get up, and was discovered by his daughter after 2 hours. She has accompanied him to hospital, where he is awaiting medical clerking.

How would you start to assess him?

An ABCDE approach should be used to ensure there is no acute medical illness that requires immediate attention. This can present with instability in those with frailty or who are prone to fall. Assuming the patient is stable, a more comprehensive assessment should be taken.

Top priorities for a foundation doctor:

- *ABCDE / NEWS score – ensure the patient is stable*
- *Quality history (including witness) and examination including injuries*
- *Focused investigations*
- *Treat acute illnesses (especially delirium)*
- *Compile a problem list of conditions contributing to falls and formulate a management plan to address these*
- *Communication – ensure other staff aware of falls risk via bedside alert system/handover sheet/online alert*

Participate in Comprehensive Geriatric Assessment process with other care professionals to address falls risk

Environment – visual/hearing/walking aids to hand?
Call bell?
Directions to toilet?
Appropriate footwear?

History - A Detailed History From The Patient And Daughter Is Needed (1)

What are the circumstances of the falls?

- *How many falls have occurred in the last 12 months?*
- *Where are they occurring?*
- *Are there any pro-dromal symptoms such as palpitations, shortness of breath, chest pain? If there is dizziness is it vertigo or light-headedness?*
- *Has there been any loss of consciousness? If so, how long has it lasted? Has the person recovered quickly? Is there a witness account available?*
- *Have any injuries been sustained?*
- *Were they using a mobility aid at the time?*
- *Is there a fear of falling?*

Past Medical History

- *Are there chronic conditions leading to difficult mobility? E.g. arthritis, parkinsonism, stroke disease.*
- *Cardiac disease, especially arrhythmias*
- *Diabetes mellitus - does the patient have hypoglycaemia awareness?*
- *Visual problems and whether visual aids are worn. Is the prescription correct?*
- *Urinary incontinence*
- *Is there cognitive impairment?*
- *Conditions that increase the risk of sustaining a fracture. E.g. Hyperthyroidism, hypogonadism, early untreated menopause*

Medication history

- *Antihypertensive and heart rate limiting drugs*
- *Antidepressants*
- *Antipsychotic medication*
- *Medication for Parkinson's Disease*
- *Sedating medication, including opiate patches*
- *Steroids*
- *Antihistamines*
- *Don't forget over the counter medication and eye drops which may contain a beta blocker*

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Family and social history

- *Is there a history of parental hip fracture?*
- *Smoking and alcohol history*
- *What is their home environment like?*
- *Do they have any mobility aids or a stair-lift? Do they use them?*
- *How is their life affected? Is there a loss of confidence*

or fear of falling; are they at risk of becoming socially isolated?

The patient says he was watching television but got up quickly to answer the telephone. He was a bit light-headed but had no palpitations or other symptoms. He walks unaided in the house but has a stick for outdoors. He thinks he may have tripped over the corner of a rug or his slipper. He did not lose consciousness but 'felt like I was about to'.

As he fell he hit his right side on the edge of a dresser and could not stand due to pain in his leg. His other fall was at night, after getting up to go to the toilet. He can't remember much about it but did not lose consciousness and was able to get up, so did not seek medical attention. He admits that there have been other occasions where he feels his balance has gone, but has not fallen.

He has a past medical history of ischaemic heart disease, osteoarthritis and gout. He is taking aspirin, a beta-blocker, angiotensin converting enzyme (ACE) inhibitor, thiazide diuretic, simvastatin, paracetamol and amitryptiline at night 'to help me sleep'. He does not smoke or drink alcohol and is relatively independent.

What features are immediately striking from the history?

The description of light-headedness associated with the feeling that he is about to black out suggests pre-syncope rather than vestibular disease. Ischaemic heart disease puts him at increased risk of arrhythmias, and his medication may be causing bradycardia or hypotension. He has osteoarthritis which may mean joint pain and deformity are affecting his mobility and balance.

What should you do next?

A thorough, focused examination is required (1)

General points

- Height and weight
- Volaemic state; oedema and dehydration may contribute to a fall, or the patient may be dehydrated from a long lie
- Examination of hands and feet – evidence of arthritis, bunions, calluses or deformities

Cardiovascular examination

- Heart rate and rhythm
- Blood pressure; including postural readings and if a drop is symptomatic (a significant drop being ≥20 mmHg in systolic pressure or ≥10 mmHg in diastolic pressure or a systolic drop to less than 90 mmHg)
- Heart sounds and presence of murmurs

Full neurological examination, paying particular attention to:

Visual acuity
Visual fields
Presence of nystagmus and cerebellar signs
Romberg test
Parkinsonism
Muscle wasting
Proprioception in feet
Assessment of gait
Cognition via Abbreviated Mental Test Score (AMTS) or Mini Mental State Examination (MMSE); assessment of delirium.
Examination of the vestibular system if indicated by history.

Consequences of fall:

Painful joints or bony injury
Signs of head injury
Pressure areas
Cuts and bruises

On examination the patient has dry mucous membranes and is mildly dehydrated. His BMI is 24. He has chronic swelling of both knees consistent with osteoarthritis, but no acute inflammation. His pulse is regular at a of rate 66 beats per minute. Lying blood pressure is 104/78 mmHg and standing is 82/60 mmHg, and the patient is symptomatic.

Cardio-respiratory examination was normal. Visual acuity is corrected with glasses. There is generalised reduced muscle bulk but neurological examination is unremarkable. He has some bruising on his right forearm and thigh, but no evidence of bony injury. He has an antalgic gait but can weight bear. His MMSE is 28/30.

What are your thoughts now?

This gentleman has documented postural hypotension and is taking several antihypertensives. His osteoarthritis and reduced muscle bulk are indicators that core strength and balance may be a problem.

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What initial investigations would you do?

- Full blood count (FBC) – to check for anaemia, evidence of infection
- Urea and electrolytes (U&Es) – is there dehydration? Acute or chronic renal impairment? Electrolyte dysfunction?
- Liver function tests (LFTs)
- Thyroid function tests (TFTs)
- Calcium
- Vitamin D
- Serum glucose
- Electrocardiogram (ECG)

You may consider the following tests:

Creatinine kinase (CK) – *if history or examination suggestive of prolonged immobility or tissue damage*

Plain film X ray – *usually of hip and pelvis to exclude fracture, or chest if concern of infection*

Our patient has a normal FBC, U&Es, LFTs, TFTs CK and random glucose. Calcium is a little low at 2.15 mmol/L. Plain film X-rays performed in Accident and Emergency of the right hip and pelvis showed degenerative change but no fracture.

What should the next step be?

One of the most important tasks is to review the medication. Are the drugs that contribute to postural hypotension necessary, or can they be reduced or stopped? The harms and benefits of each medication should be explained to the patient so they can make an informed decision.

This patient has no sign of oedema and his blood pressure remains low, so a first step could be to stop the thiazide diuretic. Amitryptiline is sedating and causes hypotension; it would be a good idea to wean this off with advice. As the pulse rate is normal and the patient has ischaemic heart disease the beta-blocker can be continued. Medications can be reduced in a step-wise fashion, especially antidepressants and anxiolytics, and the effect on blood pressure and symptoms observed.

3 days later the patient is no longer symptomatic and the postural hypotension has resolved. He was happy to stop amitryptiline.

Discussion

Falls are an important cause of morbidity and mortality in the elderly, with up to 3.4 million people over 65 having a fall each year. Up to 1 million of these are thought to be preventable. (2)

Fear of falling can have a devastating effect on patients' confidence and their physical and psychological functioning. (2,3) It is important to explain the preventable nature of many falls. Details on ways to prevent falls should be offered along with information about how to cope with a fall, and where they can seek further advice and assistance. (3)

Multidisciplinary assessment to complete a Comprehensive Geriatric Assessment (CGA) is required to identify future risk and to plan individual intervention to promote independence and prevent injury. Key areas are: medication review, strength and balance training; home hazard assessment and intervention; and visual assessment and referral. (3)

In our patient's case he has had a thorough medication review by the admitting team. He should also be assessed by the multidisciplinary team on the ward to reduce the risk of him falling in hospital, and upon returning home. Many different methods are employed by hospital trusts to help identify and communicate patients at high risk of falls (bedhead alerts, e.g. falling stars; safety briefings etc) and help mitigate that risk: for example with bed or chair alarms, extra 'special' nursing staff or high-risk bays.

It is important to familiarise yourself with local policy and communicate to ward staff to reduce the risk of a fall in hospital. Following discharge a formal programme of individualised, supervised strength and balance training may be offered. In conjunction a referral to a community occupational therapist may be helpful to ensure environmental hazards are minimised at home. (3)

Adults who have a history of falls should have an assessment of their fracture risk. (4) National Institute for Health and Care Excellence (NICE) guidance now recommends using a calculation tool such as FRAX (5) or QFracture (6) to estimate the 10-year predicted absolute fracture risk for most patients. The FRAX tool also contains a link to The National Osteoporosis Guideline Group (NOGG) (7) guidance which displays the result as high, intermediate or low risk. Such tools are easy to use and would be an excellent 'next step' in the clerking of our patient. It is worth noting that the risk can be underestimated in those who are over 80 or who have certain clinical conditions. (3)

Older patients identified as being at high risk can be offered treatment to prevent fragility fractures 6or proceed to DXA for confirmation of osteoporosis. (3) Those at intermediate risk should be offered DXA scanning. (7) For most patients first line treatments will be generic alendronate or risedronate, but if these are not tolerated or there are contraindications, IV bisphosphonates or denosumab are the most appropriate alternatives.

The use of teriparetide is generally restricted to specialist clinics. Adequate calcium intake and vitamin D levels must be ensured and supplements prescribed if necessary. (7,8) For our patient, using FRAX/NOGG shows he is at low risk and as such should be given lifestyle advice including increasing his calcium intake and sunlight exposure, before repeating the relevant blood tests in the community.

PATIENTS WHO FALL

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Self test questions

1) An 82 year old man had a long standing history of poor mobility. Over the past 12 months he has felt his walking slowing down with worsening balance. Turning is particularly difficult, and he now furniture walks. His falls have all occurred whilst working in the garden, or after climbing stairs. His wife has noticed he is breathless and complains of dizziness, before losing consciousness for up to a minute.

It can take up to 20 minutes before he feels completely back to normal. He has a history of severe aortic stenosis, asthma and has had a prostatectomy for malignancy. On examination he has mild signs of Parkinsonism, and a loud ejection systolic murmur. What is the most likely contributor to his falls?

A. Drug induced hypotension
B. Arrhythmia
C. Parkinson's disease
D. Benign Paroxysmal Vertigo
E. Epilepsy

2) A 75 year attends the falls clinic with recurrent falls. All the modifiable risk factors have been attended to. She has a past medical history of stroke, diabetes, hypothyroidism, GORD and gout. She has never suffered a fracture, although her father fractured his hip aged 85. Her BMI is 21. Her electrolytes are normal. A DXA scan revealed bone density at the femoral head to be T score -2.8. Use FRAX to calculate her 10 year probability of hip fracture. What bone protection would you recommend?

A. Nil
B. Calcium and Vitamin D
C. Alfacalcidol
D. Calcium, vitamin D and alendronate
E. Calcium, vitamin D and zolendronic acid

Answers

1) B

This is clearly a case of syncope. Elderly people may have quite a prolonged recovery from syncope but there is nothing here to suggest a seizure, making epilepsy very unlikely. Although the patient may well have Parkinson's disease causing poor mobility, it would not cause exertional syncope.

Given the history of severe aortic stenosis and symptoms of exertional syncope and breathlessness, a ventricular arrhythmia is the most likely explanation. Another explanation could be recurrent pulmonary emboli, but this is far less likely in the context of the known valvular heart disease.

2) E

This lady has osteoporosis as demonstrated by her T score of <2.5 at the femoral head. Combined with her multiple risk factors, when entered into the FRAX tool she has a very high risk of fracture (23% hip and 31% major osteoporotic) over the next ten years.

She would benefit from antiresorptive treatment with a bisphosphonate, but the history of GORD means an intravenous preparation is likely more appropriate. Alfacalcidol would only be indicated in a patient with vitamin D deficiency and significant renal disease.

Author

Laura Cook
ST6 geriatric medicine
St James University Hospital, Leeds
laura.cook25@nhs.net

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ABC OF PALLIATIVE CARE PRINCIPLES; A JUNIOR DOCTOR'S PERSPECTIVE

R Carrigan, C Daniels

Abstract

During my junior training in acute medicine and intensive care, I relied upon the ABC approach to the acutely unwell patient; airway, breathing, circulation – three simple words but arguably the most useful three words for any healthcare professional. Despite this mantra, when faced with the acutely dying patient, I often felt that these words were suddenly useless; acutely dying patients or patients in their last year of life and securely under the 'Palliative Medicine' umbrella were a mystery to me.

Through gaining more experience looking after this vulnerable and important group of patients I developed my own ABC rules, by no means an exhaustive list but a good starting point to unravel the mystery of how to care for palliative patients (Figure 1).

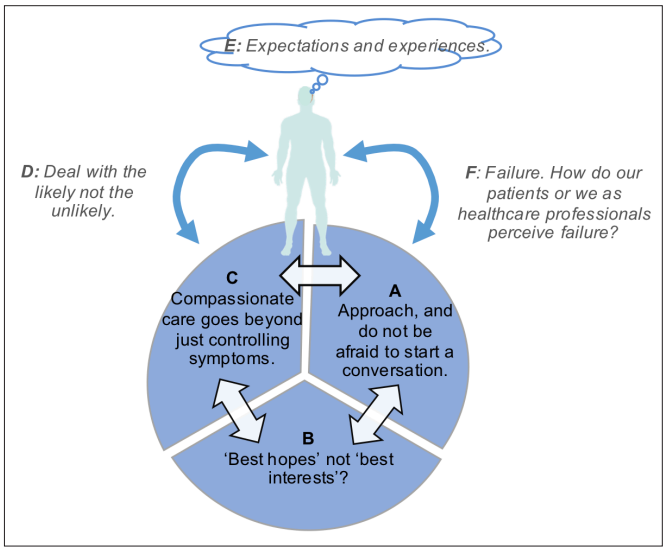

Figure 1: An 'ABC Approach' to the palliative patient.

A - Approach

And do not be afraid to start a conversation. Some of the most rewarding experiences of palliative medicine involve a simple conversation; sharing stories, views and wishes. Not being afraid to ask a patient to help you identify 'what is important to them?'. These conversations may be clinical or more holistic. Where they want to be cared for, preferred place of death and so much more. Do they have any questions? There is always time to do this, a bit of extra time is rewarding to both parties. A patient will always remember a compassionate doctor, even if they deliver bad news (Figure 2).

Understanding	What is your understanding now of where you are with your illness?
Information preferences	How much information about what is likely to be ahead with your illness would you like from me? Time? Symptoms?
Prognosis	Share prognosis as a range, tailored to information preferences.
Goals	If your health situation worsens, what are your most important goals?
Fears / worries	What are your biggest fears and worries about the future with your health?
Function	What abilities are so critical to your life that you can't imagine living without them?
Trade-offs	If you become sicker, how much are you willing to go through for the possibility of gaining more time?
Family	How much does your family know about your priorities and wishes?

Figure 2: Serious Illness Conversation Guide (1)

B – 'Best hopes' not 'best interests'?

Wherever possible start conversations earlier so we can more often make decisions based on 'best hopes' of a patient, this reduces the frequency of having to make a 'best interest' decision. Helps a patient, their family and you! In medicine we talk a lot about best interests. We may sometimes be forced to make best interest decisions. The first step to achieve this is by setting patient goals which can be hugely rewarding.

Whether it be for symptomatic control, avoidance of inappropriate treatments, managing crises better or bringing a significant life event forward so the patient can be part of it. It is surprising about how much can be achieved in a short or long time when there is so much prognostic uncertainty. However big or small the event, there is always a way of achieving realistic goals with the appropriate support and care.

C – Compassionate care goes beyond just controlling symptoms.

Key to most patient care is not 'which drug will fix which problem'. Ultimately a clear history and listening to the patient often provides the answer to their concerns. Pain as one common symptom is often wrapped up and presented as part of a complex, multi-focus pain syndrome.

How much of this pain is anxiety and how much does the pain cause anxiety? Which drug should be chosen, an opioid for pain relief or a benzodiazepine for anxiety? Would a referral to a palliative care team be indicated? Do you know your local guidelines and practices? Providing good compassionate care is an essential part of most symptom management plans. Often it is the act of listening rather than prescribing which has the more important outcome; a feeling of 'being heard' as opposed to 'being treated'.

ABC OF PALLIATIVE CARE PRINCIPLES; A JUNIOR DOCTOR'S PERSPECTIVE

R Carrigan, C Daniels

D – Deal with the likely not the unlikely.

Advance care plans are not about what cannot be done. Ask the patient what they think is important, offer the options that are available to them. Patients may be more concerned about whether and how they can be managed at home, what symptoms they might experience and what options are available to them. Learn the likely scenarios and learn how these can best be managed in a way and place of a patient's choosing. Dealing with the likely options can freely allow a conversation into what might not be possible.

Resuscitation remains a topical issue in medicine. A question that perhaps is easier to ask than a patient's preferred place of death? Without asking the question, how can you find out your patient's best wishes? It is clear that some patients value the conversation around resuscitation with a clear explanation of what this includes. Many have an intention not to be resuscitated, but this might not be documented. Sometimes the terms become interwoven, 'no doctor I haven't discussed resuscitation, but I don't want CPR, I have a form'.

E - Expectations and experiences.

We often forget when treating a patient that they come with their own expectations and experiences. Did they witness a loved one die and was it a good experience? Last night's episode of 'Casualty' proved that resuscitation is successful when 'those paddles' are used and so on. Again, the emphasis here is to explore the patient's concerns. Towards the end of life, expectations change. Our choices and what is important to us changes but our life experiences continue to guide our expectations.

F – Failure. How do our patients or we as healthcare professionals perceive failure?

If a treatment does not work, does this mean 'I have failed?'. Ultimately treatments will fail, but will only be perceived as a failure if this is used as the sole marker of outcome. Supporting our patients and ourselves to set realistic expectations and achieving these can still feel like a success. Patients can outlive their prognoses and success can be achieved through good symptomatic control and enhancing quality of life; supported by family and professionals whilst having their needs and goals addressed. Planning for this is the tough part. Whilst it might not seem possible, it can be achieved.

Palliative Medicine is a rewarding specialty. Whilst I have not touched on the details of symptomatic control, much can be learnt from a patient and their families. Discussing and achieving goals can often be as 'powerful' as treating pain with 'opioids'.

With a growing elderly population, frailty is undoubtedly going to become a larger burden on our services, not to mention the impact of dementia and other non-cancer life-limiting diagnoses. By taking a bit more time to explore patient's wishes, more can be done to treat this burden of disease. I hope this 'ABC approach' is thought provoking, but like most medical specialties, a one-step approach is never really the answer, shadowing and getting involved with the specialty is key to any future success.

Author

Dr R Carrigan
Clinical Fellow in Palliative Medicine
St Luke's Hospice(Harrow & Brent)
Kenton Grange, Kenton Road
Harrow, Middlesex, HA3 0YG

Dr C Daniels
Consultant in Palliative Medicine
St Luke's Hospice(Harrow & Brent)
Kenton Grange, Kenton Road
Harrow, Middlesex HA3 0YG
CDaniels@stlukes-hospice.org

Corresponding Author

Dr R Carrigan
RCarrigan@stlukes-hospice.org

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1) Adapted from Serious Illness Care, Adriane Labs: https://www.ariadnelabs.org/areas-of-work/serious-illness-care/

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MANAGEMENT OF NAUSEA & VOMITING IN PALLIATIVE CARE

K MacDaid, A Wijeratne

Abstract

Nausea and vomiting are some of the most common symptoms seen in many areas of medicine, but significantly so in palliative care. A thorough history of symptoms, physical assessment and a robust understanding of the mechanisms of action of antiemetic medications are essential for effective control of these troubling and distressing symptoms. This case study focuses on a gentleman with recently diagnosed oesophageal cancer and difficult to manage nausea and vomiting.

It covers the main neural pathways involved in nausea and vomiting symptoms, the principal receptors targeted by commonly used antiemetics, common side effects for the differing classes of antiemetic medication and offers some thoughts upon the concept of 'total nausea' in end of life care (EOLC).

General consensus of the treatment of nausea and vomiting focusses on a mechanism based approach, utilising the targeted efficacy of each antiemetic. Large scale randomised controlled trials looking at the effects of each antiemetic are scarce and more research is needed to provide robust evidence regarding comparisons between the varying drugs.

Confidentiality

Unfortunately the patient described in this article subsequently died and we have been unable to gain consent from his next of kin regarding the use of images and details. Therefore some of the demographic details have been amended to ensure confidentiality and for the purpose of this article the patient will be known as Edward.

Case Report

Edward, a 79 year old man was admitted to the A&E department of a district general hospital with abdominal pain, nausea and vomiting. He described two stone unintentional weight loss in the preceding three months. His past medical history included a non-leaking 6.2cm diameter abdominal aortic aneurism, ischaemic heart disease, a previous coronary artery bypass graft and femoral popliteal bypass, gastritis, diabetes (type 2) and chronic kidney disease.

He was referred, investigated and managed by the Gastroenterology team. Endoscopy revealed an inflamed lower oesophagus with deep ulcerations distally. A 6cm malignant looking ulcer was noted and biopsies were taken. MDT assessment and histology confirmed a diagnosis of poorly differentiated Adenocarcinoma of the gastro-oesophageal junction (GOJ).

CT scan was arranged and revealed circumferential thickening of the distal oesophagus, which extended 5cm to the GOJ. Staging was confirmed as T3, N1, M0, and stent insertion was recommended for a significant stricture of his oesophagus. A 12.3mm x 23mm partially covered metal stent was inserted into the cardio-oesophageal junction. No complications were noted during or immediately after the procedure. Due to his frailty and poor performance status, no curative treatment options for his cancer were recommended.

Edward was re-admitted to the acute medical ward via A&E one week later with worsening colicky abdominal pain, difficulty swallowing, vomiting and dehydration. He had been unable to tolerate solid food since the stent insertion and would vomit it straight back up. He denied any haematemesis, odynophagia or chest pain.

He was able to tolerate fluids and tablets and was commenced on hyoscine butylbromide and morphine sulphate immediate release liquid for his abdominal pain. Blood tests were unremarkable and in particular his calcium levels were normal which was important to note as a cause of nausea and vomiting in a patient with a malignancy. Radiological investigations revealed his stent had migrated significantly into his stomach. This was initially thought to be the cause of his abdominal pain, nausea and vomiting.

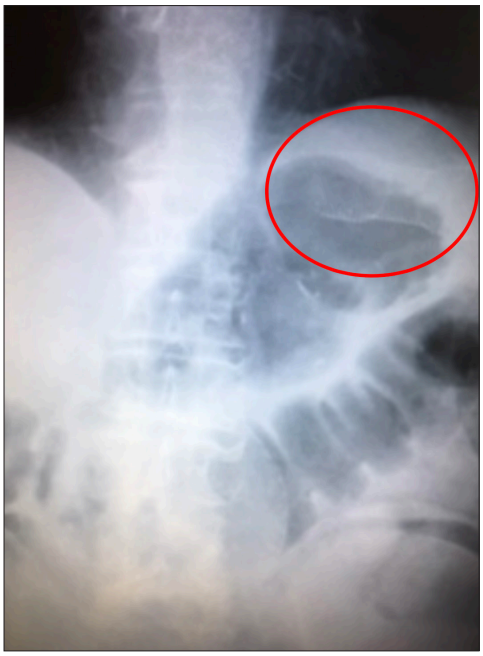

Image I: Plain abdominal film showing migrated stent in the fundus of stomach.

He was re-stented 5 days later. Follow up imaging confirmed the stent remained in the correct position. At this point, Edward's abdominal pain had improved but his nausea and vomiting continued. He was initially commenced on ondansetron 4mg but struggled with constipation, so this was stopped. Due to continued vomiting he was commenced on a continuous subcutaneous infusion via a syringe pump 24 hours later with cyclizine 150mg and morphine sulphate 20mg over 24 hours plus levomepromazine 6.25mg subcutaneously PRN.

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His symptoms continued unabated over the next 48 hours. His antiemetics were switched to metoclopramide 30mg over 24 hours as a prokinetic to try and address his nausea and his constipation. A low dose of dexamethasone was added 4mg daily as an adjunct and a proton pump inhibitor was given for added gastric protection. Cyclizine was stopped as no symptom relief was noted.

Edward described his need to vomit as worse in the mornings, often unaccompanied by nausea. Soon after waking he would feel the urge to retch and vomit. No other features of potentially raised intracranial pressure were noted. His symptoms persisted despite the medication changes and further investigation was arranged. A barium swallow test revealed un-coordinated periods between his swallow phase and the start of peristalsis, with noted reflux and normal gastric emptying.

His constipation continued and contributed to his nausea and discomfort. Metoclopramide was increased to 60mg over 24 hours via syringe pump, and levomepromezine was stopped in case it was counteracting the pro-kinetic effects of metoclopramide, but unfortunately this did not help.

It was felt Edward's psychological distress was a significant contributing factor to his symptoms throughout his admission. His recent diagnosis of a terminal condition and his very private nature challenged his ability to come to terms with his prognosis. He had declined any support or intervention from the community palliative care team. The medical team felt there were elements of somatisation to his distress.

He admitted to making himself vomit by putting his fingers down his throat in order to relieve the nausea and occasionally the "need to purge himself" and "get the cancer out" by vomiting. The palliative care team had discussions with Edward regarding his symptoms also being caused by his underlying disease and that it may not be possible to resolve his nausea entirely.

No definitive reversible cause was found for his vomiting and he became more unwell. After discussion with Edward and his family, transfer to a hospice for symptom control, end of life care (EOLC) care and psychological support was deemed most appropriate. He had been reluctant to engage in any form of conversation regarding his prognosis or his wishes for preferred place of death but did state he would prefer to be cared for in the hospice rather than home.

Edward was admitted to the local hospice for symptom control and EOLC by the specialist palliative care team. His medications were reviewed and several combinations of antiemetics were trialled. Levomepromazine 25mg in the syringe pump over 24 hours with 4mg Ondansetron PRN appeared to settle his symptoms best overall. The team also focussed heavily on supporting him emotionally and managing his psychological distress. Sadly, but not unexpectedly, Edward continued to deteriorate and died peacefully a few days later with his family at his side.

Management Of Nausea & Vomiting – What You Need To Know

There are several key areas that need to be considered in the approach to nausea and vomiting symptom control;

1. Considering the likely cause or causes. A good history of the symptoms, including timing/triggers of any episodes, any relieving/exacerbating factors, coupled with a thorough physical examination, should identify potential causes.
2. Knowledge of key nausea and vomiting pathways and the pharmacological mechanism of action of antiemetics and relevant receptors is essential.
3. An understanding of potential side effects of the different classes of antiemetics is important for appropriate medication choice in each patient.
4. Consider the route of administration in a vomiting patient – intravenous or subcutaneous medications may need to be given if the patient cannot tolerate oral medications.

Nausea and Vomiting pathways

There are several neural pathways into the vomiting centre of the brain, thought to be responsible for the production of nausea and vomiting symptoms. By targeting the specific neurotransmitters involved in these pathways, clinicians can use specific antiemetics to block their receptors and manage nausea and vomiting.

1. Peripheral receptors – *Chemoreceptors and mechanoreceptors in the GI tract, and viscera, via the vagus and splanchnic nerves, sympathetic ganglia and glossopharyngeal nerve. Visceral stimulation releases dopamine and serotonin neurotransmitters.*

2. Chemoreceptor trigger zone (CTZ) – *The CTZ lies partly outside of the blood-brain barrier in the brainstem and is influenced by both chemical signals in the circulation and numerous neuroendocrine pathways. Toxins in the blood and the CSF can result in nausea and vomiting by activating the CTZ and releasing dopamine and serotonin.*

3. Cerebral cortex – *input from all five senses, plus raised intracranial pressure, meningeal irritation, and psychological distress/anxiety can trigger the vomiting centre.*

4. Vestibular nuclei – *Nausea and vomiting is triggered by motion via the vestibulocochlear nerve and the labyrinthine system. Vestibular and central nervous system activation release histamine and acetylcholine.*

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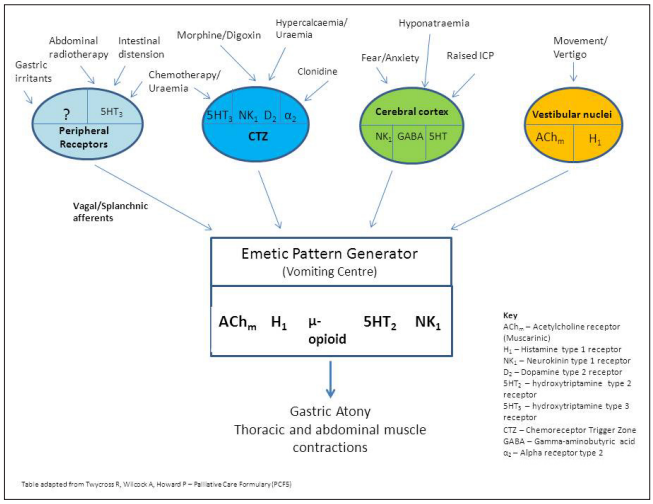

Figure 2: Neural mechanisms of nausea and vomiting

Antiemetics

There are many different types of antiemetics available, some more commonly used by junior doctors than others. Some are only really used with specialist palliative care advice, but are worth being familiar with.

Drug	D_2 Antagonist	H_1 Antagonist	Muscarinic Antagonist	$5HT_2$ Antagonist	$5HT_3$ Antagonist	$5HT_4$ Agonist	NK_1 Inhibitor
Metoclopramide	++				+	++	
Domperidone	++						
Cyclizine		++	++				
Hyoscine hydrobromide			+++				
Haloperidol	+++				+/-		
Levomepromazine	++	+++	++	+++			
Aprepitant							+++
Ondasentron					+++		
Granisetron					+++		

Table I: Main neurotransmitter receptors targeted by commonly used anti-emetics.

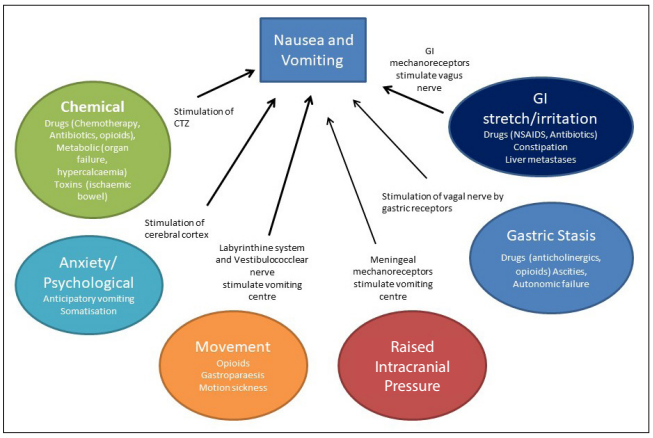

Figure 3: Common causes of nausea and vomiting in palliative care.

Cause of Nausea and Vomiting	Suggested treatment
Chemical or Metabolic • Drugs including opioids • Uraemia/Hypercalcaemia	• Domperidone • Haloperidol • Metoclopramide • Levomepromazine
Gastric Stasis/Gastric outlet obstruction • Local tumour • Opioids, anticholinergics • Autonomic failure • Hepatomegaly • Peptic ulceration	**Prokinetic** • Metoclopramide (caution regarding possible stent migration) • Domperidone
Bowel obstruction • Abdominal cancers • lymphadenopathy • Autonomic neuropathy • Constipation	**Peristaltic failure:** • Metoclopramide – only if partial bowel obstruction with no colicky abdominal pain **Mechanical obstruction:** • Hyoscine butylbromide (colicky pain) • Haloperidol • Levomepromazine • Octreotide – somatostatin analogue
Cranial disease • Raised Intercranial Pressure (ICP) • Brainstem/meningeal disease	• Cyclizine • Dexamethasone (if raised ICP)
Movement related • Vestibular disease • Base of skull tumour • Motion sickness	• Cyclizine • Levomepromazine • Prochlorperazine (motion sickness)
Unknown cause/multiple causes	• Metoclopramide • Cyclizine+/- Haloperidol • Levomepromazine

Table II: Selection of antiemetic for specific causes of nausea and vomiting.

Drug	Mechanism of Action	Notable side Effects	Red flags
Metoclopramide	• Dopamine$_2$ receptor antagonist • Prokinetic action via $5HT_4$ receptor • Acts on the CTZ and GI tract.	Extrapyramidal symptoms: • Parkinsonism, • Agitation, • Akathisia, • Acute dystonic reaction Diarrhoea	• Use with caution in cardiovascular disease • Can cause prolongation of the QT interval which can lead to Torsade de pointes • Avoid in patients with Parkinson's Disease • Don't use if total bowel obstruction is suspected as it can result in bowel perforation
Haloperidol	• Neuroleptic butyrophenone, and dopamine2 receptor antagonist • Targets the CTZ.	• Extrapyramidal symptoms • sedation, • lower seizure threshold • prolongation of QT interval.	• Avoid use in Parkinson's Disease and Lewy Body Dementia.
Cyclizine	• An antihistamine, and an antimuscarinic. • Acts on the vomiting centre and vestibular nucleus • Useful for patients with raised ICP, and motion sickness.	Mainly due to its anti-muscarinic properties: • sedation, • dry mouth	• Use with caution in severe heart failure, young children and the elderly.
Levomepromazine	• A phenothiazine • Targets multiple receptors including D_2, α adrenergic, cholinergic, $5HT_2$, and histamine. • Broad spectrum of action and acts on the CTZ, vestibular nucleus, and the vomiting centre.	Side effects include: • sedation, • dry mouth, • somnolence, • postural hypotension • lowers seizure threshold	• Inhibits cytochrome-P450, and should be avoided in patients with liver dysfunction.
Hyoscine hydrobromide	• An antimuscarinic that targets the vestibular nucleus and vomiting centre. • Effective in motion sickness.	Side effects include: • dry mouth, • sedation • agitation	• Avoid in patients with glaucoma
Ondansetron and Granisetron	• These are 5HT3 receptor antagonists, targeting the CTZ and gut wall. • Useful for acute vomiting post-surgery, and chemotherapy.	• Extrapyramidal reactions are unlikely and side effects commonly seen are constipation and headache.	• May cause prolongation of the QT interval.

Table III: Antiemetics and notable side effects.

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Conclusion

It is likely that Edward's sensation of nausea and subsequent vomiting was multifactorial, a combination of mechanical disturbance with the displaced stent, underlying disease, anxiety and stress surrounding his recent diagnosis and fears about his disease progression. Trials of ondansetron, cyclizine, metoclopramide and levomepromazine all failed initially to control this gentleman's symptoms adequately. The evidence for the efficacy of individual antiemetics is limited, and further research is needed in this area.

The mechanistic approach, relying upon targeting specific receptors and blocking neurotransmitter pathways is sensible as an initial approach, but failure of treatment often leads to a selection of second or third line antiemetic without significant evidence to support their use. The concept of 'total nausea' should also be considered in patients with intractable nausea and vomiting.

As with 'total pain' the underlying psychological distress a patient feels may contribute to their feelings of nausea and vomiting – hence 'total nausea'. During his admission to the hospice and his gradual acceptance of the psychological support offered to both himself and his family, Edward's vomiting reduced significantly.

Levomepromazine and PRN Ondansetron helped reduce his nausea and vomiting, and his abdominal pain was well controlled with opioid analgesia. Care and attention to the psychosocial aspects of Edward's needs, in addition to his recurrent physical symptoms attempted to ease his distress and combat his 'total nausea'.

Nausea and Vomiting in Palliative Care MCQs

1. Hazel is an 83 year old lady with a Grade IV Glioblastoma and no curative options available. She has declined palliative radiotherapy and has been transferred to the hospice for end of life care. Her main symptoms are nausea and vomiting which is worse in the morning.

She requires a continuous subcutaneous infusion over 24 hours via a syringe pump to keep her comfortable as she can no longer tolerate oral medications. Which would be the most appropriate initial prescription in the syringe pump to manage her symptoms from below?

a) Haloperidol 2.5mg

b) Metoclopramide 10mg

c) Cyclizine 150mg

d) Levomepromazine 25mg

e) Hyoscine butylbromide 60mg

2. Robert is a 42 year old gentleman with metastatic pancreatic cancer. His last cycle of chemotherapy treatment was four weeks ago. He has a distended abdomen, which on ultrasound shows loculated fluid collections. His main complaints are nausea and constipation but he denies any recent vomiting.

He has asked for a drug called Aprepitant that he was prescribed during his chemotherapy at the specialist oncology hospital. He is currently on ondansetron 4mg QDS. Why would Aprepitant not be a suitable antiemetic at this time?

A. It is too expensive to prescribe

B. It is not available on the hospital formulary

C. It is only prescribed in specialist cancer centres

D. It is most effective for chemotherapy-induced nausea and vomiting

E. He is not symptomatic enough to warrant its prescription

3. Geoffrey is a 79 year old gentleman who has a diagnosis of prostate cancer and widespread bone metastases. He also has a history of Parkinson's disease which is well controlled on Sinemet (levodopa/carbidopa). Geoffrey complains of a 1 week history of nausea but no vomiting.

The exact cause of Geoffrey's nausea is unknown and reversible causes have been ruled out. From the following antiemetics which would be the most appropriate drug to use to manage this gentleman's symptoms?

A. Metoclopramide

B. Haloperidol

C. Cyclizine

D. Domperidone

E. Levomepromazine

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4. David is a 62 year retired plumber with colon cancer. He presented to A&E with vomiting and abdominal pain and has been unable to tolerate solid food for 3 days. He has been vomiting large amounts including undigested food.

Bowel sounds are hyperactive and visible peristalsis can be seen on examination. Abdomen is distended and painful on palpation. What is the likely diagnosis?

A. Gastroenteritis

B. Bowel obstruction

C. Renal colic

D. Urinary infection

E. Oesophagitis

5. Sharon is a 51 year old school teacher with breast cancer and disease infiltration to her ribs and thoracic spine. She has been admitted to the ward and is currently being treated for a chest infection.

She is commenced on intravenous antibiotics but becomes increasingly drowsy and confused over the next few days. She complains of nausea, tiredness and general weakness. What investigation do you need to consider first?

A. CT brain

B. Repeat Chest X ray

C. Plasma corrected calcium levels

D. Urinalysis

E. CTPA

Answers

1. Correct answer is C.

Early morning vomiting may indicate raised intracranial pressure and therefore the most appropriate antiemetic to use would be cyclizine. Haloperidol and levomepromazine need to be used with caution as they can both lower the seizure threshold. There is also a risk that Hazel may become very drowsy with a dose of 25mg of levomepromazine.

Dexamethasone can also be considered if Hazel is not imminently dying as it may reduce intracranial pressure and relieve her symptoms.

Hyoscine butylbromide is not indicated to manage nausea and vomiting in this case. It is mainly used in palliative care to manage vomiting in patients with bowel obstruction due to its antiscretory properties.

Metoclopramide would not be the first choice of antiemetic in this case and a dose of 10mg is unlikely to be sufficient as a continuous infusion over 24 hours.

2. Correct answer is D.

Aprepitant is a Neuro-Kinin (1) receptor antagonist. It has been shown to be effective in the treatment of nausea induced by cytotoxic chemotherapies such as cisplatin and cyclophosphamide. It works centrally on the vomiting centre and augments the effects of other antiemetics such as 5HT3-receptor antagonists and is used in combination with corticosteroids. Side effects include fatigue, headache and hiccups.

Constipation could be causing this gentleman's symptoms of nausea and ondansetron can cause constipation. It would therefore be appropriate to discontinue ondansetron and use a laxative to manage constipation which may also help with Robert's nausea. A prokinetic drug such as metoclopramide may also be useful to aid gastric emptying especially due to abdominal distension with loculated ascites.

3. Correct answer is D.

Dopamine receptor antagonists should be avoided in patients with Parkinson's disease and are contraindicated in patients with Lewy Body dementia. Although domperidone blocks the dopamine receptor, it does not cross the blood-brain barrier and is therefore safe to use in patients with Parkinson's disease.

Cyclizine, an antihistamine and an antimuscarinic, can cause hypotension, sedation, and rarely extrapyramidal side effects. It should be used with caution in those with severe heart failure.

5HT-3 antagonists such as ondansetron are also suitable antiemetics that can be used in patients with Parkinson's disease but careful monitoring of bowel function is important as it can cause constipation. Route of administration should be considered in a patient who is vomiting as they are unlikely to tolerate oral medication and may not sufficiently absorb drugs from the GI tract.

4. Correct answer is B.

Given this patient's acute onset vomiting, large amounts of undigested food, hyperactive bowel sounds and abdominal pain, bowel obstruction as a cause should be highly suspected. Loud bowel sounds or borborygmi and visible peristalsis is caused by the bowel actively pushing against an obstruction.

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Malignant bowel obstruction is common in bowel cancer and metastatic ovarian cancer and is a poor prognostic indicator. The obstruction can be mechanical or functional and can occur at multiple sites along the bowel. Surgical intervention may need to be considered for management in the case of a single focus of obstruction.

Alternatively, using medications such as hyoscine butylbromide to reduce peristalsis and resting the bowel to try and alleviate the blockage may be considered. Hyoscine butylbromide will also reduce gut secretions and alleviate vomiting.

Octreotide, a somatostatin analogue can be used to reduce gut secretions if hyoscine butylbromide is not effective at optimum doses.

It is important to consider route of administration of medication as the enteral route will not be tolerated and drugs are unlikely to be absorbed in a patient who is vomiting. Parenteral routes should be considered.

5. Correct answer is C.

The most likely cause of this lady's confusion and lethargy is hypercalcaemia of malignancy. Significantly high plasma calcium levels will cause death within a few days is left untreated. Patients often feel fatigued, thirsty, confused and constipated. Treatment of hypercalcaemia is with fluid replacement, bisphosphonates such as pamidronate and regular monitoring.

Calcium levels start to fall after approximately 48 hours and need to be monitored for the following week. Always try and consider reversible causes of confusion and acute deterioration even in patients with progressive underlying disease.

If calcium levels are normal it would be appropriate to perform a CT brain to investigate for brain metastases and features of raised intracranial pressure which can also present with similar symptoms.

Author

Dr Kerenza MacDaid
FY2, Epsom & St Helier University Hospitals NHS Trust
Department of Palliative Care
Epsom & St Helier University Hospitals NHS Trust
Epsom General Hospital
Dorking Road, Epsom, KT18 7EG

Dr Aruni Wijeratne
Consultant in Palliative Medicine
Epsom and St Helier University Hospitals NHS Trust and Princess Alice Hospice
Department of Palliative Care
Epsom & St Helier University Hospitals NHS Trust
Epsom General Hospital, Dorking Road, Epsom, KT18 7EG

Corresponding Author

Dr Aruni Wijeratne
a.wijeratne@nhs.net

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