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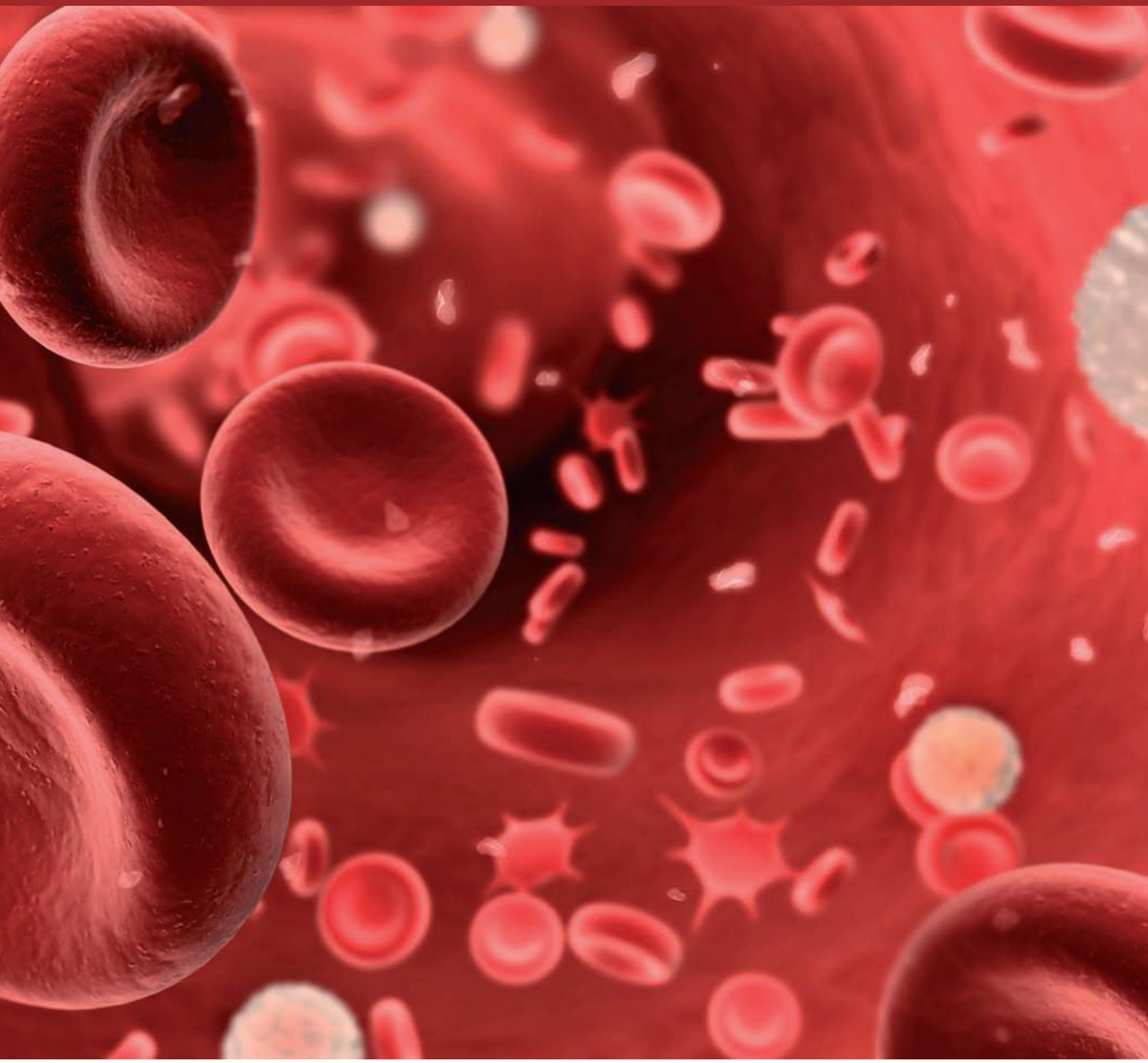

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Volume 9, Issue 3

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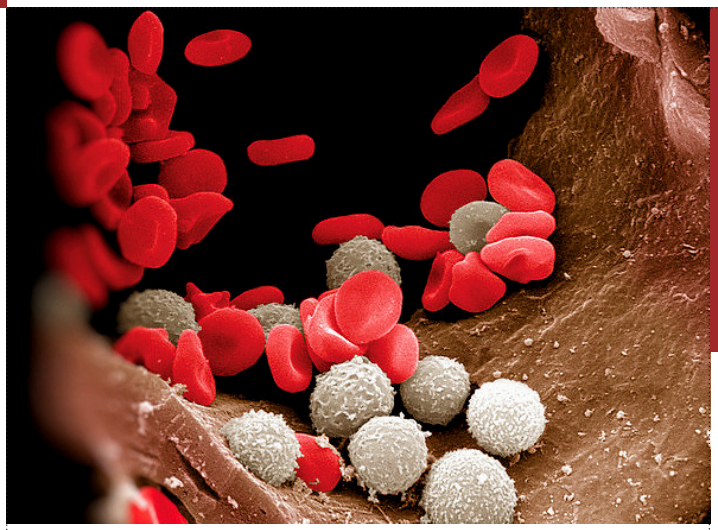
A CASE OF MIXED WARM & COLD AUTOIMMUNE HAEMOLYTIC ANAEMIA

AS Clarke & JO Cullis



Abstract

Anaemia is a common finding in patients admitted to hospital and results from either failure of red cell production, or from increased red cell destruction or loss. We present a rare case of mixed cold and warm autoimmune haemolytic anaemia. The patient's presentation, initial findings and more specialised investigations are discussed, along with management of the case and complexities of the diagnosis.

Case history

A 39 year old female presented to the Emergency Department with a 4 day history of jaundice. She had visited her general practitioner 48 hours prior to admission complaining of passing red urine and had commenced trimethoprim for a presumed urinary tract infection. On arrival she complained of dyspnoea, confusion, and diarrhoea and vomiting. Her only medical history was of childhood asthma and she took no regular medications. She was a non-smoker and rarely drank alcohol.

On admission she was extremely unwell with profound pallor and jaundice. She was afebrile but tachycardic at 130 beats per minute with blood pressure 90/50mmHg. There was no clinical lymphadenopathy or hepatosplenomegaly.

Haemoglobin was 34g/L, with a neutrophilia of 19.7 x 10^9/L and normal platelet count. Bilirubin was elevated at 152µmol/L but other liver and renal function tests were normal. Chest X-ray was normal.

A case of mixed warm & cold autoimmune haemolytic anaemia
Patient Management

What immediate further investigations would you request?

A blood film and a reticulocyte count are urgent investigations in this situation. The combination of severe anaemia and jaundice implies a haemolytic process, so the reticulocyte count should be elevated and the blood film may give clues as to aetiology. Lactate dehydrogenase (LDH) is another useful marker of haemolysis, and was markedly elevated at 3130IU/L (normal range 310-620). A direct antiglobulin test (DAT or Coomb's) test is mandatory to look for evidence of autoimmune haemoytic anaemia (AIHA). Samples for vitamin B12 and folate levels should be taken before transfusion is undertaken. Finally a urine sample should be taken for microscopy and culture: in this case no red cells were seen on microscopy.

LEARNING POINT

It is important to remember that red urine can be due to haemoglobinuria, usually due to intravascular haemolysis, rather than haematuria, which is caused by urinary tract haemorrhage. Dipstick testing will not distinguish these two possibilities: direct microscopy is needed.

G6PD† deficiency - with oxidant stress (drugs/infection)
ABO incompatible blood transfusion reaction
Red cell fragmentation syndromes (e.g. TTP/HUS)
Paroxysmal nocturnal haemoglobinuria
Paroxysmal cold haemoglobinuria
March haemoglobinuria
Unstable haemoglobinuria
Some autoimmune haemolytic anaemias

† glucose-6-phosphate dehydrogenase

Table 1: Causes of haemoglobinuria.

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What abnormalities are present on these two representative images of the patient's presenting blood film?

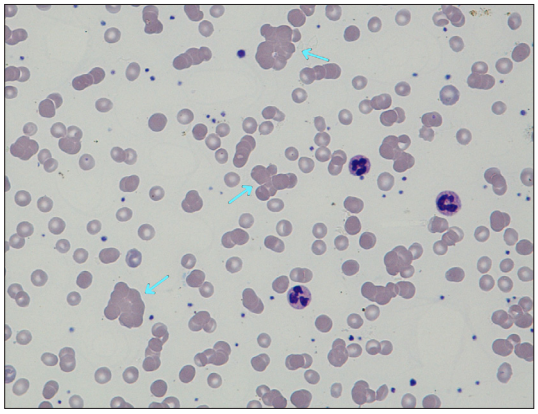

Figure 1A: Representative fields of blood film at diagnosis showing red cell agglutination (blue arrows).

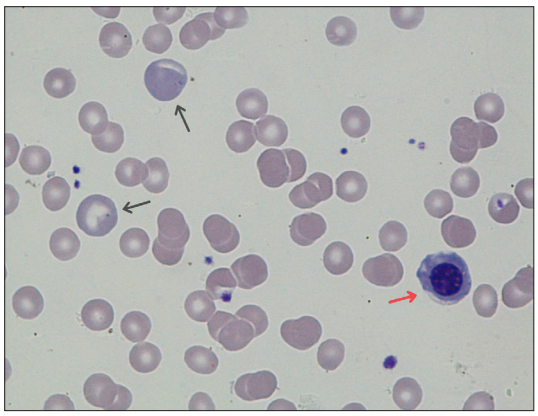

Figure 1B: Polychromatic red cells (black arrows) and a nucleated red blood cell (red arrow).

The blood film shows red cell agglutination, together with polychromasia and the presence of a nucleated red blood cell, confirming increased marrow erythroid activity. It is important to note the absence of any bite cells or red cell fragments, as conditions associated with oxidative haemolysis, such as the X-linked recessive condition, glucose 6-phosphate dehydrogenase (G6PD) deficiency, can also present with profound anaemia, jaundice and haemoglobinuria.

LEARNING POINT

Red cell agglutination (red cells clumped) must be distinguished from rouleaux (red cells stacked like coins): the former is seen in cold autoimmune haemolysis such as cold agglutinin disease, whereas the latter may be seen in conditions of increased blood viscosity such as myeloma and inflammatory diseases.

Further investigations confirmed a pan-reactive auto-antibody, with a strongly positive DAT, IgG 5+, IgM 0, C3c 2+ and C3d 5+, and the presence of a cold and warm auto-antibody. The working diagnosis was therefore mixed cold and warm AIHA.

Congenital	Acquired
Red cell membrane disorders - hereditary spherocytosis - hereditary elliptocytosis	Autoimmune - warm - cold - mixed
Red cell enzyme disorders - G6PD deficiency - pyruvate kinase deficiency	Alloimmune - transfusion reactions - haemolytic disease of newborn
Haemoglobin disorders - Thalassaemia - Sickle cell disorders	Drug induced
	Infection e.g. *Clostridium perfringens*
	Mechanical - thrombotic thrombocytopenic purpura - haemolytic uraemic syndrome - heart valves
	Paroxysmal nocturnal haemoglobinuria
	Snake bites

Table 2.1: Causes of haemolytic anaemia.

Causes of warm AIHA	Causes of cold agglutinin disease (CAD)
- idiopathic - lymphoproliferative diseases e.g. CLL‡ NHL§ - autoimmune diseases	- primary idiopathic - secondary lymphoproliferative diseases e.g. CLL‡ NHL§ *Mycoplasma pneumoniae* infection infectious mononucleosis

‡ chronic lymphocytic leukaemia
§ Non-Hodgkins lymphoma

Table 2.2: Causes of warm and cold autoimmune haemolytic anaemia.

LEARNING POINT

Mixed AIHA is rare, but often presents with severe haemolysis. Most cases of AIHA are due to warm auto-antibodies (warm AIHA) and present with anaemia and jaundice, with blood film features including polychromasia, spherocytosis and positive DAT with IgG and/or complement (C3). In contrast, cold autoimmune haemolysis (cold agglutinin disease (CAD) comprises 15% of cases of AIHA, and typically presents with cold-induced symptoms, such as acrocyanosis, livedo reticularis and often mild chronic anaemia: haemoglobinuria may follow cold exposure. Blood film will show red cell agglutination, and the DAT is typically positive to C3 products alone. AIHA with both warm and cold auto-antibodies is known as mixed AIHA.

What immediate management measures would you institute?

Given the severity of the anaemia, urgent blood transfusion is required. Obtaining compatible blood in patients with strong red cell auto-antibodies may not be straightforward as co-existent red cell allo-antibodies need to be excluded; close liaison with the blood transfusion laboratory is essential. Because of the cold auto-antibody the patient must be kept warm and blood should be transfused through a blood warmer. Folic acid supplementation should be administered as folate deficiency can rapidly develop because of the demands of compensatory increased erythropoiesis.

A CASE OF MIXED WARM & COLD AUTOIMMUNE HAEMOLYTIC ANAEMIA

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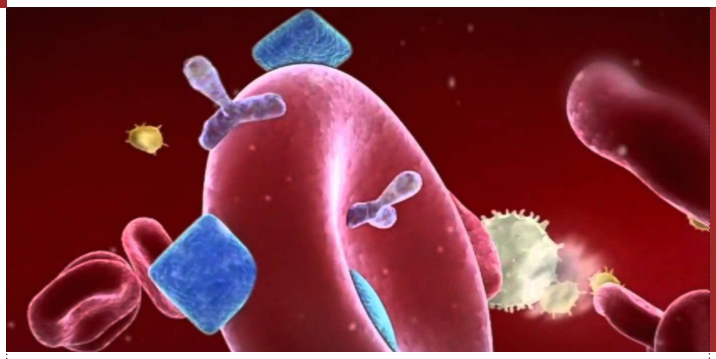

A case of mixed warm & cold autoimmune haemolytic anaemia
Patient Management

In the first 24 hours the patient was transferred to intensive care for continued resuscitation, transfused 4 units of packed red blood cells through a blood warmer, started on prednisolone 1mg/kg/day and folic acid 5mg/day. She was also covered with broad spectrum intravenous antibiotics.

LEARNING POINT

Corticosteroids are the mainstay of treatment of warm AIHA, and most patients will respond within 2-3 weeks, following which steroid dose is tapered. In contrast CAD does not normally respond to steroids, but many patients will have alleviation of symptoms from simple measures to avoid cold exposure. It is common practice to administer folic acid replacement in both conditions because of increased folate utilisation through compensatory erythropoiesis.

Despite ongoing steroid treatment, warming and further transfusions, by day 4 there was continued evidence of haemolysis resulting in recurrent severe anaemia. A bone marrow biopsy showed marked erythroid hyperplasia but no evidence of marrow infiltration by lymphoma (Figure 2). CT scan performed to look for evidence of underlying lymphoma or other malignancy revealed bilateral axillary lymphadenopathy: axillary lymph node biopsy showed reactive hyperplasia with no evidence of malignancy. Serum immunoglobulins and autoimmune profile were normal and *Mycoplasma pneumoniae* serology was negative. Paroxysmal cold haemoglobinuria, one of the rarer autoimmune forms of intravascular haemolysis, was excluded by demonstrating a negative Donath-Landsteiner antibody.

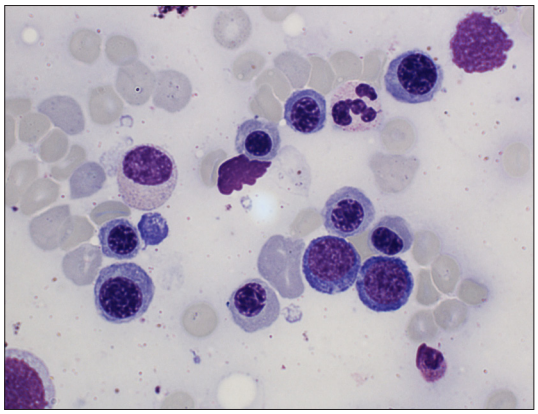

Figure 2A: Bone marrow aspirate showing erythroid hyperplasia.

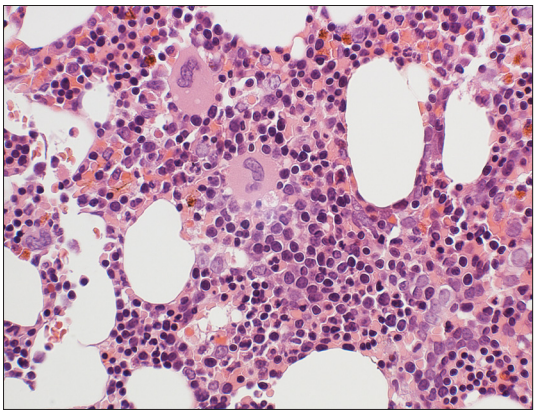

Figure 2B: Bone marrow trephine confirming erythroid hyperplasia but showing no evidence of lymphomatous infiltration.

What further treatments can be considered in steroid-refractory autoimmune haemolytic anaemia?

Most patients with warm AIHA will respond to corticosteroids (1-3), whilst CAD often responds to conservative measures such as cold avoidance (2-5). Historically options for treating refractory warm AIHA have included splenectomy, intravenous immunoglobulins, or second-line immunosuppressive agents such as cyclophosphamide or ciclosporin, whereas more severe cases of CAD have occasionally responded to cytotoxic drugs such as chlorambucil. However mixed AIHA is rare and treatment approaches are not standardised, but recent case reports suggest that responses to the monoclonal antibody rituximab may be seen (6-8).

Rituximab is active in both warm AIHA that is refractory to steroids and in more severe forms of CAD (1-5). The antibody reacts specifically with the CD20 antigen expressed on B-lymphocytes and induces B-cell depletion, which in turn interferes with the production of auto-antibodies in some immune diseases, such as rheumatoid arthritis: it is also highly effective in treatment of various B-cell non-Hodgkin's lymphomas, some of which are associated with AIHA.

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Following commencement of rituximab therapy, the patient improved rapidly with sustained resolution of haemolysis (Figure 3). Four weekly doses of rituximab therapy were completed and steroids were weaned. No recurrence of haemolysis was seen on follow-up.

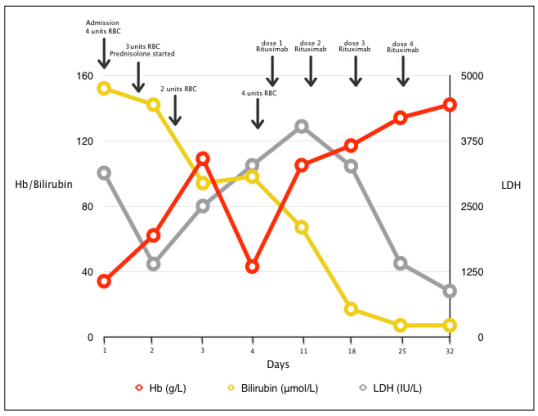

Figure 3: Graph showing Hb, bilirubin and LDH levels in response to interventions.

Discussion

We describe a rare case of mixed AIHA presenting with life-threatening anaemia and evidence of intravascular haemolysis, who failed to respond to initial treatment with warming and corticosteroids, but who demonstrated a complete and sustained response following treatment with rituximab. The case demonstrates the efficacy of this monoclonal antibody in AIHA, but also highlights the need to exclude underlying causes of AIHA, such as low-grade lymphomas, before it is used. Indeed an extensive search in this patient failed to reveal an underlying cause, but we speculate that the haemolysis may have been triggered by the combined swine and seasonal influenza vaccination which she had received a few days before presentation.

Two case reports exist in the literature describing autoimmune haemolytic anaemia, and in one case a combination of AIHA and immune thromboyctopenia (known as Evans' syndrome) following influenza vaccination (9-10). In all three of these cases, as in this case, haemolysis developed within a few days of vaccination, suggesting a true aetiological link. It is possible that vaccination may induce development of autoreactive lymphocytes through molecular mimicry of host red cell antigens by viral peptides, resulting in red cell destruction, and cases of AIHA have also been described following influenza infection, supporting this hypothesis (11).

Multiple Choice Questions

1. A 64 year old male is admitted with anaemia and jaundice. Which one of the following blood film features would support a diagnosis of autoimmune haemolytic anaemia (AIHA)?

A. Polychromasia and bite cells

B. Microcytic, hypochromic red cells

C. Polychromasia, tear drop cells and leucoerythroblastic changes

D. Polychromasia, spherocytes and nucleated red blood cells

E. Macrocytic red cells and hypersegmented neutrophils

2. Which of the following are well recognised causes of AIHA? Tick all that apply.

A. Chronic lymphocytic leukaemia

B. Acute lymphoblastic leukaemia

C. Mycoplasma pneumoniae infection

D. Systemic lupus erythematosus

E. Parvovirus infection

3. Which of the following parameters are useful in monitoring response to treatment in warm AIHA? Tick all that apply.

A. Reticulocyte count

B. Serum haptoglobin

C. Serum bilirubin

D. Serum lactate dehydrogenase (LDH) level

E. Direct antiglobulin (Coomb's) test

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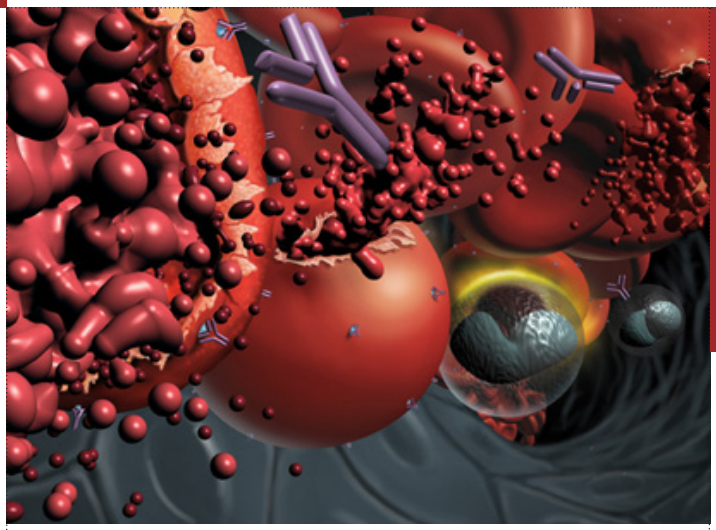

4. Which of the following are true or false.

A. Hereditary spherocytosis is inherited in an autosomal dominant fashion

B. Glucose 6-phosphate dehdrogenase (G6PD) deficiency is an X-linked recessive condition

C. Cold agglutinin disease usually responds to steroid treatment

D. Renal cell carcinoma can present with haemoglobinuria

E. Increased red cell turnover in haemolysis can cause vitamin B12 deficiency

5. Which of the following management approaches are indicated in a 58 year old man with known ulcerative colitis admitted with haemoglobin 80g/L, bilirubin 76µmol/L and positive DAT with IgG 4+ but negative to C3d? Tick all that apply.

A. Blood transfusion

B. Folic acid supplementation

C. Intravenous immunoglobulin

D. Corticosteroids

E. Splenectomy

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Patient Management

Answers

1. Correct answer D

Polychromasia is present in conditions of increased red cell production, such as following acute blood loss or haemolysis, and will result in an increased reticulocyte count. Bite cells are usually a feature of red cell fragmentation, such as seen in acute haemolytic episodes in individuals with G6PD deficiency, mechanical haemolysis resulting from conditions such as thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome, or following mechanical heart valve replacement.

Microcytic and hypochromic red cells are seen in iron deficiency or thalassaemias. Tear drop cells and leucoerythroblastic changes should suggest marrow fibrosis or infiltration, while macrocytes and hypersegmented neutrophils are seen in megaloblastic anaemias due to B12 or folate deficiency. The finding of spherocytes is most commonly due to warm AIHA or hereditary spherocytosis.

2. Correct answers A, C, D

AIHA is often idiopathic, but may be associated with chronic lymphoproliferative conditions such as CLL or low-grade non-Hodgkin's lymphoma, some congenital immunodeficiency conditions, and other autoimmune conditions such as SLE, rheumatoid arthritis, and ulcerative colitis.

It can also be seen following certain infections, such as Mycoplasma pneumoniae or Epstein-Barr virus or in association with other malignancies, or following exposure to certain drugs. Parvovirus infection can cause red cell hypoplasia and resultant severe anaemia in patients with chronic haemolytic conditions such as sickle cell disease or hereditary spherocytosis.

3. Correct answers A, C, D

The reticulocyte count reflects compensatory increased red cell production by the bone marrow, and is elevated in cases of haemolysis due to all causes: levels should return to normal as AIHA responds to treatment. Similarly bilirubin levels and serum LDH reflect increased red cell destruction, and will fall with treatment. Serum haptoglobin levels are often reduced in conditions associated with intravascular haemolysis, such as cold agglutinin disease (CAD), but are also reduced in liver disease, and are not of use in monitoring disease. The DAT often remains positive even after successful treatment.

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4. Correct answers:

A. True

B. True

Remember though that the gene frequency in some parts of the world e.g. West Africa is high because the condition affords protection against malaria, so although typically males are affected, homozygous females may be seen with clinical G6PD deficiency.

C. False

Most patients respond to cold avoidance, steroids are usually ineffective, but rituximab does produce responses in many patients with more severe disease.

D. False

Urological cancers can present with haematuria; haemoglobinuria is a manifestation of intravascular haemolysis.

E. False

Folate deficiency can occur in conditions associated with increased red cell turnover and folate supplementation may be indicated.

5. Correct answers: B, D

This patient has warm AIHA. Blood transfusion may be hazardous in patients with mild to moderate warm AIHA because the auto-antibodies detected in serum can make it more difficult to detect underlying red cell allo-antibodies (e.g. from previous transfusions or pregnancies), and should be reserved for life-threatening anaemia. Folate deficiency may occur in AIHA so replacement is recommended. Most patients with warm AIHA will respond to steroids. Intravenous immunoglobulin or splenectomy may be considered as second or third line options in patients who fail to respond to steroids.

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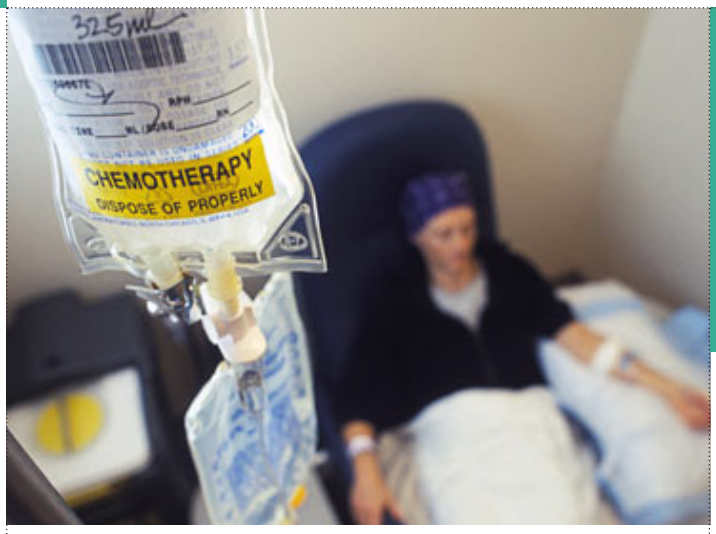
COMPLICATIONS OF CHEMOTHERAPY

G Holmes & R Hodgson



Abstract

Junior doctors will regularly come into contact with patients receiving chemotherapy whether they are doing an oncology or haematology rotation, or whether during a general medical or surgical job. It is important to be aware of the potential side effects of chemotherapy. These can be significant and in some cases life threatening. This article will cover both short and long term complications of chemotherapy. Neutropenic sepsis is discussed with attention to its management. Awareness of how to treat this life threatening complication is extremely valuable to juniors.

We will also discuss nausea and vomiting as it is such a common side effect, as well as tumour lysis syndrome, which again, can be life threatening. Specific side effect s of certain agents is covered with particular focus on those agents regularly used in haematological malignancies. Longer-term side effects are also considered including secondary malignancies and psychological impacts. The article is obviously not an exhaustive source of chemotherapy side effects but can serve as an introduction for junior doctors. With this background juniors will be able to expand their knowledge regarding specific agents when they come across patients in their practise.

All junior doctors will regularly come into contact with patients receiving chemotherapy whether during an oncology attachment or during general medical and surgical jobs. It is important to have an awareness of the potential side effects of chemotherapy that these patients may experience, as well as possible management strategies. Hopefully this article will demonstrate the wide ranging side effects which can be associated with chemotherapy. This article will cover the major side effects of chemotherapy beginning with early side effects and going on to discuss late side effects.

Neutropenic sepsis

An important and potentially life threatening complication of chemotherapy, neutropenic sepsis is defined by NICE as a temperature over 38°C or other signs consistent with infection, with a neutrophil count of less than 0.5 x 10^9/L in a patient undergoing systemic anticancer therapy (1). Care must be taken in the assessment of patients presenting unwell after chemotherapy as typical signs of infection may not be prominent in patients with low white cell counts and may also be suppressed in patients receiving corticosteroid therapy. Patients commonly present on the general medical take and it is vital that junior doctors appreciate the high mortality and need for rapid treatment. The mainstay of treatment, for patients presenting with neutropenic sepsis, is vigorous resuscitation and early broad spectrum antibiotics.

The exact agents given vary according to local guidelines but will all provide broad spectrum gram negative and anti-pseudomonal cover. The NCEPOD investigation 2008 found shortcomings in the treatment of neutropenic sepsis. In response to this, the national chemotherapy advisory group introduced guidelines which included a target 'door to needle time' of one hour. The advice is to give antibiotics before waiting for blood results in a patient who is at risk of neutropenia presenting with sepsis. Although a source of infection is not always determined blood (both peripheral and from any indwelling venous catheters), urine and sputum cultures, skin swabs and stool specimens should be sent where clinically indicated. Some units may also perform routine respiratory viral screening.

A chest x-ray should be performed in all patients with chest signs. Ideally bacterial cultures should be taken before antibiotic therapy is initiated but should not delay the prompt initiation of antibiotics. If a pathogen is identified antibiotic therapy can subsequently be altered appropriately. Indwelling iv catheter sites should be carefully examined and swabbed if there is evidence of infection. Line removal may need to be considered in some cases. Local policies frequently advocate the addition of a glycopeptides antibiotic if there is evidence of line infection to cover resistant gram positive organisms.

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GCSF therapy to shorten the duration of neutropenia should be discussed with the haematologist if the patient is haemodynamically unstable or has evidence of pneumonia but is not necessary for uncomplicated neutropenic fevers. Juniors may often to be expected to review neutropenic inpatients when they spike temperatures. NICE recommends not switching antibiotic therapy in this situation unless there is clinical deterioration or on specific microbiological advice (1).

Advice should be taken from microbiology on a case by case basis. Invasive fungal infections, pneumocystis jiroveci and viruses should be considered in patients with lung infiltrates not responding to antibiotic therapy and early CT thorax and BAL considered to try to reach a diagnosis. Every effort should be made to identify the pathogen with repeated cultures sent if patients continue to spike temperatures. Neutropenic patients are at an increased risk of developing fungal infections. These may be the cause of unresponsive fevers in those on empiric antibiotic treatment. In patients with an ongoing fever of unknown origin after 72-96 hours discussion with haematologists and microbiologists regarding starting empirical anti fungal medications and performing imaging of sinuses, thorax, liver and spleen may be appropriate. Fungal antigen and PCR testing may be available in some units.

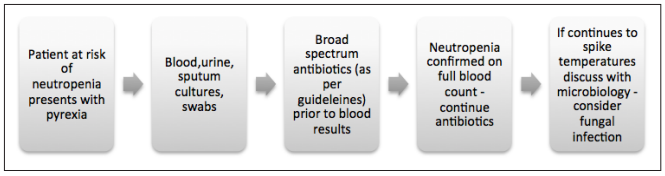

Figure 1: Inpatient management of neutropenic sepsis.

Tumour lysis

Tumour lysis syndrome is defined as metabolic abnormalities caused by destruction of malignant cells. Laboratory findings in tumour lysis syndrome include hyperuricaemia, hyperphosphataemia, hyperkalaemia and hypocalcaemia (2). It is most likely to occur within the first 7 days after the first cycle of anticancer therapy when tumour bulk is at its greatest.

Clinical turmour lysis syndrome can manifest in several ways including: renal impairment, cardiac arrhythmias, neurological deficits, seizures and potentially death. Management ideally beings with prevention. Malignancies are risk stratified according to the likelihood of tumour lysis syndrome. Risk stratification involves several factors including type of malignancy, with some being considered higher risk than others, presence of renal impairment and bulk of tumour load.

Treatment is initiated for high risk malignancies with rasburicase, which is a xanthine oxidase inhibitor, or allopurinol for lower risk malignancies. Adequate hydration is also imperative. Patients at high risk of tumour lysis should maintain a urine output of around 100mls hour and so an oral fluid intake of around 4 L day is usually required, starting before chemotherapy and maintained until the risk of tumour lysis has past.

Further Prophylaxis with rasburicase, a recombinant xanthine oxidase inhibitor, can be given for high risk malignancies or with allopurinol for lower risk malignancies. Those at highest risk of tumour lysis and also patients with poor performance status who might struggle to comply with tumour lysis prophylaxis at home may need to be admitted. Regular monitoring of patients electrolytes once commenced on chemotherapy is important to ensure tumour lysis syndrome can be picked up early. In patients with severe electrolyte disturbances or renal failure not responding promptly to medical therapy temporary renal replacement therapy may be required. These patients should be discussed with renal medicine early.

Nausea & vomiting

Chemotherapy induced nausea and vomiting (CINV) is a common and distressing side effect of chemotherapy, which can have both physical and psychological impacts on patients. In the past, up to 20% of patients were forced to refuse chemotherapy due to severe nausea and vomiting (3). Recent developments in antiemetic regimes mean that chemotherapy induced nausea and vomiting can now be avoided in up to 80% of patients (4). CINV is classified into early, late and anticipatory. Symptoms in early CINV occur within 24 hours of chemotherapy, it is thought to be serotonin mediated. Symptoms in late CINV occur over 24 hours following chemotherapy, thought to be substance P mediated. Anticipatory CINV is triggered by taste, sight, odour or anxiety linked to bad experiences of CINV in previous cycles (5).

International guidelines, on antiemetic use in chemotherapy, classify chemotherapy agents into high, moderate, low and minimal emetogenic risk. Where high risk has a greater than 90% chance of causing emesis without antiemetics, and minimal risk has a less than 10% chance. An example of a high risk chemotherapy agent is cisplatin whereas vincristine would be a minimal risk agent (6). The 5-HT3 receptor antagonists, such as ondansetron, are the most effective antiemetics for acute CINV (7). Palonostron is the newest 5-HT3 receptor antagonist and has a higher binding affinity and longer half-life than other 5-HT3 receptor antagonists. Updated MASCC/ESMO and ASCO guidelines therefore recommend its use in moderately emetogenic chemotherapy (6).

Other antiemetics used include Tachykinin NK1 receptor antagonists such as aprepitant dopamine agonists such as metoclopramide, antipsychotics and steroids. Benzodiazepines may be of use in anticipatory CINV where anxiety plays a role. Patients commonly present on the general medical take with dehydration, acute kidney injury or electrolyte disturbance secondary to CINV. Giving antiemetics by continuous subcutaneous infusion may be of benefit in severe nausea not responding to initial therapy. It is important to correct these consequences as well as addressing the vomiting.

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Emetogenic potential of intravenous antineoplastic agents:

Degree of emetogenicity (incidence)	Agent
High (>90%)	Cisplatin
	Mechlorethamine
	Streptozotocin
	Cyclophosphamide ≥1500 mg/m²
	Carmustine
	Dacarbazine
Moderate (30%–90%)	Oxaliplatin
	Cytarabine >1 gm/m²
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m²
	Doxorubicin
Degree of emetogenicity (incidence)	**Agent**
	Daunorubicin
	Epirubicin
	Idarubicin
	Irinotecan
	Azacitidine
	Bendamustine
	Clofarabine
	Alemtuzumab
Low (10%–30%)	Paclitaxel
	Docetaxel
	Mitoxantrone
	Doxorubicin HCl liposome Injection
	Ixabepilone
	Topotecan
	Etoposide
	Pemetrexed
	Methotrexate
	Mitomycin
	Gemcitabine
	Cytarabine ≤1000 mg/m²
	5-Fluorouracil
	Temsirolimus
	Bortezomib
	Cetuximab
	Trastuzumab
	Panitumumab
	Catumaxumab
Minimal (<10%)	Bleomycin
	Busulfan
	2-Chlorodeoxyadenosine
	Fludarabine
	Vinblastine
	Vincristine
	Vinorelbine
	Bevacizumab

Table 1: Table of emetogenic potential of intravenous antineoplastic agents, from MASCC guidelines (8)

Drug specific reactions

Many chemotherapy agents have their own specific side effects. A basic knowledge of these will aid junior doctors in their treatment of patients whom they encounter on the wards. The following table lists the specific side effects of several common chemotherapy agents used in haematological malignancies. The list is obviously not exhaustive. It demonstrates the varied and multisystem side effects which can accompany chemotherapy agents. When presented with a chemotherapy patient, side effects of their specific regime should be looked up in order to determine whether their symptoms are likely to be caused by their chemotherapy agent.

Drug	Class	Side Effects
Fludarabine	Antimetabolite	Nausea & vomiting, myelosupression, gastro intestina disturbance
6 mercaptopurine	Antimetabolite	Bone marrow suppression, anorexia, Nausea & vomiting, gastro intestinal disturbance, hepatotoxicity
Methotrexate	Antimetabolite	Nausea & vomiting, gastro intestinal disturbance, myelosupression
Bleomycin	Antibiotic	Pulmonary fibrosis, alopecia, mucocutaneous reactions, hypertrophic skin changes, hyperpigmentation
Doxorubicin	Antibiotic	Cardiac toxicity, nausea & vomiting, bone marrow suppression, stomatitis, alopecia, gastro intestinal disturbance
Cyclophosphamide	Alkylating agent	Nausea & vomiting, gastro intestinal disturbance, bone marrow suppression, haemorrhagic cystitis, infertility, veno-occlusive disease, secondary malignancies
Vincrisitne	Microtubule inhibitor	Nausea & vomiting, gastro intestinal disturbance, phlebitis, cellulitis, peripheral neuropathy
Cisplatin	Platinum	Nausea & vomiting, nephrotoxicity, ototoxicity, neurotoxicity

Table 2: Specific side effects of chemotherapy agents (from ABC of cancer care) (9)

Particularly relevant to haematology are the side effects of doxorubicin, cyclophosphamide, vincristine and rituximab, which make up the R-CHOP regime used to treat aggressive non hodgkins lymphoma. Doxorubicin causes a dose dependent cardiotoxicity, which can lead to a life threatening cardiomyopathy (10). A review by Lotrionte et al. showed over nine years clinical cardio toxicity, in patients treated with anthracyclines, occurred in 6% with subclinical cardio toxicity occurring in 18% of patients (11). The risk of cardio toxicity is higher in those with pre-existing heart disease. It is important to remember that the cardiotoxicity can be chronic with symptoms occurring up to ten years after the treatment.

An alarming side effect of cyclophosphamide to be aware of is haemorrhagic cystitis. Management is aimed at prevention with pre hydration and oral or intravenous mesna (2-mercaptoethane sodium sulfonate, a sulfhydryl compound). Vincristine is a neurotoxin. Its use as a chemotherapy agent can result in neurological dysfunction including bowel dysmotility and peripheral neuropathy. Sensory neuropathy tends to be more common than motor with initial symptoms of paraesthesia. More severe forms may result in muscle weakness, particularly in the distal muscle of hands and feet (12).

Cranial nerve involvement has also been described such as a case of vocal cord palsy which resolved following withdrawal of vincristine chemotherapy (13). The neurological effects of vincristine are dose dependent and reversible with cessation of treatment but can take up to several months to resolve.

Biological therapies are now commonly used in treatment of haematological malignancies. One of the most commonly used agents is rituximab. This treatment again has its own specific side effect profile. An important side effect for juniors to be aware of is infusion related reactions. Patients receiving rituximab infusions, particularly with early doses, can experience an allergic type reaction. They may develop rash, wheeze or hyportension during the infusion. If this occurs the infusion should be stopped and the patient managed appropriately with antihitamines and fluids.

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It is also important to be aware that rituximab can cause neutropenia, neutropenic sepsis in patients treated with rituximab should be treated as detailed above. A rare side effect of rituximab treatment may be interstitial lung disease. Andreas et al carried out a systematic literature review regarding the possible link between rituximab and development of interstitial lung disease. They found that rituximab did appear to be linked to interstitial lung disease in a small amount of cases. It is therofore important to consider rituximab to be a cause of patients presenting with shortness of breath following or during treatment of haematological malignancies (14).

Secondary malignancies

Secondary malignancies following chemotherapy have been widely reported. This long term side effect of chemotherapy is obviously significant and risk should be communicated to patients when consenting for chemotherapy. Particularly relevant to haematology is the risk of developing secondary malignancies following treatment for Hodgkins lymphoma. Chemotherapy has been found to increase the risk of both haematological and solid tumours (15).

Psychological impact

It is important to consider the psychological, social and financial impact of a cancer diagnosis and chemotherapy treatment. As well as coming to terms with a cancer diagnosis patients are faced with a treatment which may have many disabling and dangerous side effects as detailed above. Patients should be made aware of potential side effects of chemotherapy with written information given when they are consented for treatment.

A multidisciplinary approach including specialist nurses, psychologists and social workers may help patients adapt and cope with treatment. Cancer support charities and patient support groups may also be of great benefit in offering patients and family members specialist counselling and support and the opportunity to share experiences.

Conclusion

Side effects of chemotherapy can be wide ranging and distressing for patients. We hope that in this article we have offered junior doctors a structure to recognise both early and late complications of chemotherapy whether generic or specific to certain agents. We have also introduced some management strategies to some side effects, advice can also always be sought from haematologists, oncologists and specialist nurses involved with the patients care who will have experience in managing the various side effects.

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Financial statement

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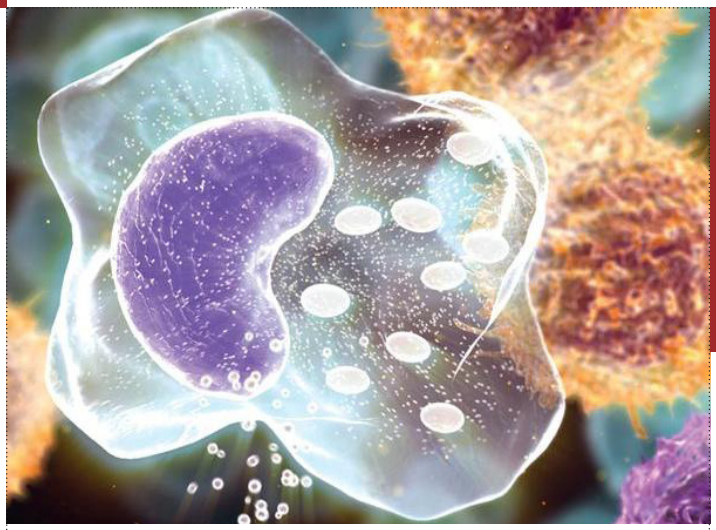
MULTIPLE MYELOMA COMPLICATED BY THROMBOSIS

G Errico & N Morley



Abstract

Multiple Myeloma is a malignancy characterised by clonal expansion of plasma cells in the bone marrow and usually the subsequent over expression of a monoclonal immunoglobulin (M-protein) in the blood. It accounts for 1% of all malignancies and 15% of haematological malicnancies (1). The median age at diagnosis is approximately 70 years of age therefore it can be considered disease of the elderly. Myeloma is heterogeneous in its presentation, from complications due to lytic lesions and hypercalcaemia to anaemia and renal failure.

Investigation of myeloma is relatively straight forward; however interpretation of immunoglobulin results as they come back is poorly understood and often proves problematic.

Although Myeloma is a largely incurable cancer, with modern therapeutics the prognosis has improved significantly in the last 15 years. A typical patient with Myeloma will have multiple remissions and relapses with a new treatment for each relapses.

Here I recount a case of myeloma in a typical patient; from diagnosis to current status in her disease. Discussion includes interpretation of immunoglobulin results and the initial investigations in myeloma. Her case is unusual in that she developed a thrombosis in an unusual site as a result of her treatment. The complication has an ongoing impact in her management and overall prognosis.

Case report

JW is a 61 year-old retired carer. She was previously fit and well other than mild asthma. She presented on in September 2012 with a 2 week history of increasing lethargy, shortness of breath and feeling light headed. On examination she was apyrexial with unremarkable observations. She was clinically anaemic otherwise examination was unremarkable.

Multiple myeloma complicated by thrombosis
Patient Management

Routine bloods found the following:

Hb 4.2g/l
Plts 166 x 10^9/l
WCC 8.2 x 10^9/l
MCV 98.1fl

Blood film examination noted marked rouleaux formation:

Na 133 mmol/l
K 3.6 mmol/l
Creatinine 108 umol/l
Urea 6.8 mmol/l
Total protein 110g/l
Globulin 78g/l
Albumin 32 g/l
AST 58iu/L
ALP 56iu/L
Adj calcium 2.19 mmol/l

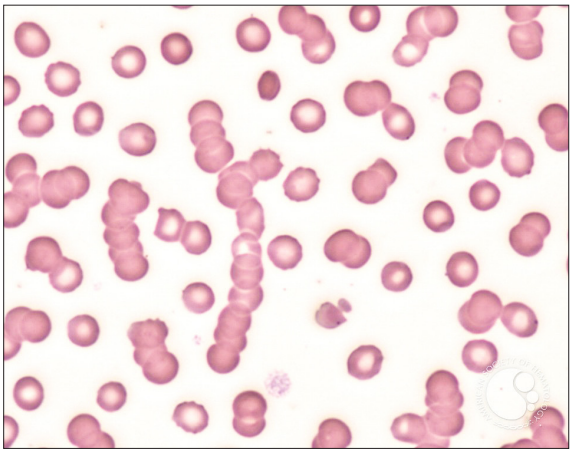


Figure 1: Marked Rouleaux formation (Red Cells stacked like coins) Source: ASH image bank.

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At this point JW was transfused 3 units of blood. Myeloma was suspected as the cause of her anaemia for two reasons: she had marked rouleaux formation on her blood film and she had a significantly elevated globulin level in the absence of acute illness.

As part of her work up for potential myeloma we performed a skeletal survey, immunoglobulins, Beta-2 Microglobulin, serum free light chains and a bone marrow aspiration and trephine.

The skeletal survey was negative for any lytic lesions.

The immunoglobulin results were as follows:

IgA 0.1g/l
IgM 0.08g/g
IgG lambda monoclone of 60.7 g/l
Marked immunoparesis
Beta-2 microglobulin 41mg/l
Lambda light chains 1490 mg/l
Kappa light chains 2.6mg/l
Kappa/lambda ratio <0.01 (0.26-1.65)

Bone marrow aspiration and trephine confirmed diagnosis with 66% plasma cells and 95% plasma cells respectively.

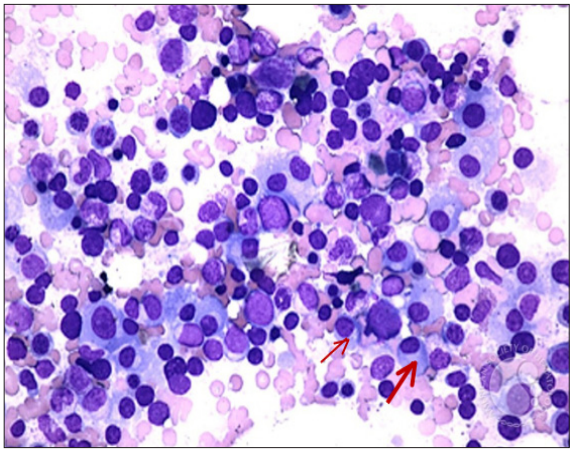

Figure 2: Bone marrow showing increased plasma cells. Note deeply basophilic (blue cytoplasm) and eccentric nucleus. Red arrow points to a typical plasma cell. Source: ASH image bank.

At this point she entered onto the Myeloma XI trial and was randomised to receive RCD (Lenalidomide, Cyclophosphamide, Dexamethasone oral chemotherapy) along with low molecular weight heparin as venous thromboembolism prophylaxis.

She received a full 2 cycles and was responding very well to treatment with a fall of her paraprotein from 60g to 4.4g. However one week into her third cycle of RCD she developed pain in her tongue and noted a blue tinge to the left hand side. Her tongue on examination was mildly inflamed and she was pyrexial. It was felt to be a potential infection therefore chemotherapy was stopped and she was commenced on oral antibiotics. 4 days later she represented with severe pain and discolouration to her tongue. On examination the left side of her tongue was frankly necrotic and malodorous.

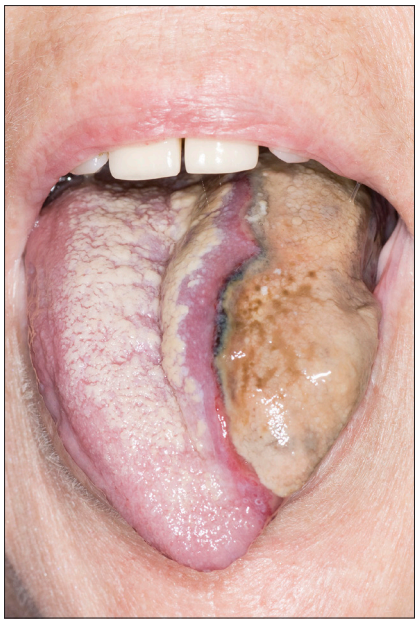

Figure 3: Tongue on presentation with well demarked area of necrosis.

She underwent MRA of her carotids and oropharynx which confirmed the necrosis of her tongue and potential lingual artery thrombosis.

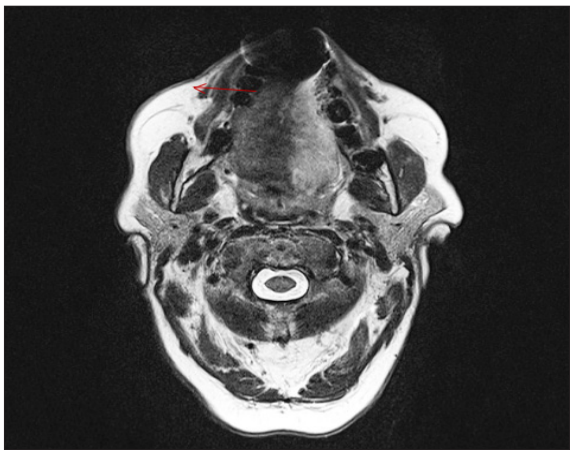

Figure 4: MRA of neck and head showing area of increased signal corresponding with necrosis (red arrow).

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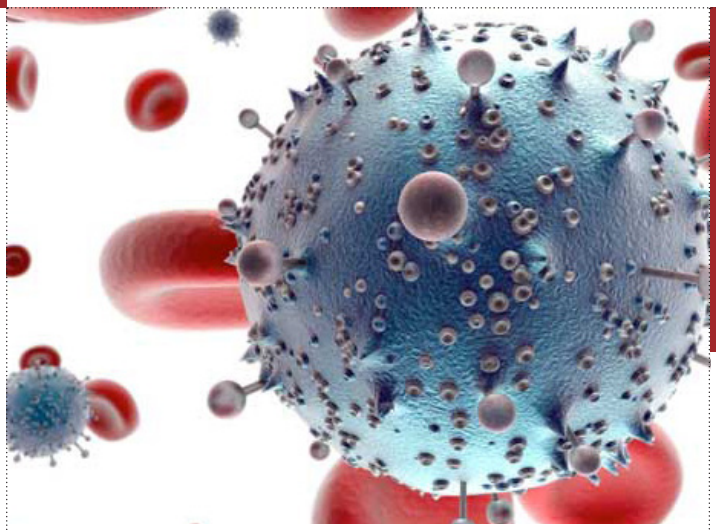

She was seen by the maxillofacial surgeons who took her to theatre for debridement. She was commenced on antibiotics and anticoagulation. Following this she recovered well and her tongue has been left with some minor taste defect over the area of necrosis. There has been some re-growth in the tongue.

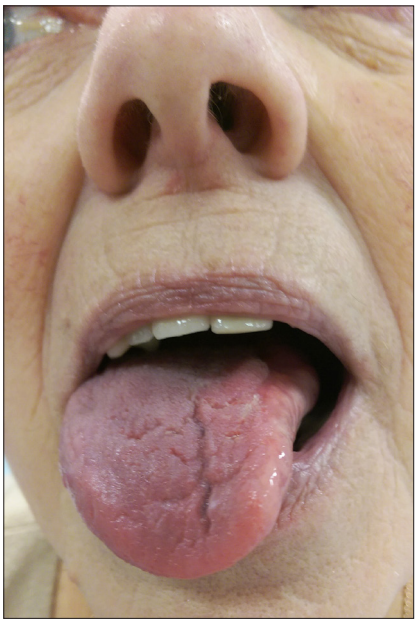

Figure 5: Tongue 1 year later with some regrowth on left.

As Lenalidomide is prothrombotic, this was discontinued and her therapy was changed to Bortezomib and dexamethasone. She responded well to this therapy and by the end of 6 cycles her paraprotein was undetectable on immunofixation- a VGPR (a very good partial response).

This remission followed up by an autologous stem cell transplant to try and prolong her remission for as long as possible.

She unfortunately has relapsesd 18 months out from transplant and has now been re-treated with Bortezomib and Dexamethasone to try regain remission. If successful she will go for a second autologous stem cell transplant to prolong the remission. It is probable that the second transplant will have a shorter remission than the first (18 months) which is typical of myeloma, which can make treatment decisions in situations like this difficult.

Discussion

Myeloma can present in many guises and to different specialities. From the orthopaedic team with pathological fractures due to lytic lesions, to the nephrologists with renal failure and the general medical take with anaemia or recurrent infections. Anaemia is present in 73% of patients at presentation and is the most common feature to be found. (2) This was the case in JW's story. Myeloma should be considered in all elderly patients with new anaemia or new back pain. I would also look to rule out myeloma in any elderly patient with a pathological fracture (and no known history of cancer) or new hypercalcaemia.

Initial investigation of myeloma

Although myeloma may not rank highly in your differential diagnosis of all new patients you meet with new anaemia, there are additional clues you can uncover to point you in its direction. Rouleaux formation on a blood film is a non-specific finding but is classical of myeloma and I would suggest requesting a blood film in any patient where you are unsure of the cause of anaemia. In JW's case the LFT results really set the ball rolling for us suspecting the diagnosis.

Often overlooked, a significantly raised globulin level can be indicative of a monoclonal immunoglobulin in the blood. Some centres do not routinely report globulin levels; the way around this is to calculate the "globulin gap". This is a simple calculation where you take away the albumin level from the total protein level, the difference between the two will be your globulin level. In the absence of acute inflammation/infection a raised globulin may be indicative of a monoclonal immunoglobulin.

MULTIPLE MYELOMA COMPLICATED BY THROMBOSIS

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Screening of suspected myeloma is relatively straight forward and an initial panel should include the following: FBC,U+E, LFT, Calcium, Immunoglobulins, Urinary Bence Jones Protein (BJP) and x-ray of any areas of unusual bony pain (3).

Interpretation of immunoglobulin results

Multiple Myeloma arises from a neoplastic clonal proliferation of plasma cells in the bone marrow. Plasma cells are terminally differentiated B lymphocytes and each individual plasma cell is committed to producing one specific antibody in one specific antibody class (IgG, IgM, IgA,IgD). Once committed, they cannot change antibody class. This is an important concept to understand and this helps understand how to interpret blood immunoglobulin levels. Clonal expansion of a single plasma cell will normally result in an increase in a specific antibody class (most commonly IgG) and this is the monoclonal immunoglobulin you find in the blood which is typical of myeloma. This is different to a polyclonal (for example the IgG level is raised but they are all distinctly different) increase in immunoglobulins which you would expect in an acute illness or infection.

In most centres, the blood and urine is initially screened for monoclonal immunoglobulins via electrophoresis. The serum is placed in a gel and a current is placed across it (top to bottom of the gel) and the different sized proteins migrate different distances according to their charge and size. This gives you several "bands" of protein which can be identified when compared to a known control. The immunoglobulins are normally found in the gamma region.

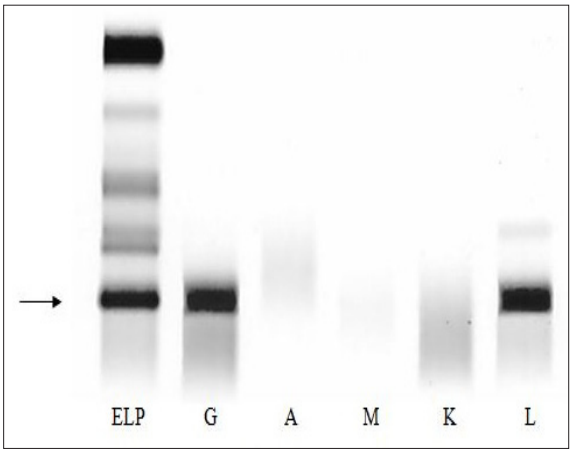


Figure 6: First strip is screening electrophoresis which has found an abnormal band in the Gamma region. The next strips are immunofixation to identify the type of monoclonal immunoglobulin (G=IgG, A=IgA, M=IgM, K=kappa, L=lambda). In this case there is an IgG lambda monoclone present.

In figure 6 you can see the screening electrophoresis on the left hand side (ELP). The first band at the top is Albumin, the next bands are: Alpha 1, Alpha 2, Beta and then Gamma at the bottom. You can see a solid band at the bottom where normally there would be a diffuse area which is the gamma region. This is an abnormal monoclonal band. Further investigation by immunofixation can be seen then from left to right.

The band above the "G" signifies this is an IgG and the band above the "L" makes this a lambda subtype. Therefore the result is an IgG Lambda monoclone. Interpretation of these results can be difficult and even experienced clinicians can get it wrong. The key here is the presence of a monoclonal immunoglobulin and potentially immunoparesis (all the other Immunoglobulins are reduced or absent). In JW's case there was an IgG monoclone and immunoparesis. This is very typical of myeloma and IgG is the most common form. Remember a polyclonal increase in any of the immunoglobulins is not myeloma or MGUS and is physiologically normal in any acute illness.

Further investigations and when to treat

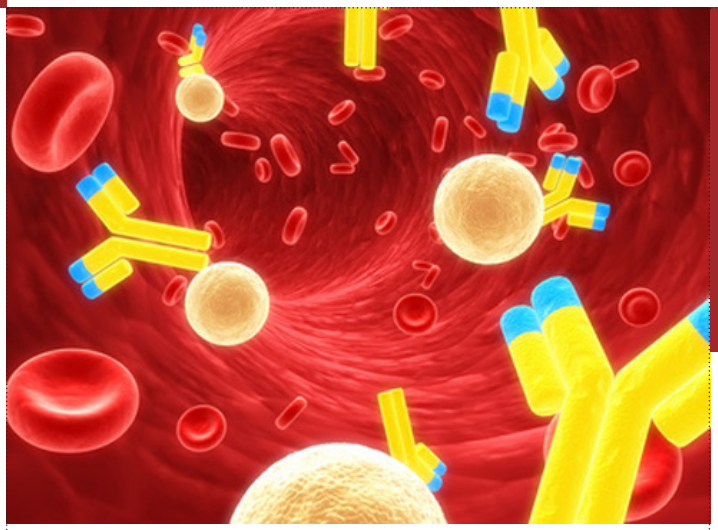
JW also had serum free light chains measured, this was not actually necessary as she had a clear monoclone on immunofixation (3). Serum free light chain measurement is useful in patients where you strongly suspect myeloma (for example anaemia and lytic lesions) but there is no monoclone to be found in the blood; this occurs in around 1-5% of myeloma and is known as "Non-secretory" Myeloma (6).

The final diagnosis of myeloma depends on the bone marrow aspirate. Here we quantify the number of plasma cells in the bone marrow. A bone marrow aspirate finding of >10% plasma cells is diagnostic of myeloma. The presence of a monoclonal immunoglobulin and <10% plasma cells in the bone marrow and no symptoms of myeloma is diagnostic of MGUS (monoclonal gammopathy of uncertain significance). This is a common finding in elderly patients with a yearly rate of transformation to myeloma of 1%.

Once myeloma is confirmed, treatment is reserved for those with symptomatic myeloma, which is those meeting one of the CRAB symptoms (Hypercalcaemia, Renal failure, Anaemia, Lytic lesions of the bone). If no symptoms are present, the patient is kept under short follow up and observed until treatment is required. This is known as asymptomatic myeloma (classically known as smouldering myeloma).

MULTIPLE MYELOMA COMPLICATED BY THROMBOSIS

G Errico & N Morley



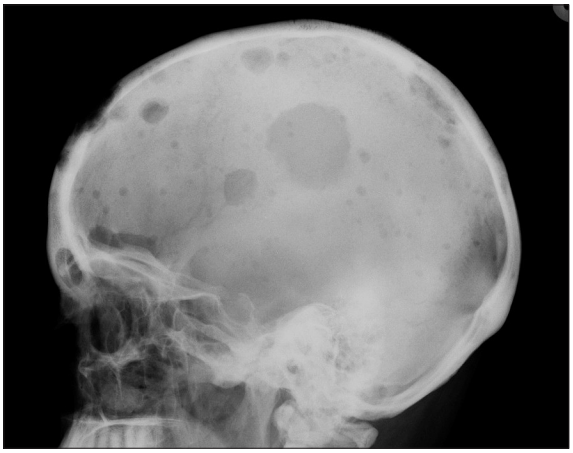


Figure 7: Evidence of lytic lesions on skull x-ray as part of skeletal survey.

In the case of JW, her myeloma was classed as symptomatic on the basis of anaemia. Treatment usually involves oral chemotherapy with consolidation with an autologous stem cell transplant if the patient is fit enough. The transplants used in myeloma are autologous and the patient receives back their own stem cells back which were harvested whilst in remission. This allows us to give patients a dose of chemotherapy so toxic their bone marrow will never recover and we essentially "rescue" them from this with their own stem cells. Though not curative, this treatment can give patients prolonged remissions of several years in length.

Thrombosis in myeloma

Venous thromboembolism (VTE) is a common complication in all malignancies. The risk of VTE is raised 28 fold in those with cancer compared to those without (4). This is also the case in myeloma. Myeloma is particularly thrombogenic for 3 reasons: it is a cancer, it can produce an abnormal protein which is thrombogenic and the drugs used to treat are often thrombogenic.

Thalidomide which is commonly used to treat myeloma and it's structurally similar cousin Lenalidomide, both significantly increase the risk of thrombosis on top of the risk of myeloma (5).

JW's thrombosis was very obvious at presentation, however this is not always the case and you should always be vigilant to thrombosis in patients with malignancy of any type. If PE/DVT is suspected, bypass the D-Dimer test (not relevant in malignancy) and image the suspected site with either a CTPA or ultrasound dopplers of the leg.

VTE is a common complication of any cancer as discussed previously. The type and length of anticoagulation in these patients can be difficult to decide on. On a whole warfarin is much less desirable in patients with cancer. Often it is difficult to control the INR (especially when on chemotherapy) and cancer patients seem much more prone to complications whilst on warfarin (7). Furthermore low molecular weight heparin has been shown to be more effective than warfarin at preventing further VTE in cancer (7).

For these reasons, the steady level of anticoagulation that therapeutic dose low molecular weight heparin can provide is preferred over warfarin. Generally speaking, once a patient has had a VTE and has an active cancer diagnosis, continuous anticoagulation is recommended until the patient is clear of cancer or coming to their end of life. Decisions around anticoagulation in cancer at this stage can be difficult and the emphasis is on good communication with the patient and family when making these decisions.

Conclusion

Myeloma can present in a variety ways and always be suspicious in elderly patients with new anaemia, pathological fractures or hypercalcaemia. The initial investigations are straight forward to organise and should be done promptly when myeloma is suspected. Immunoglobulin interpretation may seem daunting, but the key is to look for a monoclonal immunoglobulin and immune paresis. If in doubt, your local haematology specialist should be happy to advise. VTE is a common complication in malignancies but especially in patients undergoing treatment of Myeloma. Be vigilant and investigate with either ultrasound Doppler or CTPA any patient with malignancy you suspect has VTE.

MULTIPLE MYELOMA COMPLICATED BY THROMBOSIS

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Multiple choice questions

1. An initial screen of a patient with suspected Myeloma would include which combination of the following tests?

a) FBC,UE,Calcium,immunoglobulins, urinary BJP, bone scan

b) FBC,UE,Calcium, Immunoglobulins,urinary BJP, skeletal survey

c) FBC,LFT,Calcium, serum free light chains, urinary BJP, skeletal survey

d) FBC,UE,Calcium, Immunoglobulins,bone marrow aspiration/trephine

e) FBC, UE,Calcium,Immunoglobulins,urinary BJP, PET scan

2. Multiple myeloma is most likely with which of the following set of immunoglobulin results:

a) IgG 11g/l IgM 1.2g/l, IgA 3g/l- a polyclonal increase in IgG

b) IgG 15g/l IgM2.3 g/l IgA 1.2g/l- IgG kappa monoclone found

c) IgG 18g/l IgM 0.3g/l IgA 0.5g/l- IgG kappa monoclone found and immunoparesis

d) IgG 2.3g/l IgM 1.3g/l IgA 0.6 g/l- No monoclonal band but mild immunoparesis

e) IgG 3.4g/l IgM 2g/l IgA 2.3 g/l

Answers

1. Answer: B

An initial screen of any patient you suspect myeloma in would include FBC,UE,Calcium,Immunoglobulins, Urinary BJP and a skeletal survey.

2. Answer: C-

The finding of a monoclonal IgG antibody and immunoparesis would make C the most likely to have a diagnosis of myeloma. B also found a monoclone however there was no immunoparesis which makes myeloma a possibility but not as likely as C. B would go on to have the rest of the myeloma screen and if no evidence of myeloma complications are found, a diagnosis of MGUS can be made. Answer A would be consistent with an acute infection/ inflammatory process and not Myeloma.

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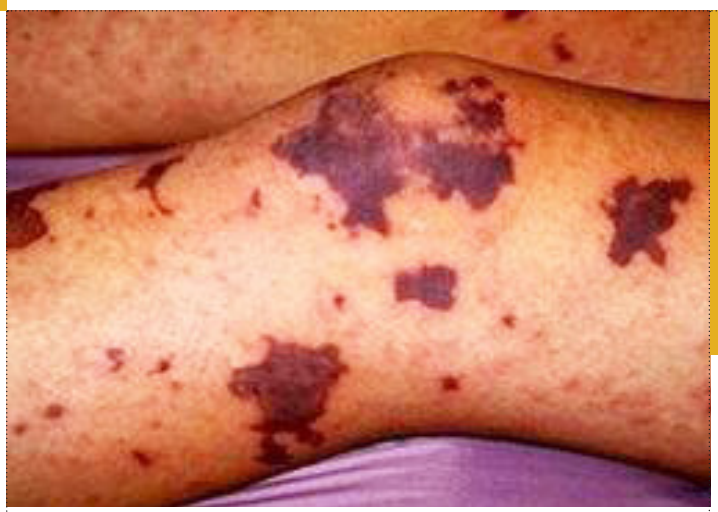
REVIEW ARTICLE: THROMBOCYTOPENIA IN HOSPITALISED ADULTS

D Taylor, R Al-Rubae & D Galvani



Abstract

Thrombocytopenia is defined as a platelet count of less than 150x10^9/L. 1It has an incidence of approximately 1% amongst hospitalised adults. Thrombocytopenia presents many challenges in identifying a cause and correctly assessing when urgent intervention is required. The causes of thrombocytopenia are numerous and highly heterogeneous; from anomalous results and simple ailments, to immediately life-threatening pathology. Pregnancy related thrombocytopenia is commonly encountered, but is beyond the scope of this review and will not be discussed.

Significantly thrombocytopenic patients are at risk of provoked and spontaneous haemorrhage. These patients must be identified promptly and swift actions taken to reduce mortality and morbidity. Thrombocytopenia also has the potential to delay surgical procedures and disrupt theatre timetables. A sound understanding of the causes and initial management of thrombocytopenic patients is therefore a key tool in any foundation doctor's arsenal.

Platelets

Platelets are produced in the bone marrow by megakaryocytes. (1) Platelet production is primarily regulated by the haemopoetic growth factor thrombopoietin (TPO) which is produced by the liver. (2) Following production platelets are released into the blood where they circulate for 8 to 10 days. One third of the body's platelet stores are sequestered in the spleen. (3)

Platelets primary function is in haemostasis. Platelets adhere to the site of vascular injury via interactions with von Willebrand factor. Aggregation of platelets then occurs via interactions with fibrinogen. Platelets are finally activated, prompting the release of coagulation factors from granules stored within the platelet itself.

Review article: thrombocytopenia In hospitalised adults
Good Clinical Care

Platelets involved in haemostasis are committed and ultimately removed from the circulation. Those platelets that remain circulate until they are phagocytised by macrophages.

Thrombocytopenia can, therefore, be divided into issues of decreased production; increased consumption and pseudothrombocytopenia. Basic knowledge of the platelet lifecycle can guide the assessment of a thrombocytopenic patient.

Initial approach

Full blood count and working with colleagues in the laboratory: The remainder of the full blood count (FBC) should be examined. A blood film will often be completed where platelet counts are less than 100x10^9/L. (4) Platelet agglutination can occur in vitro in standard blood bottles. Automated blood analysers that depend on viewing individual cells to produce blood counts will not recognise these clumps as platelets, giving rise to pseudothrombocytopenia. Platelet clumping is easily viewed on a blood film and suggests a satisfactory count. No further investigation is required.

All aspects of the blood should be morphologically examined. In genuine thrombocytopenia, the blood film often gives specific clues as to the underlying pathology, including red blood cell fragmentation or the presence of precursor cells including blasts (suggestive of bone marrow infiltration). These will be discussed throughout the review. Close liaison with colleagues in the laboratory is therefore vital.

Patient assessment

A thorough history is invaluable, often revealing potential causes for the thrombocytopenia. The significance of the thrombocytopenia and effect on the patient can also be assessed.

It is important to ascertain whether the patient is symptomatic. Thrombocytopenia is associated with mucosal haemorrhage; prolonged haemorrhage following trauma and spontaneous skin purpura. Women of reproductive age often complain of menorrhagia. (5) Spontaneous bleeding is uncommon unless the platelet count is <10-20 x 10^9/L. Joint and soft tissue bleeding is unusual and is suggestive of a coagulation factor disorder, including disseminated intravascular coagulation (DIC).

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Past Medical History (6):

Conditions commonly associated with thrombocytopenia are listed in table 1. Liver disease results in reduced production of TPO, as well as increased sequestration of platelets due to splenomegaly.

It is rare for primary bone marrow disorders to cause isolated thrombocytopenia in adults. The exception is myelodysplasia that can result in megakaryocyte abnormalities. Myelodysplasia is a disease of the elderly (although not exclusively). Therefore, (7) patients with thrombocytopenia of unknown cause over the age of 60 years should be considered for a bone marrow examination.

[6]Table 1: Conditions commonly associated with thrombocytopenia
Reduced platelet production
Bone marrow failure - aplastic anaemia - leukaemia - myelodysplastic syndrome - myelofibrosis - multiple myeloma - marrow infiltration (including by solid tumours) - megaloblastic anaemia relating to B12 and/or folate deficiency Human immunodeficiency virus (HIV) Liver disease Drugs or toxins Radiotherapy
Increased sequestration of platelets
Splenomegaly of any cause
Increased consumption of platelets
Immune causes - Immune thrombocytopenia (ITP) - Drug induced ITP - Systemic lupus erythematosus - Rheumatoid arthritis Infection - HIV infection - Viral hepatitis - Recent viral infection - Malaria - Severe bacterial sepsis - H. pylori Disseminated intravascular coagulation (DIC) Thrombotic thrombocytopenic purpura (TTP) Haemolytic uraemic syndrome (HUS)

Table 1

Drug and Toxin History:

Medications are one of the commonest culprits in thrombocytopenia. (6) Commonly implicated drugs and toxins associated with thrombocytopenia are listed in table 2. This list is not exhaustive. (8) The use of complimentary and herbal remedies should also be explored. Decisions on whether to discontinue potentially causative medications will depend on the severity of the thrombocytopenia, the patient's symptoms and the necessity of the implicated drug.

Excess alcohol consumption results in direct bone marrow toxicity and therefore thrombocytopenia. Other FBC abnormalities are often present, particularly macrocytosis.

[6]Table 2: Commonly implicated drugs and toxins associated with thrombocytopenia
Reduced platelet production / Bone marrow suppression.
Dose related - Radiotherapy - Cytotoxic drugs - Ethanol Rare - Chloramphenicol - Co-trimoxazole - Penicillamine - Benzene
Increased platelet consumption / Immune related
Analgesia: NSAIDs Anticonvulsants: Sodium valproate, diazepam, carbamazepine Antimicrobials: Penicillin, sulphonamides, trimethoprim Diuretics: Furosemide Misc: Quinine sulphate, heparin (see section), vaccinations.

Table 2

Infection: (9)

Recent viral infection is one of the leading causes of thrombocytopenia. Low platelet counts have been observed following influenza or MMR vaccinations. HIV and viral hepatitis are both associated with thrombocytopenia; as are the agents used to treat them.

It is unusual for bacterial infection to cause thrombocytopenia unless associated with septicaemia. (10) The exception is Helicobacter pylori which is associated with immune thrombocytopenia. Eradication therapy improves the platelet count in 63% of those affected.

(11) Malaria (particularly P. falciparum and P. vivax) is an important cause of thrombocytopenia and often suggests severe infection. Malaria should be sort in thrombocytopenic patients with recent travel to malarious areas.

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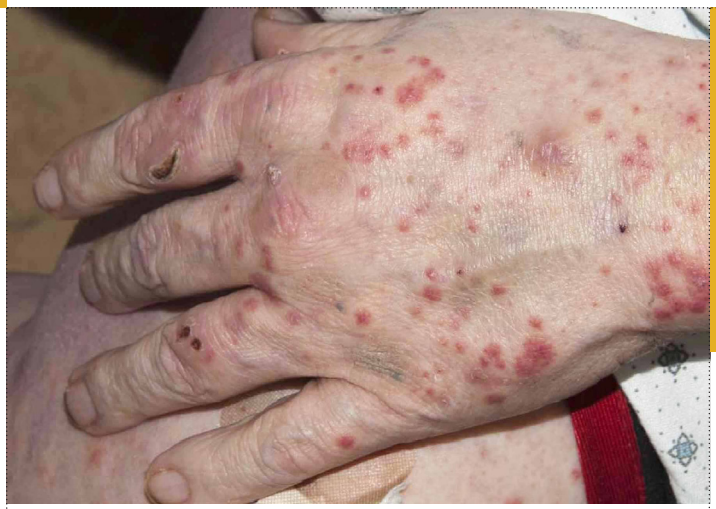

Conditions that merit special mention

Heparin Induced Thrombocytopenia (HIT):

HIT is a potentially life-threatening complication of heparin administration involving the development of IgG antibodies against heparin: platelet complexes. (6) This results in platelet activation and thrombosis which in turn leads to thrombocytopenia. In spite of moderate/severe thrombocytopenia the patient is infact prothrombotic and at significant risk of thrombosis. HIT should be suspected in any patient on heparin experiencing a decrease in platelet count of ≥50%. Clinical manifestations include arterial or venous thrombosis, systemic reactions following heparin infusion and skin necrosis. Because the condition is IgG mediated the effect does not become apparent for 5-10 days.

HIT occurs in 5% of patients on unfractionated heparin but is less common with the use of low molecular weight heparin. (12) All patients with suspected HIT should be screened using the '4Ts Score' (see table 3). If this suggests that the patient is intermediate or high risk of having HIT, heparin should be discontinued immediately and alternative therapeutic anticoagulation commenced (excluding warfarin) whilst laboratory investigation is undertaken.

[12]Table 3: The 4Ts Scoring System

	Points (0, 1, 2; maximum score = 8)		
	0	1	2
Thrombocytopenia	>50% fall; and platelet nadir ≥20x10⁹/L	30-50% fall; platelet nadir 10-19x10⁹/L	<30% fall; or platelet nadir <10x10⁹/L
Timing of platelet fall	Clear onset between 5-10 days; or ≤1 day if received heparin in last 30 days	Timing unclear; >10 days; ≤1 day if received heparin in last 30-100 days	<4 days, without recent heparin exposure
Thrombosis	New thrombosis; Skin necrosis; Post heparin bolus acute systemic reaction	Progressive or recurrent thrombosis; Erythematous skin lesions; Thrombosis not yet proven	None
OTher causes	No other cause is evident for platelet count fall	Other causes are possibly evident	Definite other cause is evident
Score 0-3 = low; 4-5 = intermediate; 6-8 = high			

Table 3

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In hospitalised adults
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DIC:

DIC describes inappropriate amplified activation of the clotting cascade which results in mass consumption of platelets and widespread deposition of fibrin. There is microvascular thrombosis, organ failure and bleeding. DIC is always related to an underlying pathology including severe sepsis, trauma, organ destruction (pancreatitis), malignancy or obstetric causes amongst others. Identification and prompt treatment of the cause is vital.

There is no single test to diagnose DIC. Instead a range of clinical and laboratory investigations can reveal the diagnosis. Thrombocytopenia is the most commonly encountered abnormality. Coagulation studies are often deranged. DIC is a dynamic situation. Therefore if DIC is suspected frequent clinical and laboratory monitoring of the patient is vital.

Thrombotic Thrombocytopenic Purpura (TTP):

(13) TTP is a rare blood condition characterised an absence of protein ADAMTS (13) which is responsible for cleaving von Willebrand Factor (vWF) into smaller, less active multimers. In TTP, large highly active VWF multimers circulate freely in the blood causing platelet aggregation, microvascular thrombi and red blood cell shearing. (13)

This gives rise to a classic diagnostic pentad of thrombocytopenia, haemolytic anaemia, neurological signs, renal failure and fever. Not all signs are present. TTP is most commonly idiopathic. It has an incidence of 6 per million. Early recognition is vital. Left untreated the condition has a mortality rate of 90%. The blood film demonstrates red blood cell fragmentation and thrombocytopenia. It is the most useful test in making the diagnosis. Unlike DIC, coagulation studies are often normal.

Specialist input from haematology should be sort immediately.

Immune Thrombocytopenia (ITP):

(5) ITP is the most common cause of isolated thrombocytopenia. It is an idiopathic condition and is a diagnosis of exclusion. (7) ITP is an immune mediated condition whereby platelets are inappropriately removed from the circulation by the immune system. The pathophysiology remains controversial but is thought to involve antibody and T cell mechanisms.

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ITP is more common in young women and those with autoimmune conditions, but can occur in males and at any age. The course of ITP varies from single episodes (more common in children and young adults) to relapsing : remitting disease to chronic thrombocytopenia. Treatment involves immunomodulation with steroids and other agents.

If ITP is associated with haemorrhage, anaemia may also be present. Asides from this, if there are any other FBC abnormalities alternative diagnoses should be considered.

Diagnostic investigation

Following a thorough history and focused examination, patients should be appropriately investigated. Investigations to be considered are listed in table 4. Where the cause is unclear, advice from a haematologist should be sort. If the patient is bleeding this should be done as a matter of urgency.

Table 4: Investigations that should be considered in thrombocytopenic patients
First line investigations
FBC Blood film Liver function tests Coagulation studies – deranged in DIC LDH – elevated in DIC, TTP and HUS Immunoglobulins and serum electrophoresis CRP HIV and Hepatitis serology B12 and serum folate
Additional investigations
H pylori screening Autoantibody screening Abdominal ultrasound scan Bone marrow examination Thick and thin blood films – if patient has travelled to a malarious area

Table 4

What to do

Management of a patient with thrombocytopenia will depend on the clinical circumstances and whether there is haemorrhage. Patients with platelet counts of >50 x10^9/L are at low risk of haemorrhage and can usually be investigated in an outpatient setting. If no apparent cause is found for the thrombocytopenia and the patient is well, referral to the haematology clinic may be the most appropriate action.

In patients with haemorrhage and / or severe thrombocytopenia (<50 x 10^9/L) more immediate investigation and management should be instigated. If the clinical history and initial investigations point to a diagnosis, this should be addressed in a bid to improve the platelet count. This may not be necessary in some situations however. Drug induced thrombocytopenia for example could be tolerated if the thrombocytopenia is mild and drug is essential e.g. antiepileptics.

Safe levels of thrombocytopenia:

(14) Recommendations for safe platelets levels in non-haemorrhagic patients.

- Evidence supports maintaining levels at >10 x 10^9/L. Below this level spontaneous haemorrhage, including intracranial haemorrhage, becomes more common. Thrombocytopenia of this severity is most commonly encountered on oncology or haematology units in patients with bone marrow failure secondary to chemotherapy use. Elective platelet transfusion to maintain counts above 10 x 10^9/L is a widely accepted practice.

- Sepsis increases platelet consumption. Maintaining platelets above 20 x 10^9/L in patients with severe sepsis is also widely practiced.

- In haemorrhagic patients, platelets should be given to keep the platelet count in excess of 50 x 10^9/L. This includes major trauma and massive transfusion.

Platelet consumption is increased during surgery. It is therefore pertinent to have knowledge of the pathology causing the thrombocytopenia prior to embarking on surgical intervention or invasive procedures.

Recommendations for safe platelet levels to undertake certain procedures (14):

- Lumbar puncture, epidural anaesthesia, gastroscopy and biopsy, laparotomy or similar procedures; the platelet count should be at least 50 x 10^9/L.

- Operations involving critical sites including the brain and eyes; platelets should be at least 100 x 10^9/L.

Where platelet levels do not meet the recommended safe standard, consideration should be given as to whether the procedure should go ahead with treatment of the thrombocytopenia; or be postponed. In the case of postponement, this should be communicated with theatre staff and necessary clinicians at the nearest opportunity to avoid disruption.

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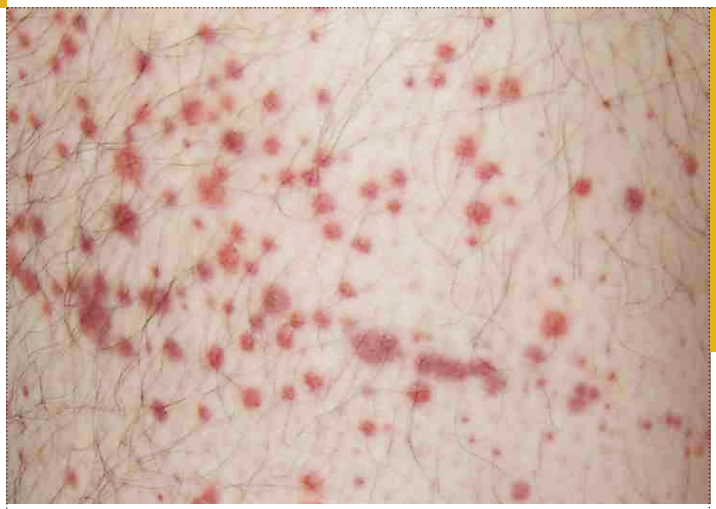

Platelet Transfusion:

Transfusion of platelets should be considered as per the indications outlined above. Platelets are given intravenously over 30 minutes. 15One unit of platelets will, on average, increase the platelet count by 25 x 10^9/L. A single adult dose of platelets will therefore often suffice in bringing the platelet count to satisfactory levels in most settings. Platelet increments may be muted where consumption is increased, including in sepsis, fever, splenomegaly and haemorrhage.

Platelets must be given within 5 days of collection from the donor. Hospitals therefore keep only minimum doses of platelets as stock, if at all. Close and prompt communication with the transfusion laboratory is encouraged to allow timely transfer of platelets from offsite locations.

Platelet transfusion is not recommended in some settings. ITP results in the rapid clearance of transfused platelets. As mentioned, treatment of ITP involves immunomodulation to reduce platelet consumption by immune processes. Platelet transfusion can be used in dire circumstances in a bid to control haemorrhage. Multiple doses are often required. Platelet transfusion is relatively contraindicated in DIC and TTP unless there is significant haemorrhage.

Tranexamic Acid (TXA):

Fibrin dissolution can be reduced by the oral, topical or intravenous administration of TXA, which inhibits fibrinolysis. It is a useful agent in reducing bleeding symptoms in thrombocytopenic patients. It is contraindicated in haematuria, thromboembolic disease, DIC and in patients with epilepsy. It can be used in pregnancy.

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Anticoagulation:

Many patients with thrombocytopenia will have co-morbidities that require them to be anticoagulated at either prophylactic or therapeutic doses. This includes the use anticoagulants or antiplatelet agents. Anticoagulation confers a risk of haemorrhage which is exacerbated in patients with severe thrombocytopenia. Very few randomised controlled trials have been undertaken in this field. Guidelines are therefore largely based on retrospective data and general opinion. Each case must be assessed on an individual patient basis following consideration of the risks and benefits to the patient.

It is widely accepted that prophylactic anticoagulation is acceptable provided the platelet count is >50 x 10^9/l. 16Some European studies suggest that this threshold could be lowered to 30 x 10^9/L. This is worth considering in patients at high risk of venous thromboembolism. Advice from haematology should be sort. Therapeutic anticoagulation can also be continued or commencing provided the platelet count is in excess of 50 x 10^9/L.

It is also accepted that antiplatelet therapy can continue in thrombocytopenia, provided the platelet count is >50 x 10^9/L. Patients with thrombocytopenia of 50-100 x 10^9/L with ischaemic heart disease had a higher incidence of mortality when antiplatelet therapy was omitted, compared to those cases where it was commenced/continued. This clearly supports the use of antiplatelet therapy in such cases. (17) Again, some guidelines would support the use of antiplatelets with a minimum platelet count of 30 x 10^9/L. This should only be considered on an individual patient basis.

Conclusion

Thrombocytopenia is a common finding amongst hospitalised patients and can relate to many potential pathologies. The initial approach to determining the cause should involve a detailed history; review of the patient's medical conditions; drug history and clinical examination. Examination of a blood film often provides key information. Foundation doctors should therefore be encouraged to liaise closely with colleagues in the haematology laboratories about thrombocytopenic patients.

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Prompt identification of the cause will allow foundation doctors to take timely action to improve the patients platelet count and in some instances reduce morbidity and mortality (particularly in relation to TTP, DIC and HIT).

It is recognised that in many cases no cause is apparent for the patient's thrombocytopenia. In these instances, and in cases of serious underlying pathology, foundation doctors should be confident to consult senior colleagues in haematology to discuss the case in more detail.

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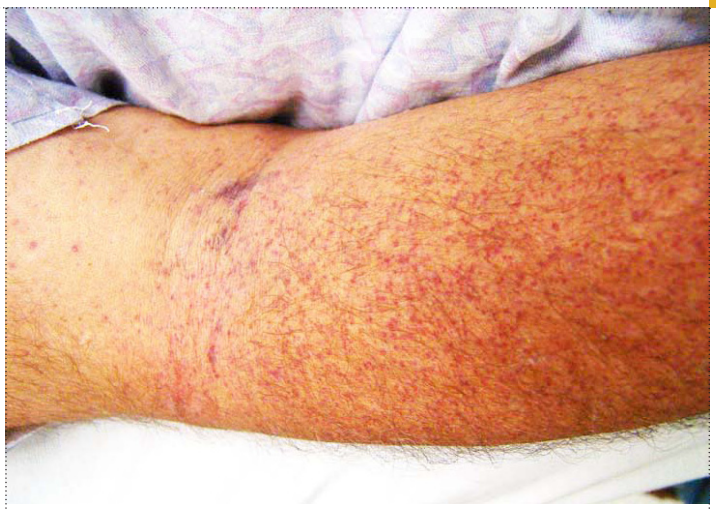

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Financial statement
The authors of this article have not been paid. The Foundation Years Journal is financed by subscriptions and advertising. The Journal does not receive money from any other sources. The decision to accept or refuse this article for publication was free from financial considerations and was solely the responsibility of the Editorial Panel and Editor-in-Chief.

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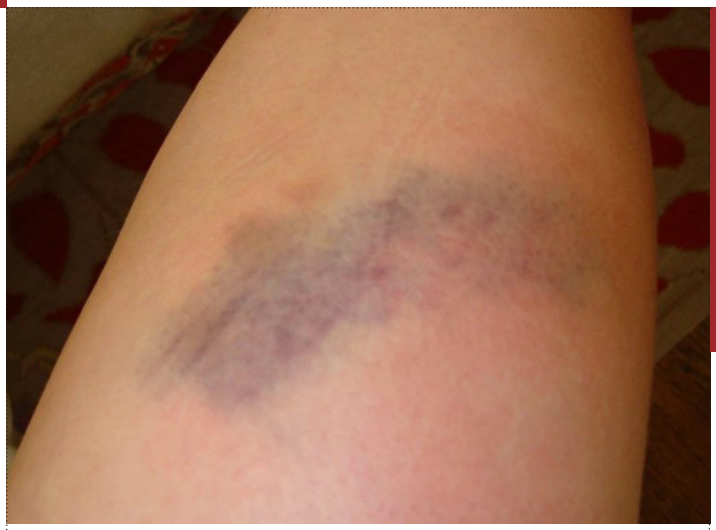
A CASE OF EASY BRUISING

B Myers & A Dillon



Abstract

We discuss the case of a 67 year old lady who presented with spontaneous bleeding and headache. Initial blood tests demonstrated a pancytopenia and deranged clotting tests. The blood film confirmed pancytopenia and demonstrated myeloid blasts with concerning features for acute promyleocytic leukaemia (APML). An urgent CT demonstrated acute intracranial haemorrhage. She was managed with aggressive blood product support and neurosurgical intervention.

She was immediately commenced on all-trans-retinoic acid and subsequently chemotherapy to treat the leukaemia. The diagnosis was subsequently confirmed on bone marrow molecular studies. She is currently in remission from her leukaemia and has no neurological sequelae. We discuss an approach to the assessment of patients with spontaneous bruising and a summary of the pathophysiology and management of patients with APML.

Case history

A 67 year old lady attended the Emergency Department with a several days' history of general malaise, fatigue and a 24 hour history of spontaneous bruising. She described a severe headache associated with significant nausea. She had no personal or family history of bleeding disorders. She had a background history of well managed hypertension, and was on no anti-coagulant medications.

On clinical examination, she had a widespread petechial rash and ecchymoses overlying the abdomen. Neurological examination did not demonstrate any focal neurology and GCS was 15. She was haemodynamically stable and afebrile. There was no gum bleeding or swelling and no clinical evidence of bleeding from elsewhere. Fundoscopy did not demonstrate retinal haemorrhage.

A case of easy bruising
Patient Management

How to assess the patient with easy bruising/spontaneous bleeding

Current bleeding symptoms

Determine the severity and site of the bleeding: is there any evidence of life threatening bleeding such as significant gastro-intestinal haemorrhage or intracranial haemorrhage.

Personal history

Establish a personal bleeding history; this can be done using a standardized bleeding score such as the ISTH Bleeding assessment tool (1), which tries to quantify the presence and severity of bleeding symptoms for example assessing the patient's response to previous haemostatic challenges such as surgery or dental extraction. Using the bleeding score will clarify if the bleeding is confined to one site (such as menorrhagia with fibroids), or if the symptoms indicate a global problem with haemostasis. It will establish whether the bleeding history is recent or longstanding.

Family history

Determine any family history of a known bleeding disorder, or of a significant bleeding history.

Medications

- *Establish whether the patient is on and anticoagulant or antiplatelet drugs.*

- *Establish whether the patient has commenced on any new medications which could cause thrombocytopenia such as quinine or heparin (heparin induced thrombocytopenia).*

Review of symptoms

- *Rarely, spontaneous bleeding or bruising may be a sign of a more severe underlying haematological disorder such as acute leukaemia or lymphoma. A thorough review of symptoms for evidence of B symptoms and detailed clinical examination will help to identify these patients.*

A CASE OF EASY BRUISING

B Myers & A Dillon

Intital blood tests

Full blood count
Haemoglobin: 11g/l l
Platelet count: 32 × 10^9 /l
White Cell Count: 67 10^9/l

Coagulation screen
Prothrombin Time 16.8 seconds (11-13)
Activated Partial Thromboplastin

Time
32 seconds (28-38), Fibrinogen 0.7 g/L (1.5-4.5).

The bloods demonstrated a significant anaemia and thrombocytopenia with elevated white cell count. This is concerning for an acute leukaemia, as the raised white cell count can represent abnormal blast cells rather than normal leucocytes.

The differential for pancytopenia is wide an can range from acute infection, to consequence of drug therapy but marked cytopenias alongside a high white cell count raise concerns about acute leukaemia.

Coagulopathy and associated haemorrhage is a life threatening complication of acute leukaemia and a coagulation screen and fibrinogen should always be sought as soon as the diagnosis of leukaemia is suspected. The patient's coagulation screen was consistent with disseminated intravascular coagulopathy or hyperfibrinolysis. This is often seen in conjunction with a subtype of acute myeloid leukaemia called acute promyelocytic leukaemia (APML).

Further investigations

Blood film
A blood film or blood smear is simply an aliquot of the full blood count sample thinly spread across a slide and stained to allow direct examination of the different blood cells. This is essential in pancytopenic patients or patients with a raised white cell count to confirm the pancytopenia and establish the appearance or morphology of the raised white cells. When leukaemic or blast cells are demonstrated their appearance may help to differentiate between a myeloid or lymphoid leukaemia.

Bone marrow
The bone marrow aspirate examination will allow more detailed information on the cellularity of the bone marrow and the appearance of the blast cells, confirming the diagnosis of acute leukaemia and giving further detail on the type of acute leukaemia. It is performed by aspirating a small sample of liquid bone marrow under local anaesthetic via a bone marrow needle usually from the posterior iliac crest.

The aspirated material is then spread onto a slide, stained and the cells can be directly examined. The bone marrow aspirate samples are also sent for further diagnostic testing such as immunophenotyping, cytogenetic and molecular studies. Immunophenotyping is a technique which categorizes different cells according to the antigens they display on their surface. Thus subgroups of cells can be identified according to particular 'antigen panels'. The immunophenotyping and molecular studies allow confirmation of the subtype of leukaemia in cases where the morphology is indistinct and increasingly, gives a prognostic risk profile for the leukaemia.

Results

The patient's blood film and subsequent bone marrow aspirate demonstrated the classical morphology of APML with hypergranular myeloid blasts with clefted nuclei and Auer rods within the cytoplasm. The diagnosis was confirmed with a classical immunophenotyping profile of the bone marrow blast cells and molecular identification of the fusion gene PML-RARA.

An urgent CT was arranged due to the patient's headache. Unfortunately, this showed a left subdural haematoma and associated midline shift.

European leukaemia net guidelines

Once a diagnosis of APL is suspected, the disease should be managed as a medical emergency.

Diagnosis should be confirmed by molecular detection of PML-RARA fusion (or rare molecular variants).

In addition to conventional karyotyping, FISH, and RT-PCR, immunostaining with anti-PML antibody can be used for rapid diagnosis of APL. (2)

Management

Aggressive blood product support is critical in APML as the patients are at risk of life threatening haemorrhage. (3) The patient was transfused with platelets with a target platelet count of 80-100 due to her intracranial bleed, cryoprecipitate to a target fibrinogen of 2 and fresh frozen plasma to keep her PT /APTT within normal limits.

ATRA treatment was commenced as soon as the diagnosis was suspected.

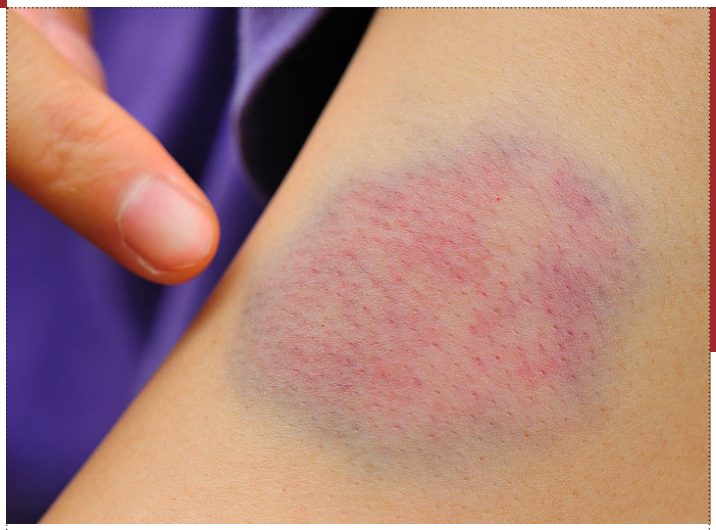
European leukaemia net guidelines

Treatment with ATRA should be started immediately that a diagnosis of APL is suspected.

Liberally transfuse with fresh frozen plasma, fibrinogen, and/or cryoprecipitate and platelet transfusions to maintain the fibrinogen concentration and platelet count above 100-150 mg/dL and 30-50 x 10^9/L, respectively. (2)

A CASE OF EASY BRUISING

B Myers & A Dillon



Blood products

Platelet transfusions

Are given when there is a quantitative platelet problem or a qualitative problem such aspirin use and significant haemorrhage. Prophylactic platelet transfusions are used in patients with haematological malignancy when the platelet count is under 10, however this threshold can be increased in higher risk patients.

Fresh frozen plasma

Contains the human clotting factors and can be used to correct coagulopathies in bleeding patients in the short term when the underlying factor deficiency is unknown or to replace a global deficiency of clotting factors such as in massive haemorrhage.

Cryoprecipitate

Is a plasma product which is prepared in a certain way so that it contains higher concentrations of certain clotting factors. Importantly, it contains higher concentrations of fibrinogen and is used to correct low fibrinogen in some hospitals. Other hospitals prefer to use fibrinogen concentrate which is a plasma derived product which contains standardized amounts of fibrinogen.

Progress

The patient underwent neurosurgical intervention with subdural haematoma evacuation and burr hole creation. Following this she received chemotherapy alongside her ATRA therapy. Her blood counts dropped following the chemotherapy and she required intensive blood product support to keep her platelets between 80-100.

Happily, she is currently in remission from her leukaemia after her first cycle of chemotherapy and has no neurological sequelae. She is currently completing her consolidation chemotherapy.

Acute promyelocytic leukaemia

Acute promyleocytic leukaemia is highly curable subtype of acute myeloid leukaemia (4). Classical APML morphology demonstrates hypergranular, clefted myeloid blasts with Auer rods. The genetic abnormality is balanced translocation of chromosome 15 and 17, which results in the PML-RARA oncoprotein from the fusion of the ProMyelocytic Leukaemia protein (PML) and Retinoic Acid Receptor Alpha (RARA) (5).

Thus, the cornerstone of treatment is the use of all-trans retinoic acid (ATRA) which targets this genetic abnormality and allows differentiation of these blasts cells into mature leucocytes (6). The standard of care for APML remains combination therapy with ATRA and an anthracyline chemotherapy, but the use of chemo-free regimens with ATRA and arsenic therapy are showing excellent remission rates with less toxicity (2).

APML has an excellent long term prognosis with complete remission rates of 90–95% (4).The vast majority of mortality occurs within the first 10 days and is due to fatal haemorrhage thus stringent supportive care is crucial to the survival of this highly curable patient cohort. (3) Historically, the coagulopathy in APML was thought to represent a disseminated intravascular coagulopathy, but it is there is increasing evidence that there are a number of mechanisms and that hyperfibrinolysis is crucial especially at presentation (7).

Although there is a global activation of coagulation pathways there is currently no consensus evidence for prophylactic use of heparin, tranexamic acid, or other anticoagulant or antifibrinolytic therapy, although interest is growing in the use of tranexamic acid (7). The ATRA corrects many of these mechanisms and its administration critical in controlling the coagulopathy and haemorrhagic complications (8).

Best of 5 MCQ questions

1: A 67 year old man presents to A& E with spontaneous bleeding and bruising. He is clinically well. A full blood count and coagulation screen is arranged, the results of which are shown below.

Haemoglobin: 14.5 g/l (13-18)
White cell count: 6.5 x 10^9/l g/dl. (4-11) Normal white cell differential
Platelets: <10 × 10^9 /l (150-450)
Prothrombin time (seconds) 12 (11-13)
Activated partial prothrombin time (seconds) 31 (28-38)

A CASE OF EASY BRUISING

B Myers & A Dillon

Which is the likeliest diagnosis?

1. Haemophilia A (Factor VIII deficiency)
2. Acute leukaemia
3. Disseminated intravascular coagulopathy (DIC)
4. Immune thrombocytopenia
5. B12 deficiency

2: A 67 year old gentleman presents to A&E with spontaneous bleeding and bruising. A coagulation screen is arranged, the results of which are shown below. Which of the following problems would NOT explain the abnormalities shown?

Prothrombin time (seconds): 45 (11-13)
Activated partial prothrombin time (seconds) 61 (28-38)

1) Warfarin therapy
2) Severe malabsorption
3) Aspirin overdose
4) Liver disease
5) Disseminated intravascular coagulopathy (DIC)

Answers

1. The answer is 4

Immune thrombocytopenia as patients with ITP are usually clinically well and have an isolated thrombocytopenia as the underlying problem is peripheral consumption of the platelets rather than a global bone marrow problem which affect the white cell count and haemoglobin too. Patients with severe haemophilia can have problems with spontaneous bruising and bleeding, however the underlying problem is a factor deficiency so the full blood count including platelet count would be normal, but the coagulation screen would show a prolonged APTT.

Patients with acute leukaemia often have a thrombocytopenia, however, it is extremely unlikely that the rest of the FBC would be normal and they are often unwell. Patients with DIC can have low platelets, but they are unwell due to the underlying condition which is triggering the DIC. Patients with severe B12 deficiency can be thrombocytopenic, rarely to this extent, and they would have low haemoglobin and low white cell count in association with this reflecting the global deficiency.

2. The correct answer is 3, aspirin overdose.

Warfarin is a vitamin K antagonist which stops production of the vitamin K dependent factors, causing a prolonged PT and mildly prolonged APTT. Severe malabsorption and Liver disease can also lead to Vitamin K deficiency and thus cause the same effect. DIC causes a coagulopathy due to consumption of the clotting factors. Aspirin overdose will cause a functional problem with the platelets which could cause bruising or bleeding but would not impact on the coagulation tests.

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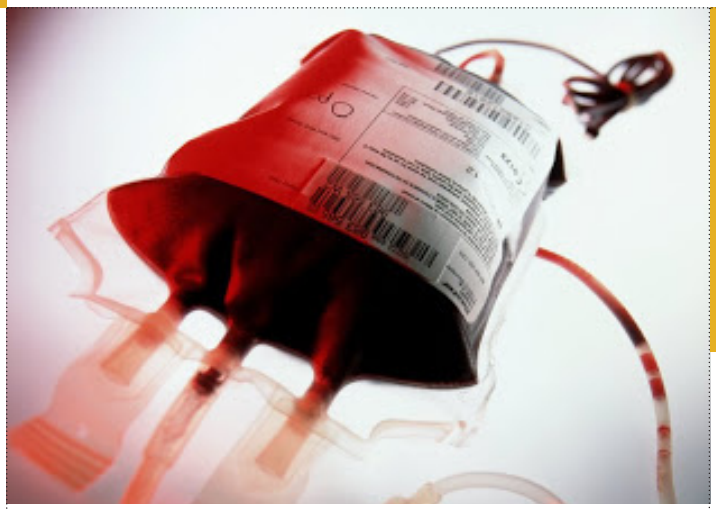
BLOOD COMPONENT TRANSFUSION - A PRACTICAL GUIDE

J Hanley & M Horan



Introduction

In almost every hospital based specialty, at some point as a foundation doctor you will be involved in looking after a patient who needs a blood component transfused. As part of your induction training you should be assessed on the basic transfusion competencies to ensure you are safe to prescribe and administer blood components.

The most important safety issue in transfusion is to make sure the correct component is given to the correct patient. A vital part of this is to ensure the blood sample for cross matching is taken from the correct patient. The purpose of this article is to augment this training by increasing knowledge of the components prescribed, the process of consent, placing an order and prescribing in adult patients requiring blood component transfusion.

Component

Background

The term "blood component" is used to describe any constituent of whole blood for the purpose of replacement therapy. In the UK after a donation of whole blood is collected, the blood is depleted of circulating leucocytes ("leucodepletion") before centrifugation to separate it into a red cell concentrate, fresh plasma and a buffy coat (which contains white cells and platelets).

From these layers, the blood components packed red cells, and fresh frozen plasma (FFP) are derived. It is possible to collect platelets in this way, however the majority of donations are extracted in a separate donation by a technique called apheresis.

Blood component transfusion - a practical guide
Good Clinical Care

Packed red cells

After separation the red cells are mixed with an additive solution to make the unit of packed red cells (Mean volume 282ml) The unit has a lifespan of 35 days whilst refrigerated (2-6°C), reducing to 4 hours once removed from the fridge.

It is optional to "wash" the red cells to remove surface proteins or "irradiate" the cells to destroy all of the circulating leucocytes. Both of these processes reduce the unit lifespan to 14 days and 24 hours respectively.

A standard unit of packed red cells cost approximately £122 to the NHS in 2013/2014 (1) and raises the serum haemoglobin by approximately 10g/L in a 70kg adult.

Indications

Transfusion of packed red cells is indicated in a broad range of clinical situations. Detailed guidance for the individual scenarios can be found in the Transfusion Handbook (2), but in general transfusion should be considered when the haemoglobin falls to ≤ 80 g/L in most asymptomatic patient groups (2). For symptomatic patients, the threshold of transfusion consideration is < 100 g/L, where the symptoms are as a result of anaemia and have significant clinical impact (2).

Common symptoms of anaemia include breathlessness, chest pain, dizziness, fatigue and malaise. It is important to remember that haemoglobin thresholds are unreliable in rapid, acute haemorrhage and therefore should not be used alone to guide transfusion. Chronic anaemia caused by a reversible underlying disorder (e.g. iron deficiency) should not be offered transfusion except in exceptional circumstances where immediate rising of the haemoglobin concentration is required.

BLOOD COMPONENT TRANSFUSION - A PRACTICAL GUIDE

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Platelets

The mean total volume of a unit of platelets is 199ml if derived by apheresis and 300ml if derived from pooled buffy coat donation. The lifespan of a unit is 7 days from donation if kept agitated at 20-24°C. The units must not be refrigerated or frozen.

Options for washing and irradiating are the same as for packed red cell units except that they maintain their usual lifespan with either treatment.

A standard unit of platelets cost approximately £197 to the NHS in 2014 (1) and would be expected to raise the serum platelet count by approximately 20–40 x 10^9/l in a 70kg adult.

Indications

Platelet transfusions can be indicated for both prophylaxis and haemorrhage. Prophylaxis for invasive procedures and in stable patients with any cause of bone marrow failure (e.g. recent chemotherapy, myelofibrosis etc.) should be considered if the platelet count falls below recommended thresholds.

The British Society of Haematology recommends that for prophylaxis in reversible bone marrow failure a target of greater than 10 x 10^9/l platelets is sufficient. If additional risk factors for bleeding are present such as sepsis, or abnormalities of haemostasis then the target should be 20 x 10^9/l. Prophylaxis for surgery and invasive procedures should generally target 50 x 10^9/l with the exception of central nervous system (CNS) and eye procedures for which the target should be 100 x 10^9/l (3).

In haemorrhagic patients, platelet transfusions should be used to maintain a platelet count of 75 x 10^9/l, or 100 x 10^9/l for those with multiple or CNS trauma (3).

Platelet transfusions may also be helpful as an adjunct when abnormal platelet function is present.

Platelet transfusions are contraindicated in patients with Thrombotic Thrombocytopenic Purpura (TTP) or those with Heparin Induced Thrombocytopenia (HIT). Platelet transfusion is of limited value for other causes of thrombocytopenia such as Idiopathic Thrombocytopenic Purpura (ITP).

Fresh Frozen Plasma (FFP)

Donated plasma is quickly frozen to maintain the integrity of the clotting factors. Storage at less than -25°C allows a lifespan of 36 months while frozen, reducing to 24 hours at 4°C when thawed. At ambient temperature FFP should be used within 4 hours. The mean total volume of a unit of FFP is 274ml.

FFP contains normal concentrations of coagulation factors II, V, VII, VIII, IX, X, and XI. ABO compatibility is important but as there are no circulating red cells or leucocytes, washing or irradiation is not necessary.

Pooled FFP treated with solvent/detergent is available (e.g. Octaplas) in the UK. The product has the advantage of inactivating most blood borne viruses and provides greater standardisation of factor concentrations per unit. A standard unit of FFP cost approximately £28 to the NHS in 2014 (1)

Indications

The British Committee for Standards in Haematology (BCSH) recommends use of FFP in multiple clotting factor deficiency associated with significant bleeding and/or Disseminated Intravascular Coagulation (DIC) with bleeding and in the treatment of TTP. FFP is also used when a single factor deficiency exists without the availability of a virus free concentrated product (eg. Congenital factor V deficiency) (4). FFP is used in major haemorrhage and every hospital has a major haemorrhage protocol that you should become familiar with.

It is important to note that FFP should not be used for warfarin reversal or as a volume expander. Prothrombin Complex Concentrates (PCCs) which contain the vitamin K dependent clotting factors should be used to reverse warfarin when there is serious bleeding.

FFP is contraindicated in patients with intolerance to plasma or it's components and patients with IgA deficiency in the presence of anti-IgA antibodies.

Cryoprecipitate

Cryoprecipitate is obtained by centrifugation of FFP to extract the cryoproteins: fibrinogen, fibronectin, factor VIII, von Willebrand factor (vWF) and factor XIII. The cryoproteins are then suspended in a reduced volume of the original plasma (20-40ml).

The storage, lifespan, ABO compatibility, "washing" and "irradiation" guidance is identical to FFP. A standard unit of cryoprecipitate cost approximately £32 to the NHS in 2014 (1).

BLOOD COMPONENT TRANSFUSION - A PRACTICAL GUIDE

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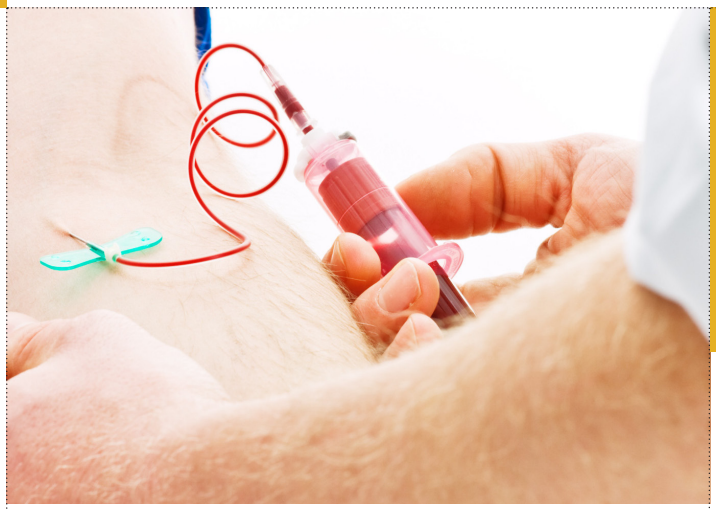

Blood component transfusion - a practical guide
Good Clinical Care

Indications

Cryoprecipitate is mainly used as a source of fibrinogen replacement in either congenital or acquired fibrinogen deficiency. For replacement in congenital deficiency Fibrinogen Concentrate - a specific, single factor, virus inactivated product is licenced in the UK as an alternative to cryoprecipitate. The BCSH recommends the use of cryoprecipitate to correct low fibrinogen levels in patients with haemorrhage or disseminated intravascular coagulation (DIC) (4).

Consent

In 2011 the advisory committee to the Safety of Blood, Tissue and Organs (SaBTO) produced a report, advising that formal consent should be gained when transfusing blood components (5). The guidance recommends that the discussion should include: blood component; indication; benefits; risks, alternatives and how the transfusion is administered in order for informed consent to be given (6).

When considering offering transfusion it is important to ask about religion. Jehovah's Witnesses generally do not accept blood components but may choose to accept certain blood products (7). They might have advanced directives and senior specialist counselling of alternatives may be necessary.

Risks of transfusion

Mild/moderate allergic reaction

Allergic reactions occur when recipients have antibodies to donor plasma proteins or other allergens (e.g. nuts, medications etc.). The clinical consequences range from mild to severe with possible symptoms including fever, rash, headache and dizziness; to rigors, hypotension, bronchospasm and shock.

Mild reactions are often self-limiting and usually only require slowing of the transfusion rate. In contrast to the moderate/severe reactions, which may require component cessation, patient resuscitation and further investigation of the underlying cause.

Anaphylaxis

This is rare, occurs by the same mechanism as allergic reactions and is life threatening.

Transfusion Associated Circulatory Overload (TACO)

TACO is characterised by acute breathlessness due to pulmonary oedema resulting from either too rapid a transfusion rate and/or too large a volume transfused. The most common patients at risk of this are those with a low BMI, the elderly, those with cardiac/renal failure and those requiring numerous components.

Lung injury (TRALI)

This is a serious immune mediated response caused by donor human leucocyte antigen (HLA) antibodies reacting with recipient leucocytes causing pulmonary infiltrates and damage. The most severe reactions are seen with ABO group mismatch but less severe reactions are seen with Rhesus group and other less common group mismatches. It is now rare but treatment is supportive only and morbidity rates are high. The incidence of TRALI has been reduced significantly in recent years by avoiding the use of plasma from multiparous women (8).

Acute haemolytic transfusion reaction (AHTR)

These reactions although uncommon, are most likely to occur as a result of an error whereby an incompatible blood component is transfused. The most severe reactions are seen with ABO group mismatch and less severe in Rhesus group and less common group mismatches. Undetected low levels of antibodies from previous sensitisation can cause this reaction by re-activation of the antibody response. This is uncommon and usually only problematic for multiply transfused patients.

Bacterial contamination

It is rare that bacterial contamination occurs. It is most commonly occurs from transfusion of platelets. There have been no reported cases in the UK since 2009 (9).

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Virus contamination

As with bacterial contamination, virus contamination risk is very low. Since 2005 there have been only 2 cases (one hepatitis B and one hepatitis E).

Variant Creutzfeldt-Jakob disease (vCJD)

There have only ever been 3 cases recorded of transmission from blood transfusion, all of which have been prior to the introduction of leucodepletion and stringent rule changes affecting blood donors.

The numbers of reported cases to the Serious Hazards of Transfusion (SHOT) committee in the UK 2013 regarding the risks are shown in Table 1.

Reaction type	Number of cases reported
Allergic (excluding anaphylaxis)	159
Circulatory overload (TACO)	78
Acute haemolytic reaction (AHTR)	17
Anaphylaxis	6
Lung injury (TRALI)	4
Viral contamination	2
Bacterial contamination	0
Variant CJD (vCJD)	0

Table 1: Transfusion cases reported to SHOT by category in 2013 (10).

Requesting and prescribing

Once the laboratory receives a "group and save" sample, they should be able to commence processing the request for the required component. It is important that the lab know the component required, the urgency, the quantity and any special requirements of the blood component. Special requirements will be discussed later in this section.

For safe prescription of a blood component the necessary information recorded should include patient details, date, component for transfusion, number of units, rate of transfusion, special requirements and a signature.

Packed red cells

A full crossmatch takes approximately one hour once the sample is received and is sufficient in non-urgent cases when antibodies are not detected. Full crossmatching provides type specific red cells and checks the suitability of the donor cells to the recipient. It is the safest and most thorough way of testing compatibility. In an emergency type O, rhesus negative packed red cells can be issued in a matter of minutes if clinical need arises.

Unit quantities for crossmatch depend on clinical indications. As a guide it would be appropriate to request and transfuse 1-2 units in the non-urgent clinical setting and recheck haemoglobin post transfusion to evaluate the response. Further units can be transfused if indicated. In major haemorrhage, local protocols will exist to guide quantities and monitoring. Guidance should be used in conjunction with senior and multidiscipline support.

A typical prescription for a unit of packed red cells in the non-urgent setting should be given over 90-120 minutes unless the patient is a high risk of TACO. High risk patients can be given at a slower rate providing that time out of refrigeration does not exceed 4 hours. These patients should be considered for 20-40 mg furosemide before transfusion (11).

Platelets

Platelets only require ABO and rhesus matching and therefore do not required a crossmatch. In larger hospitals platelets are often stored on site and can therefore be made available rapidly. Smaller hospitals however, usually need to order requests from the Regional Blood Transfusion Service.

Planning in advance and early lab request are advisable when it is known that platelets will be needed to avoid delay in supply. The platelet count should be monitored to assess response and the need for further platelet transfusion. A typical prescription for a unit of platelets should be given over 30 minutes

FFP

FFP must be thawed before transfusion and can take up to 30 minutes. The standard dose is 20 ml/kg (12). More may be required in major haemorrhage where monitoring of the prothrombin time (PT) and activated partial thromboplastin time (APTT) can be used to guide the need for further FFP. A unit of FFP is usually administered over 30 minutes.

Cryoprecipitate

Cryoprecipitate can be used from either single or pooled donors and is issued in packs of five units. The usual dose is 10 units. This is expected to raise the plasma fibrinogen by approximately 1 g/l.

Special Requirements

Washed cells

Both red cells and platelets can be washed to remove unwanted surface plasma proteins (including antibodies). They are indicated for patients who have had previous severe allergic or febrile reactions with no identifiable cause and those with IgA deficiency and IgA antibodies.

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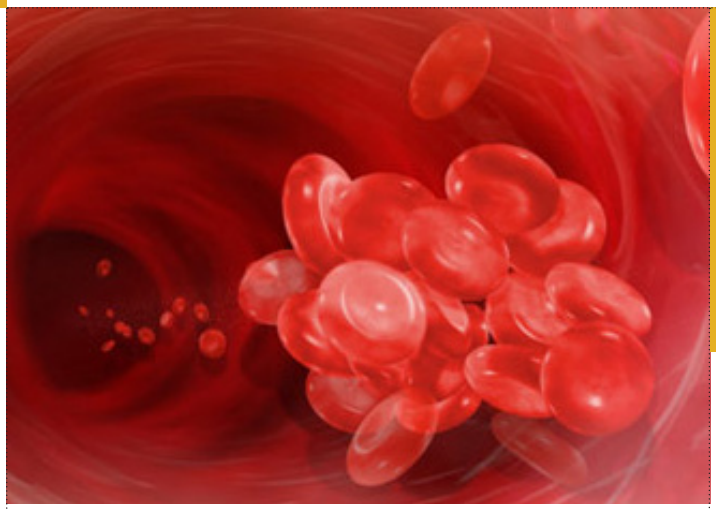

Irradiated components

Red cells and platelets must be irradiated to remove the donor lymphocytes for patients at risk of the rare complication of Transfusion-Associated Graft versus Host Disease (TA-GvHD). This occurs when donor lymphocytes engraft in a susceptible recipient and mount an immune response to the recipient's native lymphoid tissue. Mortality is in excess of 90% and standard leucodepletion techniques are not sufficient to prevent TA-GvHD. Patients requiring irradiated components are shown in table 2.

Indication for irradiation	Duration required
Allogeneic bone marrow transplant Allogeneic peripheral stem cell transplant	7 days prior until no immunosuppression required (at least 6 months post)
Autologous bone marrow transplant Autologous peripheral stem cell transplant	7 days prior to until 3 months post transplant (6 months if total body irradiation occurred)
Hodgkin's Disease Treatment with a purine analogue (eg fludarabine, cladrabine) Treatment with a purine antagonist (eg bendamustine, clofarabine)	Lifelong
Treatment with anti-thymocyte globulin	Uncertain - no recommendation

Table 2: Indications for and duration of irradiated blood components (13)

CMV negative components

In adult practice CMV seronegative packed red cells and platelets are only recommended for use in pregnant women (of any CMV status) unless unable to obtain in an emergency. In all other situations (including BMT and PSCT) standard leucodepletion is adequate (14).

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Human Leucocyte Antigen (HLA) matched components

HLA matched platelets are required for patients who have developed HLA antibodies and are refractory to standard platelets. Antibodies usually occur as a result of previous pregnancies or multiple transfusions.

Summary

Before prescribing blood components it is important to have an understanding of what the component is and why it is clinically indicated. Consent is vital given the associated risks and although serious complications are uncommon, the majority are caused by human error at some point during the sampling process.

Transfusion medicine is complex and most hospitals employ Specialist Practitioners of Transfusion (SPOT) who are available for help and support. If in doubt with any aspect of transfusion it is wise to ask either a SPOT or one of the haematology team for advice.

Questions

For the following questions, please answer either "True" or "False".

1. Packed red cells should:

a) Be used within 4 hours once out of the refrigerator
b) Be used to treat an asymptomatic patient with a haemoglobin of 100 g/l
c) Raise the haemoglobin level by approximately 10 g/l per unit
d) Be crossmatched and type specific unless needed in an emergency
e) Usually be given over 90-120 minutes per unit

2. Platelets should:

a) Be kept agitated at 20-24°C
b) Be thawed fully before transfusion
c) Be kept above 50 x 10^9/l as a target for all patients with bone marrow failure
d) Increase the platelet count by approximately 20–40 x 10^9/l per unit
e) Be given over 90-120 minutes per unit

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3. Fresh frozen plasma (FFP) should:

a) Be "washed" for those who have had previous allergic reactions to FFP
b) Be considered for patients with Disseminated Intravascular Coagulation (DIC)
c) Be given to a patient who is has intra-cerebral bleeding on warfarin with an INR of 9.0
d) Be given at a dose of 20-25ml/kg
e) Be given at a rate of 30 minutes per unit

4. Cryoprecipitate:

a) Is derived from fresh frozen plasma
b) Contains fibrinogen, von Willebrand factor and factor VIII
c) Should be used to treat bleeding in patients with haemophilia A
d) Would be expected to raise the fibrinogen by 1 g/l
e) Poses no risk of transmission of a virus infection

5. Indications for irradiated bloods components include:

f) A patient who has had an autologous peripheral stem cell transplant 1 week ago
g) A patient with HIV
h) A patient who has previously received chemotherapy with a purine analogue
i) A patient who has relapse with Hodgkin's lymphoma
j) A patient on oral methotrexate treatment

Answers

1. a) True	**b) False**	**c) True**	**d) True**	**e) True**
2. a) True	**b) False**	**c) False**	**d) True**	**e) False**
3. a) False	**b) True**	**c) False**	**d) False**	**e) True**
4. a) True	**b) True**	**c) False**	**d) True**	**e) False**
5. a) True	**b) False**	**c) True**	**d) True**	**e) False**

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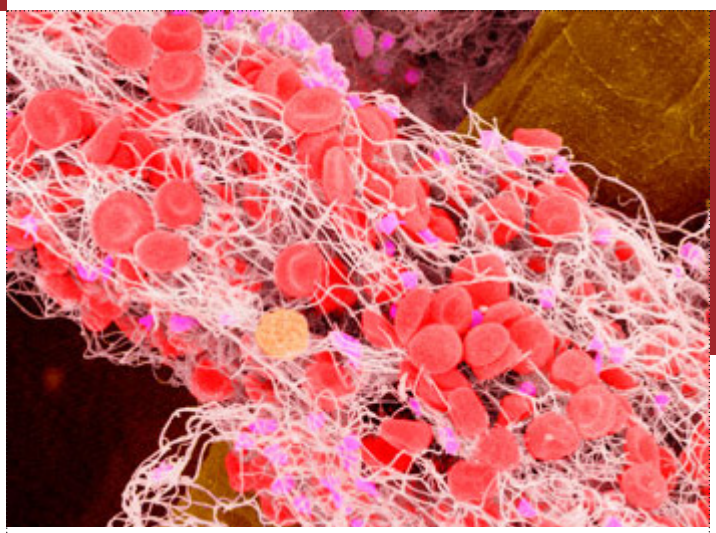
ANTICOAGULATION, ADVERSE EFFECTS & ANTIDOTES

W Siow, F Chowdhury & G Cho



Abstract

Warfarin has been the most commonly prescribed oral anticoagulant for many years until the recent introduction of the novel anticoagulants such as Dabigatran and Rivaroxaban. The presence of a mechanical heart valve is an indication for anticoagulation. The main side effect of warfarin is bleeding, with intracerebral haemorrhage being one of the most serious bleeding risk requiring immediate reversal management. This patient had immediate warfarin reversal but developed pulmonary emboli as a result. This case highlights the difficulties managing a patient with concurrent haemorrhage and thrombosis.

Case

A 58 year old male shop keeper was admitted following acute onset of left sided weakness and facial droop. He previously had mitral and aortic valve replacement for rheumatic heart disease and had been on warfarin for 14 years. There was a subarachnoid haemorrhage following a fall that needed Burr Hole surgery 7 years previously. He was known to have diabetes mellitus and atrial fibrillation.

On admission observations showed a blood pressure 150/86, GCS 15/15, with left sided upper and lower limb weakness, with an upgoing plantar response on the left.

A CT Head Scan (Figure 1) showed a moderately large intra-parenchymal haemorrhage within the right parietal lobe with surrounding oedema and local mass effect.

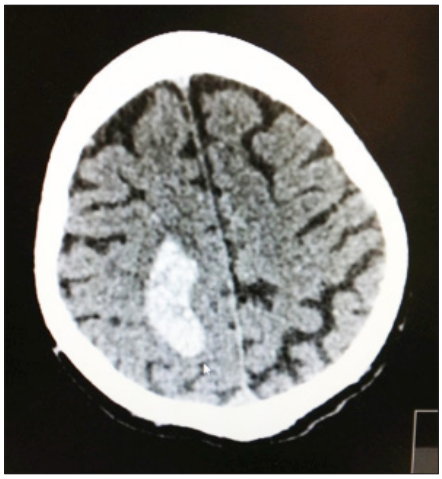


Figure 1: CT head with contrast on admission.

Based on the CT findings, the patient was given 2000 units of intravenous Prothrombin Complex Concentrate (PCC) and 5mg intravenous Vitamin K. The neurosurgical advice was to manage conservatively and to reverse the warfarin. The warfarin was discontinued and the patient was transferred to the Hyperacute Stroke Unit on site. Six hours after the CT scan, the patient complained of worsening weakness, and he underwent a repeat CT head scan. (Figure 2), which showed moderately increase in size of the acute parenchymal haemorrhage.

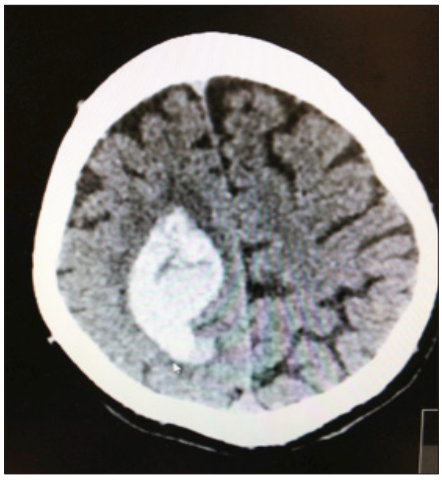


Figure 2: Second CT head with contrast showing increase in size of haemorrhage.

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The case was discussed again with neurosurgical services who advised conservative treatment. The patient remained stable the following day.

However, in the following evening, the patient was given 8mg of warfarin by the night staff, which was not prescribed. Overnight, he was neurologically stable. An urgent INR done the following day was 1.1. The patient made steady improvement and was fully self-caring and mobile on ward. He was not on low molecular weight thromboprophylaxis. On the 5th day of admission, he developed acute onset and shortness of breath, and a Chest Xray (Figure 3) was done which showed prosthetic mitral and aortic valves and plethoric lung fields.

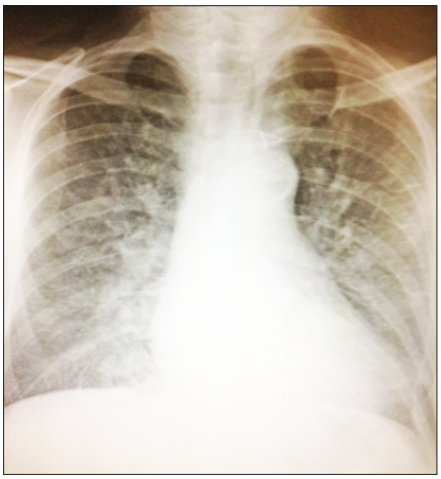


Figure 3: CXR showing plethoric lung fields and prosthetic aortic and mitral valves.

The patient was started on piperacillin/tazobactam, frusemide and a glyceryl trinitrate infusion. Blood tests showed a neutrophilia and a markedly raised D-Dimer of 7000 ug/L FEU. (Normal range 0.00-500ug/L FEU). The raised D-Dimer was attributed to the large intracranial haemorrhage. On the 6th day, his condition failed to improve, his oxygen saturations continued to deteriorate, with saturations of 88% on air. A CTPA showed bilateral sub-segmental pulmonary emboli. He was started on CPAP. He underwent a third CT brain scan which was unchanged.

He was commenced on IV unfractionated heparin with aim to keeping the APTTR at 1.5-2.0, on the advice of the haematology consultant. The APTTR was 2.5 at 4 hours after the start of the heparin infusion. The medical registrar on call decided to make no change to the infusion rate.

The following morning, he had a pulse of 155/ minute, a respiratory rate of 55/ minute and with a systolic blood pressure of 95/46. The patient had a PEA cardiac arrest and underwent intubation and resuscitation. A Chest Xray showed increasing airspace shadowing. The patient unfortunately passed away later in the day in the intensive care unit.

This case illustrates the difficulties encountered during the management of a patient with a high risk of thrombosis whilst being at high risk of bleeding.

Introduction

Warfarin acts as an anticoagulant by inhibiting the carboxylation of Vitamin K-dependent coagulation factors II, VII, IX and X. This leads to a prolongation of both the prothrombin time (PT) and activated partial thromboplastin time (APTT). The major adverse effect of warfarin is bleeding, including intracranial haemorrhage whose incidence is roughly 1% per annum (1). The incidence of bleeding increases with the intensity of anticoagulation and age. (2,3,4)

Management of bleeding patients on warfarin

General non-pharmacological measures

This includes taking a history documenting the timing, dose of drug taken and any history of liver or renal disease. Baseline bloods which should include full blood count and a coagulation screen. Patients with haemodynamic compromise need full resuscitation. Causes of bleeding should be investigated and treated. Table 1 illustrates the general non pharmacological measures.

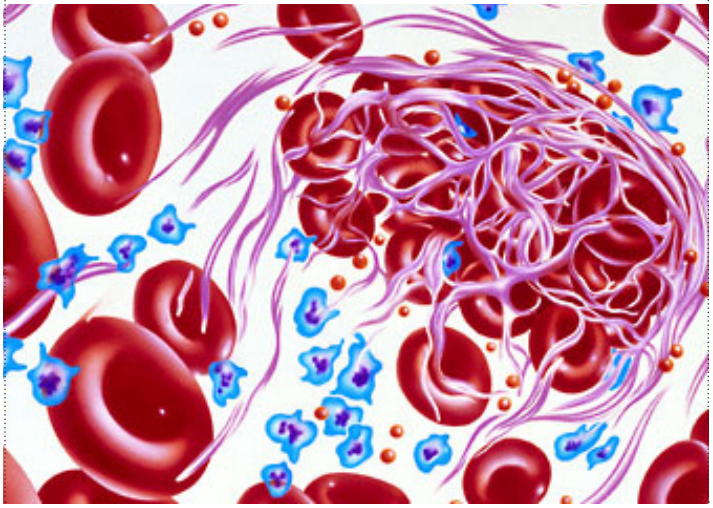
Stop the antithrombotic Drug
Document the timing and amount of the last drug dose and presence of pre-existing renal/liver impairment
Estimate the half-life and length of functional defect induced by the drug
Assess source of bleeding
Request Full blood count, prothrombin time, activated prothrombin time, thrombin time, fibrinogen concentration, creatinine
If available, request a specific laboratory test to measure the antithrombotic effect of drug
Correct haemodynamic compromise with intravenous fluids and red cell transfusion
Apply mechanical pressure, if possible
Use endoscopic, radiological or surgical measures.

Table 1: General non-pharmacological measures (5)

Pharmacological agents

Agents commonly used include Vitamin K, Prothrombin Complex Concentrates (PCC) and Fresh Frozen Plasma (FFP).

Non-major bleeding can be managed with Vitamin K combined with dose reduction or temporary discontinuation. (6) Intravenous vitamin K works faster than oral Vitamin K, and correction of the INR would usually be within 6-8 hours.



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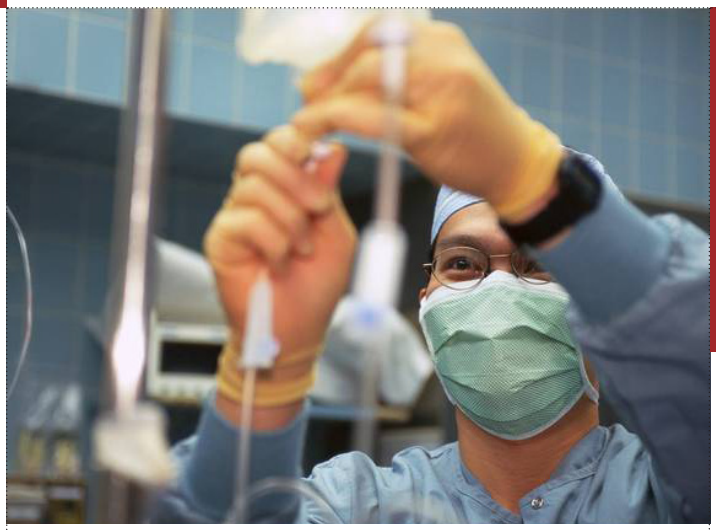

For major bleeding, which is defined as limb/life/sight threatening, PCC containing factors II, VII, IX and X should be used. (6) However, factor VII has a half life of around 4 hours. It is hence crucial that 5mg intravenous vitamin K is also given. Undesirable effects of PCCs include (7):

- *Risk of thromboembolic disease*
- *Headache*
- *Fevers*
- *Allergic or anaphylactic reactions*
- *Formation of antibodies against human prothrombin complex factors*
- *Increase in liver transaminases*
- *Heparin induced thrombocytopenia (HIT)*
- *Disseminated Intravascular Coagulation (DIC)*
- *Myocardial infarction*

Due to the risks above, the use of PCCS should always be discussed with a haematologist.

FFP can also been used to reverse effects of warfarin. FFP use in major bleeding is not recommended due to suboptimal correction and it is not practical to give the patient large volumes of dilute clotting factors. (6) There are also risks of blood products which include allergic reactions, transfusion associated circulatory overload (TACO), and transfusion associated infections. FFP should only ever be used if PCC is not available or contraindicated (6), at a dose of 12-15ml/kg.

Recombinant Factor VIIa has been used for warfarin reversal, and produces rapid INR correction, but the impact on bleeding is unclear. (8) It is not recommended for use in warfarin reversal8. Undesirable effects include thrombotic events and disseminated intravascular coagulation (DIC). (9)

New alternatives to warfarin?

The New Oral Anticoagulants (NOACs) including the thrombin inhibitor Dabigatran, and the factor Xa inhibitors Apixaban and Rivaroxaban, are approved by the National Institute for Health and Care Excellence (NICE) for use in stroke prevention (10,11,12). The advantages they have over warfarin include fewer drug interactions compared to warfarin and routine blood test monitoring is not required. They also have equal efficacy and a more favourable bleeding profile compared to warfarin. (10,11,12,13)

NOACs however, are cleared mainly by the kidneys, and their use is contraindicated in severe renal impairment. NOACs also appear to have a higher incidence of gastrointestinal bleeding (14,15), hence current/ recurrent gastrointestinal ulceration is a contraindication for their use. The factor Xa inhibitors interact with medications which inhibit or induce CYP3A4 and /or P-glycoprotein 1. To date, there are no antidotes for NOACs.

Dabigatran and Rivaroxaban have been approved by NICE for the prevention of venous thromboembolism after total hip or total knee replacement in adults. (17,18)

Rivaroxaban has been approved by NICE as an option for the treatment of Deep Vein (DVT) and Pulmonary embolus (PE) following an acute DVT in adults. (19)

The reversal of NOACS would include general non pharmacological measures described in Table 1. There are no specific antidotes for NOACS. For Dabigatran, consider oral activated charcoal if drug taken in last 2 hours to prevent further absorption. Haemodialysis, haemofiltration and charcoal haemofiltration can be used to enhance clearance of Dabigatran. For life threatening bleeding in patients on NOACs, PCC, Activated Prothrombin Complex Concentrate (APCC) and recombinant Factor VIIa should be considered. (5)

Discussion

When should we restart anticoagulation in a patient with an intracranial haemorrhage who then develops bilateral pulmonary emboli?

Clearly the risks of bleeding and thrombosis have to be carefully considered. The patient has a large intracranial haemorrhage (ICH) and given the high risk of haematoma expansion in the early phases, the immediate management would be for warfarin reversal and discontinuation of warfarin (2).

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A significant proportion of (27%) patients with warfarin associated ICH develop haematoma expansion within the first 24 hours. (20) Administration of PCCs are associated with a reduced incidence and extent of haematoma growth compared to FFP and Vitamin K. (20)

This patient had risk factors for thrombosis including metallic heart valves, especially the one in the mitral position, immobility and non-valvular atrial fibrillation. The risks of valve thrombosis of a mechanical heart valve is around 1.7 per 100 patient-years and the incidence of major embolism at 4 per 100 patient-years in the absence of anticoagulation. (21) A prosthetic mitral valve has almost twice the risk compared to an aortic valve. (21) Warfarin reduces the risks to 1 per 100 patient-years. (21)

There are no clinical guidelines regarding the most appropriate time to restart anticoagulation. The benefits and risks would need to be equally considered. Clinicians would generally start subcutaneous heparin in low doses and increase it to therapeutic dose or start oral anticoagulation after the next few days or a week (2). In a retrospective review looking at 35 patients (13 patients with prosthetic heart valves) presenting with ICH post oral anticoagulation, reintroducing anticoagulation did not appear to result in a high rate of recurrent fatal intracranial haemorrhage in the 2 year period after the initial bleed. (22)

This patient developed respiratory complications with evidence of pulmonary embolism. Restarting anticoagulation earlier was not an option due to haematoma expansion. He was managed with haematology input, and the anticoagulation was commenced once there was no radiological evidence of haematoma extension. He unfortunately died due to respiratory complications.

Questions

1. How would you manage a 75 year old gentleman who presents in Accident and Emergency with an INR of 11. He does not report any bleeding.

a. Prothrombin Complex Concentrates with vitamin K
b. Do nothing, as he is well.
c. Give him a small dose 1-2mg Vitamin K, stop the warfarin, investigate the cause of the raised INR, and check the INR the following day.

2. A 76 year old gentleman on warfarin for Atrial Fibrillation. He has had a mechanical fall, with lacerations to his face. His INR is 2.4 and his GCS is 15/15. The management is:

a. Send him home as his GCS is 15/15.
b. Arrange for a CT head immediately as patients on warfarin can bleed with minor head injuries.
c. Arrange for a scan only if the INR is above therapeutic range and if there are neurological findings.

3. Which of the following New Oral Anticoagulants (NOACs) has been approved by NICE for use in the treatment of deep vein thrombosis?

a. Dabigatran
b. Rivaroxban
c. Apixaban

4. An 75 year old gentleman is admitted to A+E with haematemesis. His blood pressure is 70/35 and he is clammy and unwell. He is on Rivaroxban for thromboprophylaxis following a total right hip replacement. What measures would you suggest?

a. Ring the blood bank and ask for 4 units of blood as there is no antidote for Rivaroxaban.
b. Take a history documenting the timing, dose of drug and history of liver and renal disease. Urgent bloods including full blood count, prothrombin and activated prothrombin time, thrombin time, fibrinogen and creatinine. Full resuscitation measures, including airway, breathing and circulation. Investigate for causes of bleeding. Give IV fluids and red cells. Contact the on call haematologist for help as he will need treatment with either PCC, APCC or recombinanant Factor VIIa.
c. Activated Charcoal.

5. Which clotting factors does warfarin inhibit?

a. Factors II, VII, VIII, X
b. Factors II, V, VIII, IX
c. Factors II, VII, IX, X

Answers

Q1. c
The INR is greatly elevated, and the cause of this needs to be investigated. A common cause include antibiotics.

Q2. b
In general if the head injury was sufficient to cause facial or scalp laceration or bruising with persistent headache, the patient should have a CT scan. (5)

Q3. b
Only Rivaroxaban is currently licensed for treatment of deep vein thrombosis and pulmonary embolus (19).

Q4. b
The patient has haemodynamic compromise. General non-pharmacological measures need to be undertaken as well as contacting the haematologist urgently for advice and obtaining pharmacological agents such as PCC, APCC and recombinant Factor VIIa.

ANTICOAGULATION, ADVERSE EFFECTS & ANTIDOTES

W Siow, F Chowdhury & G Cho

Q5. c

Warfarin inhibits the carboxylation of factors II, VII, IX, and X, causing prolongation of both PT and APTT.

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Disclaimers

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Financial statement
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THE INVESTIGATION OF A BLEEDING PATIENT

A Aggarwal & A Khan

The investigation of a bleeding patient
Patient Management

Abstract

A case of sudden onset bruising which demonstrates the approach to a general medical patient with bruising or bleeding. This article outlines the key investigations and their interpretation, followed by the management of acquired haemophilia A.

Case

Mr X is a 66 year old with a background of COPD, insulin dependant diabetes, peripheral vascular disease, leg ulcers, angina and osteoarthritis. He presented with a two week history of extensive bruising at the sites of his insulin injections and two days of bruising over his forearms.

He had not experienced any bleeding from elsewhere and denied trauma to his forearms. He took aspirin, but had not had any problems with bruising before. He had recently had a course of clindamycin for an infected leg ulcer.

On examination, he had extensive bruising over his forearms and small haematomas on his abdomen at the sites of his insulin injections. He also had bruising over his right knee.

His blood results are summarised in table 1.

Haemoglobin 130-180g/l	62
White cell count 4-11 x10^9/l	14.4
Platelet 150-400 x 10^9/l	328
MCV 76-96fl	85.2
PT 11-16s	11.0
APTT 27-33s	55
50:50 APTT mix 27-36s	38
Fibrinogen 150-400mg/dl	490
Iron 10-32µmol/L	6
B12 251-900ng/L	176
Folate 5-20µg/L	7.3
Urea 2.5-6.6mmol/l	18
Creatinine 70-120µmol/l	187

Table 1: The admission bloods of Mr X.

The bloods showed anaemia, a prolonged APTT and an element of acute renal failure. The APTT did not correct with the addition of 50% normal plasma ie with a 50:50mix. He was transfused with red cells before being transferred to a comprehensive care haemophilia centre for further investigation and management.

THE INVESTIGATION OF A BLEEDING PATIENT

A Aggarwal & A Khan

The investigation of a bleeding patient

This involves evaluating the platelet count, the clotting cascade and anatomical sources of bleeding. Further tests such as platelet function and von Willebrand screening may also be necessary. A careful history must also be taken to determine if the patient is on any antiplatelet agents, anticoagulation e.g. warfarin, unfractionated heparin, low molecular heparins, novel oral anticoagulants (NOACs). This article will focus on the clotting cascade.

A bleeding patient requires urgent assessment, resuscitation and discussion with a senior colleague.

Clotting cascade

The PT can identify problems in the extrinsic pathway, and the APTT identifies problems in the intrinsic pathway (Figure 1). The thrombin time (TT) can be used to investigate a prolonged APTT further. The TT is extremely sensitive to heparin therefore even if the APTT is only mildly prolonged the TT will be significantly prolonged in the presence of heparin. Other causes of a prolonged TT include hypofibrinoginaemia, dysfibrinoginaemia and fibrinogen degradation products.

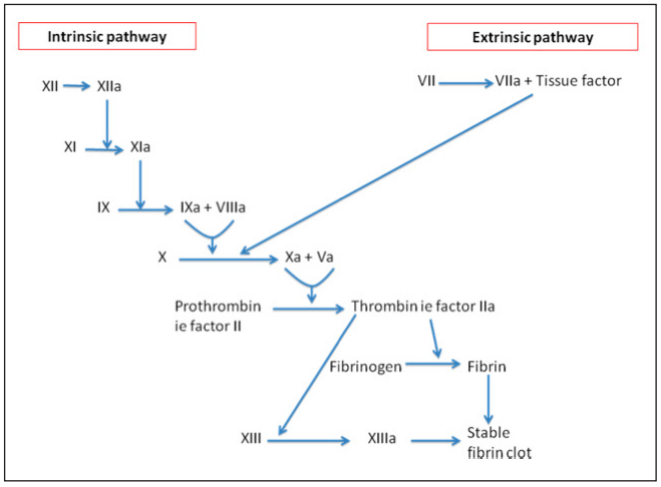

Figure 1: The clotting cascade.

Possible causes of a deranged clotting profile are outlined in table 2.

Deranged	Possible causes
PT only	Warfarin administration
	Liver disease
	Mild vitamin K deficiency
	Factor VII deficiency
	Acquired inhibitor
	Lupus anticoagulant
APTT only	Heparin administration
	Deficiencies of factor VIII, IX, XI, XII
	Lupus anticoagulant
	Von willebrand disease
	Acquired inhibitor
Both APTT and PT	Liver disease
	Disseminated Intravascular coagulation
	Severe vitamin K deficiency
	Over-anticoagulation with warfarin
	Combined factor deficiencies
	Deficiency of prothrombin, fibrinogen or factors V or X.
	Rivaroxaban
	Dabigatran

Table 2: Causes of abnormal clotting results.

In order to investigate an abnormal clotting result further, information can be gleaned from mixing studies. 50% normal plasma is added to 50% of the patient's plasma in vitro to determine if the clotting abnormalities correct ie 50:50 mixing.

If the APTT corrects to within 3 sec of the normal range on mixing this suggests the deficiency of a clotting factor because the deficient clotting factor is supplied by the normal plasma. However if the APTT fails to correct to within 3 sec of the normal range this suggests the presence of an inhibitor as the inhibitor will also prolong the clotting in the normal plasma. An algorithm for investigating a bleeding patient is suggested in Figure 2.

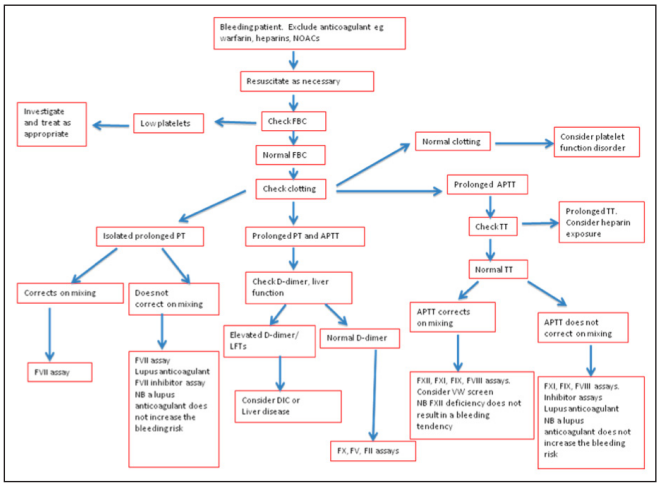

Figure 2: The evaluation of a patient with unusual bleeding.

THE INVESTIGATION OF A BLEEDING PATIENT

A Aggarwal & A Khan

The investigation of a bleeding patient
Patient Management

Acquired haemophilia

Acquired haemophilia A is a rare disorder, with an incidence of 1.5/million per year. It is caused by specific autoantibodies that inhibit the action of factor VIII. The average age of onset is 75-80 years of age (1).

In approximately half of all cases, no cause for inhibitor formation is identified. However, in the remainder, the inhibitor is associated with a variety of conditions, such as polymyalgia, rheumatoid arthritis, malignancy, pregnancy and pemphigoid (2).

Patients often present with sudden onset of abnormal bleeding, as in the case of Mr X. Unlike in congenital haemophilia A, bleeding into joints (haemarthroses) is unusual. More commonly, patients bruise, or bleed into the retroperitoneal space, muscle, gastrointestinal tract or urogenital tract. These bleeds or resulting compartment syndrome can be fatal (1, 3).

Acquired haemophilia A is suspected when there is an abnormally prolonged APTT that does not correct in a mixing study. A factor VIII assay and inhibitor screen should then be undertaken. Despite this, diagnosis of acquired haemophilia A is often a delayed. In 10% of cases there is 4 weeks or more between onset of bleeding and diagnosis (3).

Treatment

There are 3 aspects to treatment:

1*) Avoiding the precipitation of bleeds by iatrogenic actions e.g. invasive procedures, excessive venepuncture and blood pressure monitoring. Also, intramuscular injections are contraindicated (1).*

2) Managing the acute bleed. If bleeding is severe, urgent haemostatic treatment is required. This requires an agent that bypasses the inhibitor (4), examples include recombinant factor VIIa and factor eight inhibitor bypassing activity (FEIBA). FEIBA is plasma derived activated prothrombin complex concentrate. Treating with these substances is more effective than treated with recombinant factor VIII.

These treatments are associated with an increased risk of thrombosis, predominantly of the arterial variety. Therefore, they should not be used freely in minor bleeding (1). In addition, tranexamic acid can be considered, especially for mucosal bleeds (5).

Packed red cells, platelets and cryoprecipitate should also be administered as necessary.

3) Eradicating the inhibitor to prevent further bleeds. This is performed by immunosuppression to prevent further production of the antibody (2). Meta-analysis has shown that treatment with oral prednisolone and cyclophosphamide achieves a more stable remission than treatment with prednisolone alone (6). Rituximab, a monoclonal antibody targeting B cells, can also be considered (7).

Complications and relapse

Despite treatment, relapse rates are 10-20%. These patients often achieve a second remission but may need life-long immunosuppression (2,7).

Aside from relapse, patients often experience complications of treatment. One of the most serious is infection in the context of immunosuppression. This is responsible for up to 12% of deaths of patients with acquired haemophilia (2).

Another potential complication is, paradoxically, venous thromboembolism. The rebound in factor VIII levels that often occurs after successful treatment can cause venous thromboses, and so prophylactic anticoagulation may be required (1).

THE INVESTIGATION OF A BLEEDING PATIENT

A Aggarwal & A Khan

The case of Mr X

Mr X's bloods demonstrated an isolated APTT which did not correct fully on 50:50mixing. Further tests showed a low FVIII level and an inhibitor, findings were therefore consistent with acquired haemophilia A. Mr X received FEIBA and was commenced on prednisolone and cyclophosphamide to eradicate the inhibitor. He experienced some nosebleeds and had spontaneous bruising for a few weeks after admission but this settled.

His factor VIII levels rebounded to 308% of the upper limit of normal within 2 months of discharge. He was given compression stockings and advised to exercise regularly. His factor VIII levels gradually returned to normal and his prednisolone was weaned. Apart from unstable blood sugar control, he did not experience any other complications of treatment.

MCQs

1. The PT is usually prolonged by the administration of which drug?

- warfarin

- unfractionated heparin

- clopidogrel

- low molecular heparin

- aspirin

Explanation: *Warfarin is a vitamin K antagonist. Vitamin K is required for the carboxylation of several clotting factors. However, the factor most affected is factor VII, a key component of the extrinsic pathway. The extrinsic pathway is represented by the PT.*

2. A patient has an unexpected prolonged APTT and a normal PT and FBC. Which test should be done next?

- U&E

- LFTs

- 50:50 mixing study

- Fibrinogen

- Haematinics

Explanation: *Normal plasma is added to the patient plasma in vitro to determine if the clotting abnormalities are corrected. If the APTT corrects on mixing to within 3 sec of the normal range this suggests the deficiency of a clotting factor, however if it fails to correct this suggests an inhibitor.*

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Financial statement
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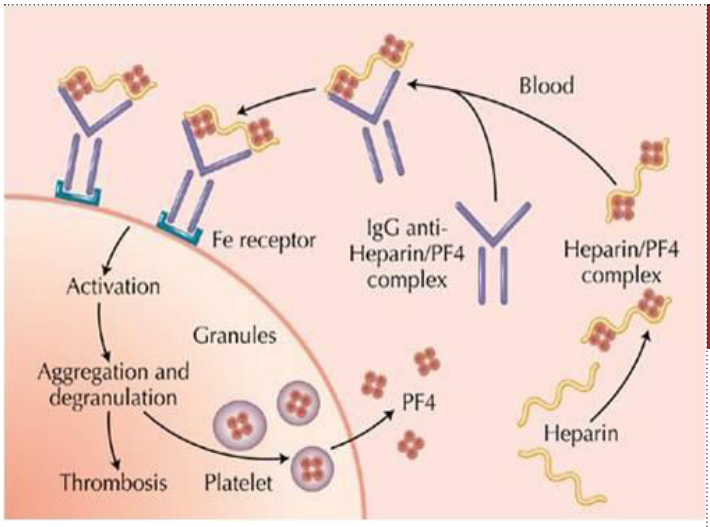
A CASE OF HEPARIN INDUCED THROMBOCYTOPENIA

R Soutar & C Betts



Abstract

This article describes a case of heparin induced thrombocytopenia (HIT) in a patient following above knee amputation for an acute ischaemic lower limb. It discusses the differential diagnoses which should be considered in surgical patients with thrombocytopenia, who is at risk of heparin induced thrombocytopenia, when a diagnosis of HIT should be clinically suspected and briefly how HIT is diagnosed and managed.

Case history

A 34 year old man is admitted to the vascular surgeons with a pale, pulseless right leg. Acute lower limb ischaemia is suspected and arterial emboli in both common iliac arteries and the right proximal superficial femoral artery are confirmed on CT angiography. He is commenced on unfractionated heparin (UFH) with a bolus dose of 5000units, followed by a continuous infusion of 1000units/hr, aiming for an APPT ratio of 1.8 – 2.8, and subsequently taken to theatre for an attempt at limb salvage. This is unsuccessful and subsequent above knee amputation is performed. He continues on UFH post operatively, switching to subcutaneous therapeutic low molecular weight heparin (LMWH) on his second post-operative day.

After seven days of heparin therapy his platelet count falls to 115 x 10^9/l, from a baseline of 258 x 10^9/l on admission. Around the same time, he develops an ischaemic right hand with radial and ulnar arterial emboli confirmed on Doppler imaging. He is discussed with the on call haematologist and a suspected diagnosis of heparin induced thrombocytopenia is made. His 4Ts score is calculated as 6/8 so the LMWH is immediately stopped and he is commenced on an intravenous danaparoid infusion. The presence of HIT antibodies are confirmed by ELISA testing. The ischemia of his right hand resolves. Warfarin therapy is started after his platelet count normalises and he is discharged home.

Discussion

How to approach thrombocytopenia in a post-operative patient

Thrombocytopenia is defined as a platelet count of <150 x 10^9/l. (1) Clinically spontaneous bleeding does not usually occur unless the platelet count is <20 x 10^9/l. However when there are additional risk factors for bleeding e.g. post-surgical procedure or presentation with trauma, clinically significant bleeding may occur with a higher platelet count.

When considering a diagnosis of HIT, the initial fall in the platelet count is often moderate and may not result in a platelet count of <150 x 10^9/l. The differential diagnosis of thrombocytopenia in post-operative patients is broad and is shown in Table 1. Establishing the cause in hospitalised patients can be particularly challenging and multiple causative factors may be present. (2)

Cause	Clues for diagnosis
Pseudothrombocytopenia	Is the blood sample clotted? EDTA dependent antibodies can cause platelet clumping in the sample tube after venepuncture. Confirm by repeat platelet count in lithium heparin or citrate sample and review of a blood film.
Major blood loss and haemodilution	Did the patient have a major haemorrhage (defined as 50% blood loss in 3 hours or >150ml/min) necessitating large volume transfusion of blood products causing haemodiluation? Has the patient been fluid resuscitated with large volumes of crystalloid?
Drug induced	Check for new medications including antibiotics (vancomycin), UFH or LMWH or IIb/IIIa inihibtors (tirofiban).
Sepsis	Are there signs of sepsis causing platelet consumption?
Disseminated intravascular coagulation (DIC)	Are there signs of DIC e.g. coagulopathy or bleeding?
Pre-existing liver disease	Often the patient with have pre-existing thrombocytopenia but the platelet count falls post operatively due to other factors listed above.
Mechanical fragmentation	Post cardiac bypass surgery, renal dialysis
Thrombotic microangiopathies eg Haemolytic uraemia syndrome, thrombotic thrombocytopenia purpura	Review of blood film for features of microangiopathic haemolytic anaemia e.g. red cell fragments and microspherocytes and nucleated red cells
Immune mediated disorders	Post transfusion purpura is rare. It is caused by platelet specific alloantibodies in the recipient reacting with transfused platelets. It typically occurs 5 to 9 days after transfusion of usually platelets but can occur after red cell transfusion.

Table 1: A differential diagnosis of thrombocytopenia in post-operative patients

A CASE OF HEPARIN INDUCED THROMBOCYTOPENIA

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Key points to consider

What is the baseline platelet count?

Are there previous results showing it to be within the normal range or is there a history of previous thrombocytopenia?

What is the timing of the thrombocytopenia?

Does the fall coincide with the initiation of any new drugs e.g. UFH, LMWH or vancomycin? Is there any history of heparin exposure in a the last 100 days or a previous history of drug induced thrombocytopenia?

What new drugs have been started?

Causes of drug induced thrombocytopenia include antibiotics such as vancomycin, quinine and heparin.

Is there any evidence of sepsis or
disseminated intravascular coagulation (DIC)?

Often an isolated thrombocytopenia is the first sign of DIC. A coagulation screen and measurement of D-Dimers can be helpful in these circumstances to provide supporting evidence of DIC.

Has a blood film been examined?

Pseudothrombocytopenia is caused by in vitro platelet clumping in a standard EDTA blood sample. This can be easily excluded on a review of a blood film. Red cell fragmentation raises the possibility of a thrombotic microangiopathy as the cause. Thrombotic thrombocytopenic pupura (TTP) is a medical emergency and requires immediate clinical management.

Our patient has a previously normal platelet count on admission and review of his blood film does not show any platelet clumping. He is not overtly septic and his coagulation screen is normal. New medications include LMWH which was started on conversion from UFH on the second post-operative day. Therefore HIT is suspected as a potential cause of his thrombocytopenia.

Who is at risk of developing HIT?

The risk of developing heparin induced thrombocytopenia depends on the patient group and the duration and type of heparin exposure. The frequency of HIT is greater in patients receiving UFH compared to LMWH. Patients at highest risk of developing HIT are orthopaedic or cardiac surgery patients, in whom the incidence is 1-5% for patients receiving UFH and 1% for those receiving LMWH. This is in comparison to 0.1-1% for medical patients receiving LMWH and <0.1% for obstetric patients receiving LMWH

The main clinical manifestation of HIT is thrombocytopenia (platelet count of <150 x 10^9/l) which occurs in 85 -90% of cases. This increases to 90-95% of cases when a proportionate fall in platelet count is seen but the absolute platelet count remains within the normal range. Due to this, recommendations for platelet count monitoring are suggested. These are:

- *All patients receiving heparin have a baseline platelet count checked.*

- *Post-operative patients receiving UFH including obstetric patients, should have a platelet count monitored every 2-3 days from day 4 to day 14 of heparin therapy or until the heparin therapy is stopped.*

- *Patients who are post cardiopulmonary bypass (CPB) receiving low molecular weight heparin should also have platelet count monitoring every 2-3 days from day 4 to day 14 of heparin therapy or until the heparin therapy is stopped. Development of a marked thrombocytopenia within 72 hours of stopping CBP is very common in these patients and a second fall in platelet count occurring between days 5 and 10 post operatively is much more suspicious of HIT than a persistent low platelet count beyond day 4.*

- *Medical and surgical patients receiving LMWH do not need routine platelet count monitoring.*

- *Obstetric patients receiving LMWH do not need routine platelet count monitoring.*

HIT is an immune mediated adverse drug reaction caused by formation of IgG antibodies which recognise the complexes formed by heparin on the surface of platelets. It is a prothrombotic condition which is characterised by the formation of new arterial and venous thrombosis. Despite the severe thrombocytopenia, clinically significant bleeding is rare. If bleeding does occur, then platelet transfusion is indicated.

Clinical manifestations of HIT include;

- *Thrombocytopenia.*

- *Formation of new venous thrombosis (DVT/PE) or new arterial thrombosis (acute coronary syndrome, stroke and peripheral arterial thrombosis).*

- *Skin necrosis at injection sites.*

- *Acute systemic reactions after receiving an intravenous bolus injection of heparin.*

Our patient develops new peripheral arterial emboli causing ischaemia of his right hand after ten days of heparin therapy. This, combined with the timing of the fall in his platelet count, raises the possibility of heparin induced thrombocytopenia, necessitating calculating his HIT score, switching him to alternative anticoagulation and testing him for HIT antibodies.

A CASE OF HEPARIN INDUCED THROMBOCYTOPENIA

R Soutar & C Betts

A case of heparin induced thrombocytopenia
Patient Management

How is HIT diagnosed?

HIT should be suspected in any patient receiving heparin who has a fall in their platelet count of >30% from baseline or in whom the platelet count is <100 x 10^9/l during treatment. The lowest or nadir platelet count in patients with HIT is usually 20-50 x 10^9/l and the fall in platelet count typically occurs 5-10 after initiation of heparin therapy. 30% of cases occur earlier, within 24 hours of heparin exposure. These are due to preformed antibodies from heparin exposure within the last 100 days. (3)

The decision to proceed to laboratory testing is supported by the use of the 4Ts score. (4) The 4Ts score adapted from the BCSH guidelines (3) for HIT is shown in table 2. This is used to stratify patients with suspected HIT into low, intermediate and high risk groups. Calculation of the HIT score is crucial before initiating laboratory testing as this has a high sensitivity but a low specificity. In critically unwell patients the cause of thrombocytopenia is often not clear and there may be multiple causative factors. (2)

4Ts	Points (max score =8)		
	2	1	0
Thrombocytopenia	>50% or nadir of >20 x 10^9/l	30-50% fall and platelet nadir 10-19 x10^9/l	Fall<30% or platelet nadir <10 x10^9/l
Timing*	Clear onset between days 5 and 10; or <1d if heparin exposure within past 30 d	Consistent with immunisation but history not clear (eg missing platelet counts) or onset after day 10; fall is <1 day after heparin exposure 30-100 days ago	Fall is <4 days without recent heparin exposure
Thombosis or other sequalae	New thrombosis; skin necrosis, post heparin bolus acute systemic reaction	Progressive or recurrent thrombosis, erythematous skin lesions, suspected thrombosis	None
AlTernative cause for thrombocytopenia	No other cause	Potential other cause	Definite other cause

Table 2: The 4Ts score Table adapted from Watson W, Davidson S and Keeling D. Guidelines on the diagnosis and management of heparin induced thrombocytopenia: second edition. BJH 2012;159:528-540, reproduced from Lo et al 2006 in the BCSH guideline.

Pre test probability: score 6-8 high, 4-5 intermediate, 0-3 low.

**First day of heparin exposure should be counted as day 0. The day the platelet count begins to fall should be considered as the day of onset of thrombocytopenia . The first fall in platelet count may be relative thrombocytopenia and may not fall beneath 150 x x10^9/l. Typically it may take 1-4 days before a threshold that defines thrombocytopenia is passed (usually <100 x10^9/l).*

A low risk 4Ts score (0-3) can clinically exclude HIT without the need for laboratory testing. (4) An intermediate risk score of 4-5 or a high risk score of 6-8 necessitates treating the patient for HIT whilst laboratory testing is carried out. Laboratory testing for HIT antibodies typically take one to two hours to perform. A strongly positive result is much more indicative of HIT that a weakly positive result. A negative test makes HIT unlikely but a positive test must be interpreted along with the 4Ts score.

Calculation of our patient's pre-test 4Ts score is 6/8 and therefore he is immediately switched to danaparoid which is a non-heparin alternative anticoagulant. He has a very strongly positive ELISA test for HIT antibodies and the diagnosis of HIT is confirmed. This is a straightforward case of HIT and the diagnosis here is not in doubt. In our experience, the majority of suspected HIT cases occur in critically ill patients who have undergone cardiothoracic surgery. In these patients the diagnosis of HIT is much less straightforward as they often have multiple potential causative factors for thrombocytopenia. Therefore calculation of the 4Ts score pre laboratory testing is crucial to guide any suspected diagnosis of HIT. (4)

How is HIT managed?

The main principle of treatment for patients with suspected or proven HIT is the discontinuation of heparin and commencement of an alternative anticoagulant. The current licensed options in the UK are danaparoid and argatroban, both of which are available in the UK. (3) Danaparoid is not available in the USA. Patients with suspected or proven HIT must be managed in conjunction with a haematologist.

- *Danaparoid is administered intravenously and indirectly inhibits Xa and thrombin. It is given by continual intravenous infusion and usually does not require monitoring. Where drug level monitoring is required e.g. patients with bleeding, renal impairment or at the extremes of body weight, then levels can be monitored using a specific anti Xa assay for danaparoid. (3)*

- *Argatroban is a hepatically excreted direct thrombin inhibitor which is administered intravenously and is monitored using the APTT ratio. It has a short half-life (approximately 50 minutes) and is often used in critical care settings where there is a high risk of bleeding.*

- *Fonduparinux is not licensed for the treatment of HIT but can be used in specific circumstances e.g. renal impairment or as an alternative to warfarin for ongoing anticoagulation.*

Once heparin has been discontinued, the platelet count should normalise.

A CASE OF HEPARIN INDUCED THROMBOCYTOPENIA

R Soutar & C Betts

What is the appropriate length of anticoagulation in patients with HIT and how to achieve this as an outpatient?

Patients presenting with a thrombotic complication of HIT should be anticoagulated for 3 months after diagnosis. (3) Patients with isolated HIT and no thrombotic complications should be anticoagulated for four weeks after diagnosis. (3) The majority of patients will require initiation of warfarin therapy to complete this period of anticoagulation.

Warfarin should not be initiated until the platelet count has normalised. Danaparoid should continue for 2 days once the INR is greater than 2.0. Argatroban causes a prolongation of the PT and therefore the INR should be maintained at more than 4.0 for 2 days prior to discontinuation of argatroban therapy. With all non heparin anticoagulants, a minimum of 5 days overlap with warfarin therapy is recommended. (3,5)

Management in the future

HIT antibodies are typically only detectable for 50 – 80 days after discontinuation of heparin but further heparin exposure is likely to lead to the development of new acute onset HIT. (3,6) Stringent efforts should be taken to reduce re-exposure to heparin including avoidance of heparinised flushes for central venous catheters. Our patient was given a HIT alert card to show whenever he is admitted to hospital and his diagnosis of HIT recorded as a clinical alert in his case records. He will require alternative DVT prophylaxis for future admissions to hospital e.g. fonduparinux.

Self test questions

1. A 72 year old woman is admitted to hospital with a fractured neck of femur. Her baseline platelet is 400 x 10^9/l on admission. She undergoes hemiarthroplasty the next day. Post – operatively she is commenced on enoxaparin 40mg subcutaneously as DVT prophylaxis.

Her platelet count is checked eight days post operatively and is 115 x 10^9/L. A blood film shows genuine thrombocytopenia only and her only new drug is enoxaparin. She is otherwise well and has no signs of sepsis or DIC. HIT is suspected and a HIT score is calculated as 6/8 or high. What would you do next?

a) Continue her LMWH as HIT safely excluded
b) Continue her LMWH and request a HIT screen
c) Stop her LMWH and request a HIT screen
d) Stop her LMWH, start an non heparin anticoagulant at a prophylactic dose and request HIT screen
e) Stop her LMWH, start an non heparin anticoagulant at a treatment dose and request HIT screen

2. Patients with a previously confirmed diagnosis of heparin induced thrombocytopenia can be safely re-exposed to heparin after the following time period has elapsed:

a) Once their platelet count has returned to within the normal range.
b) Once the HIT antibodies are no longer detectable.
c) Stringent efforts should be taken to avoid further heparin exposure and alternative forms of anticoagulation should be used if required.
d) After 100 days since the diagnosis of HIT.
e) Once they have completed their period of alternative anticoagulation after their diagnosis of HIT.

Answers

1. Answer: e

This lady has a low risk of HIT as she has not been exposed to UFH during her admission. Despite this, she has been exposed to LMWH and her platelet count has fallen to >50% of her baseline. Therefore HIT should be clinically suspected. When calculating her 4Ts score, she scores 2 for the degree of thrombocytopenia (>50% fall from baseline) and 2 for the timing (clear onset between days 5 and 10 of heparin exposure).

She does not have a new thrombosis or skin necrosis and there is not an alternative cause for her thrombocytopenia. Therefore her total 4Ts score is 6, placing her in the high risk group (score 6-8),. LMWH should be stopped immediately, she should be anticoagulated fully with a non-heparin anticoagulant and a HIT screen should be requested. The patient should also be discussed with a haematologist to assist with management. Therefore answer e is the only correct answer as due to the prothrombotic nature of HIT, treatment dose alternative anticoagulation is required, even without a diagnosis of thrombosis.

2. Answer: c

Explanation: HIT antibodies persist in the circulation for typically 50 to 80 days after formation and therefore re-exposure to heparin during this period is likely to cause an acute drop in platelet count within 24 hours of exposure. (7) Therefore answer a is incorrect. Thereafter recurrence is rarer as is appears HIT antibodies are transient. There are reports of patients who have been safely re-exposed to heparin after a diagnosis of HIT but these are typically patients who require cardiac surgery and are known to be antibody negative.

They are exposed to unfractionated heparin only during the period of cardiac bypass and alternative anticoagulation is used pre and post procedure. This limits their heparin exposure to an absolutely minimum period which does not appear to re-stimulate antibody production for a second time. (8)

A CASE OF HEPARIN INDUCED THROMBOCYTOPENIA

R Soutar & C Betts

The BCSH guidelines state that for patients with a previously documented episode of HIT who require a period of anticoagulant prophylaxis or therapeutic anticoagulation, a non-heparin anticoagulant should be used. These include fondupariunux, and danaparoid. The newer oral anticoagulants such as rivaroxaban, apixaban and dabigitran can also be used as per their licensed indications e.g. post-operative venous thromboembolism prophylaxis after orthopaedic surgery.

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A case of heparin induced thrombocytopenia
Patient Management

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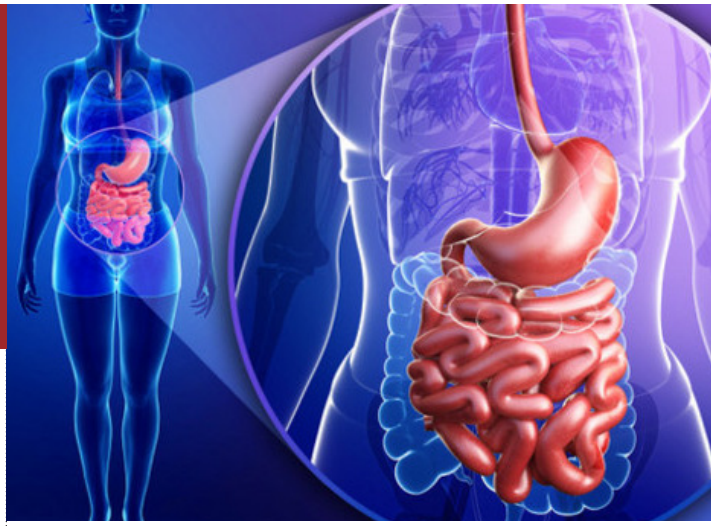
INVESTIGATING RAISED SERUM FERRITIN

EJ Fitzsimons & NT Mabvuure



Investigating raised serum ferritin
Patient Management

Abstract

This report describes the case of a 59 year old Scottish Caucasian woman with a history of alcohol excess and bipolar disorder was referred to the Haematology clinic after investigations revealed a serum ferritin (SF) level of 5346 ug/l (reference range 10 - 275 ug/l). Molecular testing revealed that the patient was homozygous for the C282Y mutation, confirming the diagnosis of hereditary haemochromatosis.

However, since the patient had an excessive alcohol intake, deranged LFTs, clinical features of chronic liver disease and an abnormal appearance of left lobe of the liver, alcoholic liver disease might have been accepted as the sole explanation for her hyperferritinaemia. This case demonstrates the challenge of differentiating causes of hyperferritinaemia, especially in patients in whom more than one potential explanation exists. Investigations which may help in this regard are discussed as a prompt to Foundation Year trainees who may be consulted by such patients who may present to haematology, rheumatology or gastroenterology.

Case presentation

A 59 year old Scottish Caucasian woman with a history of alcohol excess and bipolar disorder was referred to the Haematology clinic after investigations revealed a serum ferritin (SF) level of 5346 ug/l (reference range 10 - 275 ug/l). Her General Practitioner (GP) noted that the patient's SF level had also been raised three years prior to the present episode (4988 ug/l). However, this had not been investigated at the time.

Systemic enquiry did not reveal any symptoms. The patient, however, admitted to chronic excessive alcohol intake (>50 units/week). There was no relevant family history. Physical examination revealed liver palms and spider naevi in keeping with chronic liver disease. There were no other positive findings on physical examination.

FBC revealed only a marginal leucocytosis of 11.7 x10^9/l with other indices within normal limits. Serum folate was low (1.8 ug/l) whilst serum vitamin B12 was within normal limits (406 ng/l). Liver function tests (LFTs) were mildly disturbed (bilirubin 47umol/L, ALT 58U/L and AST 41 U/L). Urea, electrolytes and thyroid indices were all within normal reference ranges.

Further investigations were performed to explain this patient's presentation. Iron studies revealed low serum transferrin (1.29 g/L: ref range 2.0-3.6 g/L), marginally raised serum iron (32 umol/l: ref range 11-30 µmol/L) and markedly raised transferrin saturation (Tsat) (99 %: ref. range 25-50 %). Fasting blood glucose was 6.6 mmol/L.

Alpha fetoprotein (AFP) was normal (4 kU/L). Abdominal ultrasound showed that the left lobe of liver was small with a slightly irregular pattern and normal portal flow. The remainder of the liver was echogenic (consistent with fatty infiltration or parenchymal disease) but was smooth and homogeneous. Molecular testing revealed that the patient was homozygous for the C282Y mutation.

Discussion

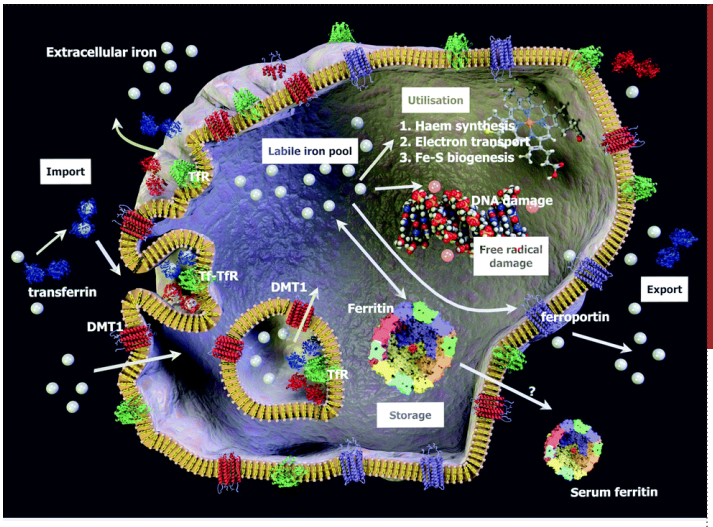
The differential diagnosis for a raised SF is wide but can be broadly grouped into(1):

- *Primary iron overload (hereditary haemochromatosis).*
- *Secondary iron overload (eg. liver disease, metabolic syndrome, diabetes, transfusion dependent anaemias, ie. thalassaemia major, myelodysplasia, etc).*
- *Reactive hyperferritinaemia (excess alcohol intake, malignancy, infective and inflammatory conditions).*

The great majority of patients with raised SF do not have Hereditary Haemochromatosis (HH) but Hearnshaw et al found that HH patients did have higher median SF levels than any other cause of hyperferritinaemia (2). Although alcohol excess is the most common cause of raised SF values, HH was an important diagnosis to exclude in this patient. The markedly raised Tsat 99% strongly supported the diagnosis of HH which was confirmed via molecular testing.

INVESTIGATING RAISED SERUM FERRITIN

EJ Fitzsimons & NT Mabvuure



Investigating raised serum ferritin
Patient Management

Hereditary haemochromatosis is an autosomal recessive condition resulting in increased iron absorption in the small intestine. This in turn leads to high serum iron and Tsat levels. Excess iron may deposit in organs including the heart, liver, skin, pancreas, gonads and joints (3) leading to several clinical manifestations. Several mutations can result in HH but the most important one clinically, is homozygous C282Y i.e. both alleles carry the C282Y mutation.

The majority of affected patients (85-90%) carry this mutation. Homozygotes for the H63D mutation carry a 1-2% risk of iron overload. Compound heterozygotes (C282Y on one allele and H63D on the other) are at a much lesser risk (approximately 1%) of clinically significant iron overload. The highest prevalence of HH is in Caucasian patients, especially those with Nordic or Celtic heritage (1 in 8 Celts are C282Y carriers and 1 in 2-300 are C282Y homozygotes and genetically predisposed to HH) (6), hence the moniker 'Celtic Curse.'

For reasons that are not yet understood, less than 50% of C282Y homozygotes develop iron overload. Males are at greater risk of iron overload than females who are protected by blood loss during menstruation and parturition. The clinical consequences of HH include liver cirrhosis (and hepatocellular carcinoma), skin pigmentation (hence the moniker 'bronze diabetes'), diabetes, arthritis and subfertility (1-4, 6). All complications can be prevented by early diagnosis and treatment. A major problem with diagnosis however is the insidious presentation of HH.

Although the diagnosis of HH became apparent after further investigations, this patient posed a diagnostic challenge. Alcoholic liver disease is the most common cause of hyperferritinaemia (2). This patient clearly had an excessive alcohol intake, deranged LFTs, clinical features of chronic liver disease and an abnormal appearance of left lobe of the liver.

Therefore, without further enquiry, alcoholic liver disease might have been accepted as the sole explanation for her hyperferritinaemia. Despite the eventual diagnosis of HH, alcohol is likely to have contributed to her marked hyperferritinaemia as SF values began to fall as the patient reduced her alcohol intake even before venesection was commenced.

Hepatocellular carcinoma (HCC) was also in the differential diagnosis. However, this was ruled out on account of a normal level of alpha fetoprotein and a reassuring liver ultrasound. Had transferrin saturation been normal, hepatic steatosis (as shown on ultrasound) may have also have explained the hyperferritinaemia (4). Furthermore, although there was no evidence of inflammation and infection in this patient, it is important to exclude such conditions since serum ferritin is an acute phase reactant. However, levels of serum ferritin would be expected to be less than 1000 ug/l.

Treatment & follow up

In order to reduce the magnitude of iron overload, patients undergo regular venesection; aiming for a ferritin level of <50 ug/l and a transferrin saturation of <50%. Each 500mls of whole blood contains about 250mg of iron. Once a diagnosis has been confirmed patients' siblings should also offered genetic testing. Homozygotes then undergo treatment and surveillance whilst heterozygotes (carriers) are reassured but counselled of the risk of bearing homozygous offspring should their partner be either a carrier (heterozygous) or affected (homozygous).

Weekly isovolaemic venesection was commenced to reduce this level of iron overload. At the time of reporting four venesections had been performed Serum ferritin was still >2000 ug/l, serum iron 35 umol/l and Tsat 97%. Haemoglobin was 141 g/l and venesections continue with the aim to achieve SF <50 ug/l and a Tsat <50%. Family screening is not yet complete. Another important therapeutic goal in this patient's management was the reduction of alcohol intake.

INVESTIGATING RAISED SERUM FERRITIN

EJ Fitzsimons & NT Mabvuure

This is important since patients with HH who drink excessive alcohol amounts are nine times more likely to develop cirrhosis than those with normal intake (2). The patient reassured the medical team that she had reduced her alcohol intake. This was in keeping with an improvement seen in her LFTs which after four venesections had normalised bar a high AST, albeit reduced from previous readings, of 43 U/L. Oral serum folate supplementation was also commenced and the patient remains under active follow up.

Conclusion

This case demonstrates the challenge of differentiating causes of hyperferritinaemia, especially in patients in whom more than one potential explanation exists. Investigations which may help in this regard are discussed as a prompt to Foundation Year trainees who may be consulted by such patients who may present to haematology, rheumatology or gastroenterology.

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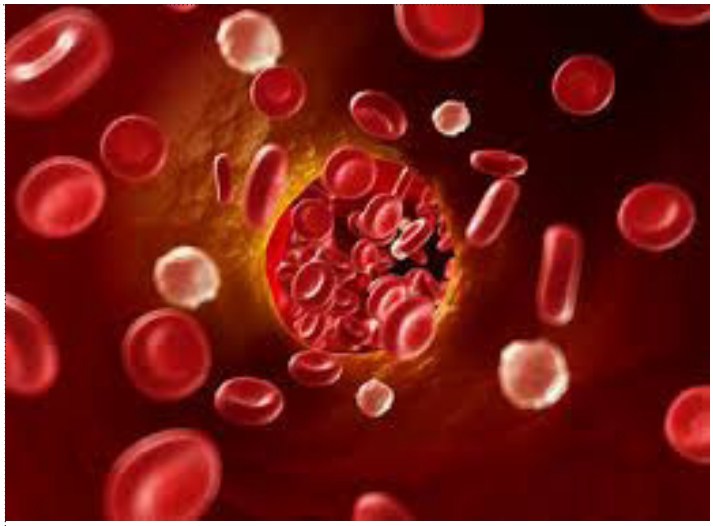

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HODGKIN LYMPHOMA PRESENTING WITH SUPERIOR VENA CAVA OBSTRUCTION (SVCO)

C Rowntree & S Obaji

Abstract

This case based discussion focuses on a 17 year old female who presented with dyspnoea as a consequence of superior vein cava obstruction (SVCO). The case explores the presentation, investigations and management of SVCO in a patient with previously undiagnosed Hodgkin lymphoma.

Case history

A 17 year old female presented to the Accident and Emergency department of her local hospital with a 3 month history of tiredness and a 2 week history of breathlessness on exertion. She had also been experiencing headaches and had noticed that her face had become increasingly swollen. On further questioning she admitted to unintentional weight loss of approximately 6kg over 6 months and had noticed a change in the pitch of her voice. She had no significant past medical history.

On examination she was hypoxic at rest with oxygen saturations of 88% on room air and a respiratory rate of 24 breaths per minute. Prominent neck veins were visible with obvious facial swelling clinically. Heart sounds were quiet but audible. Examination of the chest revealed stony dullness to percussion at the left lower lobe with reduced air entry and vocal resonance. There was no palpable peripheral lymphadenopathy or hepatosplenomegaly

In view of her symptoms of facial swelling, breathlessness, headache and distended neck veins a clinical diagnosis of SVCO was suspected. An urgent chest radiograph (CXR) was performed and is shown in Figure 1.

Hodgkin lymphoma presenting with superior vena cava obstruction (SVCO)
Patient Management

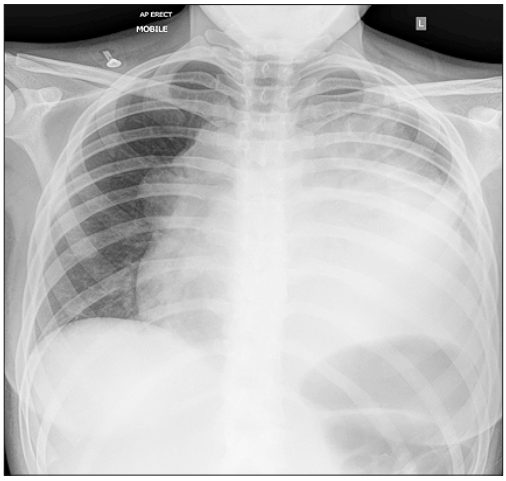


Figure 1: What finding does Figure 1 demonstrate?

The chest X-ray shows a left-sided pleural effusion in addition to a large mediastinal mass which is predominantly projected over the left hemithorax. The cardiac shadow is enlarged raising the possibility of an associated pericardial effusion.

As a consequence of the CXR findings, an urgent computed tomography (CT) scan of the chest was requested and is shown below in Figure 2.

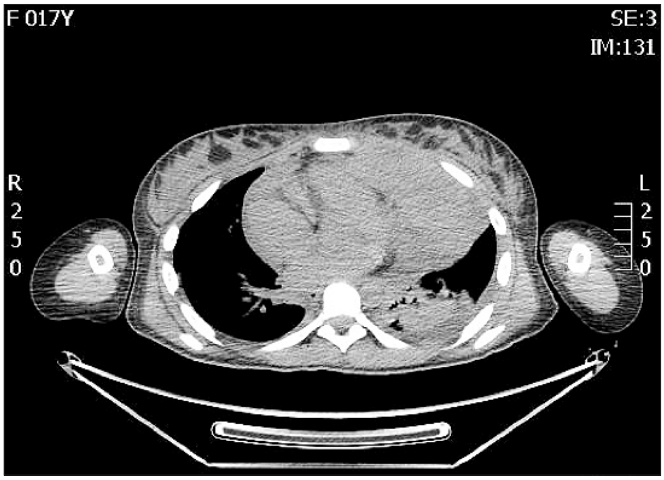


Figure 2

HODGKIN LYMPHOMA PRESENTING WITH SUPERIOR VENA CAVA OBSTRUCTION (SVCO)

C Rowntree & S Obaji

The CT scan showed a large mediastinal mass extending into the lung with a pericardial and pleural effusion. Further imaging of the abdomen and pelvis was unremarkable. An ultrasound guided biopsy of the mass was unsuccessful. The patient subsequently had a video assisted thorascopic surgery (VATS) procedure to biopsy the mass and drain the pericardial fluid, which helped her symptoms of breathlessness. The histology confirmed a diagnosis of classical Hodgkin lymphoma, nodular sclerosing type.

Learning point

An initial assessment of the severity of symptoms and signs is important in SVCO since the presentation may be severe or life-threatening in approximately 15% of cases requiring immediate urgent intervention. Particular attention should be given to the airway and to the neurological and haemodynamic status of the patient. The clinical signs associated with SVCO and their frequency are shown in Table 1.

Haemodynamic	(%)	Respiratory	(%)	Neurological	(%)
Facial oedema	82	Dyspnoea	54	Syncope	10
Arm oedema	46	Cough	54	Headaches	9
Distended neck veins	63	Hoarseness	17	Dizziness	6
Distended chest veins	53	Stridor	4	Confusion	4
Facial plethora	20			Obtundation/CVA	2
Visual symptoms	2				

Table 1: Symptoms and signs associated with SVCO and their estimated incidence (%) (1)

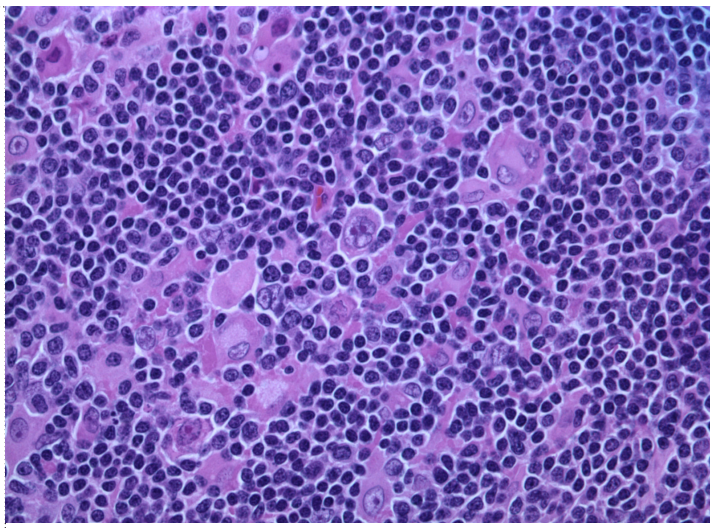
A proposed scale for grading severity of symptoms from SVCO has been proposed by a team at Yale University and is shown in table 2.

Grade	Category	Incidence (%)	Definition
0	Asymptomatic	10%	Radiological evidence only
1	Mild	25%	Facial oedema, cyanosis, plethora
2	Moderate	50%	Facial oedema with functional impairment (cough, dysphagia, visual disturbance)
3	Severe	10%	Mild/moderate cerebral oedema (headache/dizziness), diminished cardiac reserve (syncope after bending), laryngeal oedema.
4	Life-threatening	5%	Significant cerebral oedema (confusion, obtundation), stridor, significant cardiac compromise (syncope with no precipitating factor)
5	Fatal	<1%	Death

Table 2: Severity of symptoms; grading proposed by Yale University (1)

What are the possible causes of SVCO?

The majority of cases of SVCO occur due to a malignancy and can be caused by compressive symptoms from the tumour or blockage of the SVC by a secondary thrombosis. Bronchogenic carcinoma (non-small cell > small cell lung cancer) is the most common cause of malignancy-associated SVCO occurring in over 50% of cases, followed by non-Hodgkin lymphoma (approximately 10%). (2)



Malignant disorders	Non-malignant disorders
Non haematological Lung - non small cell lung cancer, small cell lung cancer Other – e.g. thymoma, germ cell neoplasms, mesothelioma, solid tumours with lymph node metastases(breast)	Thrombosis - e.g. associated with central venous catheters, cardiac pacemaker leads
Haematological Non Hodgkin lymphoma – e.g. diffuse large cell lymphoma, lymphoblastic lymphoma, primary mediastinal large B cell lymphoma. Hodgkin lymphoma - uncommon	Infection e.g. tuberculosis, syphilis, actinomycosis, histoplasma capsulatum (leading to fibrosing mediastinitis)

Table 3: Causes of SVCO.

Initial management and investigations of SVCO:

• Patients with SVCO should be nursed sitting up.

• Patients should be assessed for hypoxia - oximetry, arterial blood gases – and given oxygen therapy as required.

If the patient's airway is severely compromised then dexamethasone 16 mgs od should be prescribed to reduce oedema.

• The following blood investigations should be performed – full blood count, renal and liver function tests, bone profile. A coagulation screen should not be routinely performed prior to biopsy unless this is indicated by the patient's bleeding history.

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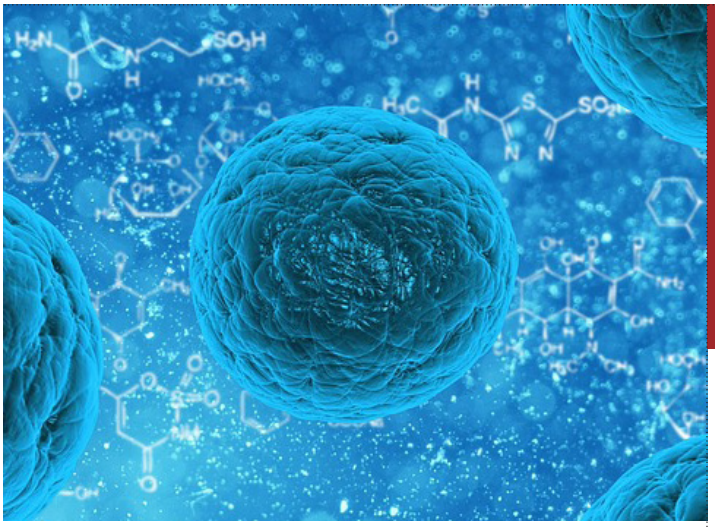
C Rowntree & S Obaji



Hodgkin lymphoma presenting with superior vena cava obstruction (SVCO)
Patient Management

If there is evidence of an undiagnosed malignancy then tumour markers may be helpful - Beta HCG (germ cell tumours), AFP (hepatocellular carcinoma), LDH (lymphomas), CEA (colo rectal tumours), CA15-3 (breast cancer).

• CT scan of the chest is essential - to assess the level of obstruction and to differentiate between tumour and thrombosis. It is important to consider an associated thrombosis even when there is a proven tumour.

• Venous angiography/venogram - may be indicated if thrombosis is suspected.

• Histology is essential if there is an undiagnosed tumour and an urgent biopsy should be organised.

Treatment of SVCO

What are the treatment options for SVCO?

Short term high dose corticosteroids e.g. dexamethasone 16 mgs daily, are recommended for emergency presentations of SVCO such as airway compromise. Wherever possible a histological biopsy is required in cases of malignancy-associated SVCO to guide appropriate anti-tumour therapy.

Where symptoms are life-threatening, urgent intravascular stenting is recommended to provide rapid relief of SVCO. (3) However, stenting is rarely required in haematological malignancies as the tumours are so exquisitely sensitive to treatment and rapid responses can be gained with steroids plus chemotherapy. In cases of malignancy–associated SVCO where symptoms are not life-threatening, definitive treatment with chemotherapy, surgery or radiotherapy is guided by the histology, tumour type and stage.

Stenting may also be considered in patients where treatment options of the tumour is limited (e.g. mesothelioma) or in recurrence where initial therapy has failed. (1)

If a thrombosis is demonstrated on imaging then the patient should be anticoagulated. Prophylactic anticoagulation should be considered for patients with compressive symptoms due to tumour without evidence of a clot as these patients are at high risk of developing a secondary thrombosis. Thrombolytics should be considered where an extensive thrombus is causing SVCO, often prior to urgent stenting. (1)

When a thrombus is present, systemic anticoagulation is required to limit extension of the clot. Anticoagulation or anti-platelet therapy in the absence of a thrombus after stent placement has been recommended but there is currently no evidence-base for this practice. (4,5)

The patient described in this report initially received steroids for symptomatic relief from her breathlessness and facial swelling. Following the histology results, a chemotherapy regime was started (adriamycin, bleomycin, vinblastine and dacarbazine) with a good clinical response. She received prophylactic low molecular weight heparin during the course of her treatment.

Discussion

SVCO is caused by either extrinsic compression from lymph nodes, mediastinal masses and adjacent lung pathology or internal thrombus. As the blood flow within the SVC becomes obstructed, collateral veins form often over several weeks allowing venous return to the right atrium. The elevated upper body venous pressure results in the clinical signs and symptoms of SVCO as described above.

The speed of onset of life-threatening symptoms is determined by the rate of formation of venous collaterals in relation to the degree of complete SVC obstruction. Often patients with SVCO are acutely unwell upon initial presentation and should be treated as a medical emergency. As shown in this case, obtaining accurate histology is essential in undiagnosed malignancy to guide effective definitive treatment. (6)

HODGKIN LYMPHOMA PRESENTING WITH SUPERIOR VENA CAVA OBSTRUCTION (SVCO)

C Rowntree & S Obaji

Self-assessment questions

1) A 65 year old lady is admitted to hospital with progressive dyspnoea due to suspected SVC obstruction. Which symptom would be considered as life-threatening in grading the severity of SVCO?

a) facial swelling and cyanosis
b) difficulty in swallowing
c) persistent cough and hoarseness of voice
d) collapse with no clear cause
e) dizziness on bending

2) Which is the most common cause of malignant-associated SVCO?

a) Mesothelioma
b) Hodgkin lymphoma
c) Non-Hodgkin lymphoma
d) Small cell lung cancer
e) Non-small cell lung cancer

Answers

1. Answer d

Syncope without a precipitating factor suggests significant cardiac compromise and is therefore classified as a life-threatening symptom in the grading system for the severity of SVCO. Severe symptoms include headache and dizziness (mild or moderate cerebral oedema) or syncope after bending (diminished cardiac reserve).

2. Answer e

Lung cancer and non-Hodgkin lymphoma constitute approximately 95% of SVCO caused by malignancy. Non-small cell lung cancer is the commonest malignant cause. Hodgkin lymphoma typically presents with cervical lymphadenopathy and rarely presents with symptoms of SVCO.

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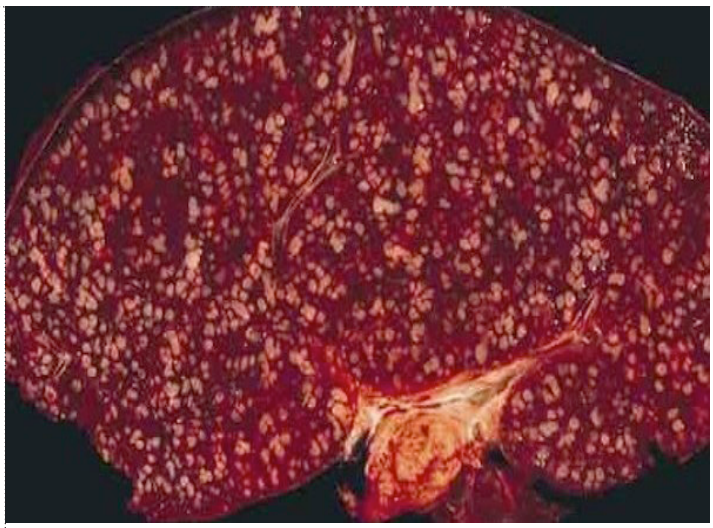

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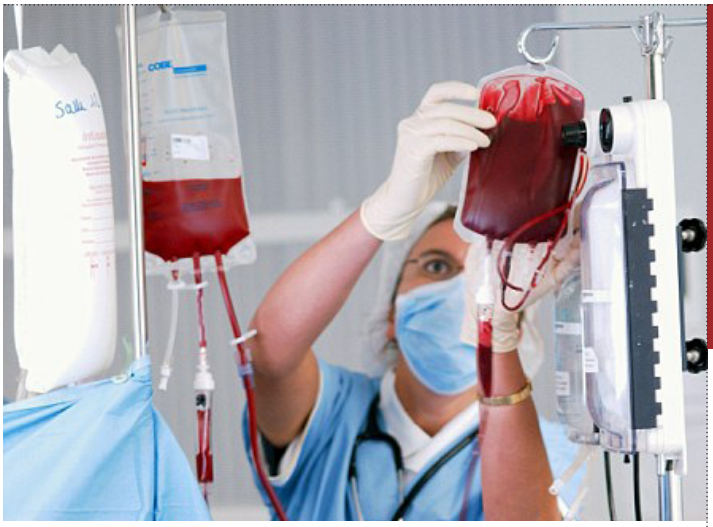
CAUTIONS & HAZARDS OF BLOOD TRANSFUSION - A CASE OF HYPERVISCOSITY SYNDROME

I Koutsavlis



Abstract

Transfusion of blood products can be life saving in certain scenarios but careful assessment should be carried out to balance the risks and benefits. We explore situations where transfusion of red cells could potentially increase the risk of complications and give as example, a patient with severe anaemia and hyperviscosity syndrome. This article also addresses the management of acute transfusion reactions, a common scenario that junior doctors will have to tackle in their daily practice.

Case history

A 68 year old man presented in the acute medical assessment unit with a 4 day history of exertional dyspnoea, fatigue and blurred vision. Collateral history from family members revealed confusion with intermittent memory loss. He did not have any other significant personal or family history of note and was not on any regular medications.

He was found to be disorientated in time and place. Cardiac and abdominal examination was unremarkable with normal breath sounds. However, fundoscopy showed beading of the retinal veins bilaterally. Blood pressure was 100/55mmHg, radial pulse regular 100 beats per minute with a respiratory rate of 18 breaths per minute and oxygen saturation on pulse oxymetry of 95% on room air. Temperature was 36.5°C on admission.

Initial laboratory investigations of full blood count showed marked anaemia with a haemoglobin of 49g/L, mean corpuscular volume (MCV) of 81,6fL and mild thrombocytopenia with platelets of 10^9 x 10^9 /L. White cell count was normal. Biochemistry abnormalities included high total protein levels (110 g/L) and hypoalbuminaemia (albumin 22 mg/L) only. The plain chest X-ray was normal and his resting 12 lead-electrocardiogram showed sinus rhythm. A CT head was also performed demonstrating only age related atrophic changes.

Cautions & hazards of blood transfusion - a case of hyperviscosity syndrome
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In view of his severe anaemia associated with dyspnoea, he was transfused, however, following 1 unit of red cells over 2 hours the patient appeared more confused with symptoms of worsening dyspnoea.

Approach to anaemia

Investigation of the anaemia is of paramount importance. An easy approach is to consider anaemia as impaired production, increased loss or increased destruction of red cells (1) (Table 1). I find this a useful alternative to the traditional approach that compares the size of red cells (MCV); where as a rule of thumb you see low MCV in iron deficiency or thalassaemia, normal MCV in bone marrow failure/ infiltration or chronic conditions and a high MCV in B12/folate deficiency, myelodysplasia or alcohol/ liver disease.

In order to differentiate between the above, perform targeted investigations which may include haematinics, reticulocyte count, kidney, liver and thyroid function tests, ESR and a blood film. Further investigations might be necessary to exclude haemolysis (LDH, Direct Antiglobulin test (DAT), haptoglobins) and/or myeloma (immunoglobulins, electrophoresis, urine for bence jones protein). A haematology referral may be appropriate if the anaemia is unexplained.

Impaired production of red cells	Loss of red cells	Destruction of red cells
• **Infectious** (bacterial-tuberculosis, viral-HIV, Parvovirus) •**Neoplastic** (Haematological malignancies, metastatic disease) •**Endocrine** (Thyroid Dysfunction, Erythropoietin Deficiency, Renal Failure) •**Nutritional Deficiency** (Iron,B12,Folate) •**Anemia of Chronic Disease**	•**Acute blood loss** (traumatic, malaena, haematemesis, menorrhagia) •**Chronic blood loss** (occult bleeding, colonic polyp/ carcinoma)	•**Due to antibodies - Immune mediated** (IgM,IgG) •**Defect in red cell wall** (membrane or enzyme defects, e.g G6PD deficiency) •**Haem or globin abnormalities** (haemoglobinpathies, e.g sickle cell disease) •**Hypersplenism** •**Microangiopathy** (DIC, TTP, HUS)

Table 1: Principles of anaemia.

CAUTIONS & HAZARDS OF BLOOD TRANSFUSION - A CASE OF HYPERVISCOSITY SYNDROME

I Koutsavlis

Hyperviscosity syndrome (HVS)

In our patient with normocytic anaemia, no cause was found initially but we suspected bone marrow infiltration as he also had a reduced platelet count. The large globulin gap (total protein minus albumin) pointed towards the presence of a paraprotein and serum electrophoresis confirmed a very high level of an IgM paraprotein. Monoclonal proteins (usually IgG, IgA or IgM) are derived from the same neoplastic clone of lymphocytes or plasma cells. High levels of monoclonal IgG or IgA are more in keeping with multiple myeloma. High IgM paraprotein is more likely to be associated with certain types of lymphomas(2).

Bone marrow biopsy showed infiltration from lymphoplasmacytic lymphoma (cells with characteristics between lymphocytes and plasma cells). When these cells produce IgM paraprotein, the disease is called Waldenstrom's macroglobulinaemia. Very high levels of paraprotein can make the blood thicker and increase the blood's viscosity.

Hyperviscosity syndrome (HVS) is a group of symptoms triggered by an increase in the viscosity of the blood. Symptoms are the result of impairment in the microcirculation of the central nervous system, resulting in neurological manifestations. Reduced platelet function may lead to mucosal haemorrhage and expanded plasma volume may cause heart failure(3). Signs of HVS may be identified through fundoscopy, as in this patient. The causes of hyperviscosity are summarized in table 2(5).

1. Increased paraprotein levels	Myeloma/ Lymphoma - especially IgM (as intravascular molecule)
2. Markedly increased white cells, red cells or platelets	Acute or chronic leukaemia, Polycythaemia (primary or secondary), essential thrombocythaemia
3. Other plasma proteins	High bilirubin, cholesterol, inflammatory factors
4. Abnormalities with red cell shape	I.e Sickle cell disease

Table 2: Common causes of hyperviscosity.

Although the diagnosis of HVS is based on clinical grounds and history, laboratories can directly measure plasma viscosity (PV). PV reflects the force needed to send a fixed amount of plasma along a thin tube in a given time at a standard temperature. Typically distilled water at 20^{0}C will have a viscosity of 1.00mPs (milli-Pascal-second), whereas normal plasma at 37^{0}C may have a viscosity of around 1.7mPs(6).

The higher the result, the "stickier" the blood. Normal values range between 1,4mPs and 1,8mPs depending on the laboratory, while symptoms occur in most patients with values above 5mPs. As per ESR and CRP, any inflammatory condition can increase PV. Very high PV levels are seen in association with paraproteinaemias, as discussed here, and temporal arteritis.

When not to transfuse

The critical question is whether to transfuse this patient or not. The difficulty being that the patient appears to have symptomatic anaemia, yet blood transfusion itself would increase the viscosity of the blood with potentially catastrophic complications in a patient with HVS (exacerbation of neurological symptoms, bleeding, heart failure). A methodological approach is useful before the transfusion of any blood products to weigh up the risks and benefits (table 3).

Is the Hb below the threshold set by local or national guidelines?	Usually this is Hb < 70g/L. Generally, there is a push towards restrictive transfusion practice.
Is there evidence of massive haemorrhage for example trauma,surgical,GI bleeding or obstretic bleed?	You might consider transfusion even with normal Hb levels if severe blood loss
Is the patient symptomatic? (breathless, tachycardia or other)	You may withhold transfusion if patient stable, especially out of hours
B12, folate deficiency, hyperviscosity syndrome, sickle cell disease?	Treat underlying cause of the anaemia rather than transfuse where at all possible

Table 3: Considerations prior to blood transfusion.

B12 and/or folate deficiency can cause severe megaloblastic anaemia, which can impair cardiac muscle function. Red cell transfusion may cause potentially fatal circulatory overload and these patients are best treated with bed rest and high-concentration oxygen while a response to B12 or folate replacement occurs (the Hb concentration starts to rise in 3 or 4 days). If red cell transfusion is essential, single units of red cells should be transfused over 4 hours with close monitoring and diuretic cover(7).

Patients with sickle cell disease generally run an asymptomatic low Hb level (potentially even < 70g/l). Do not transfuse these patients on the basis of an isolated Hb result as there is a risk of causing hyperviscosity as well as other complications of transfusion, including alloimunisation and hyper-haemolysis syndrome. Blood transfusion may however be life saving, particularly in acute illness(8). Always discuss individual cases with a haematologist.

It would also be useful to mention the Patient Blood Management (PBM) scheme. PBM is a multi-disciplinary, evidence based approach to optimising the care of patients who might need a transfusion. A core activity of the PBM team is to support the appropriate use of blood components including the promotion of alternatives to transfusion. PBM was launched in England in June 2012 as a collaboration between the National Blood Transfusion Committee and NHS Blood and Transplant (NHSBT). There is a national guidance published in June 2014 with recommendations on how PBM should be implemented in hospitals(9). (www.transfusionguidelines.org.uk/uktransfusion-committees/national-blood-transfusion-committee/patient-blood-management)

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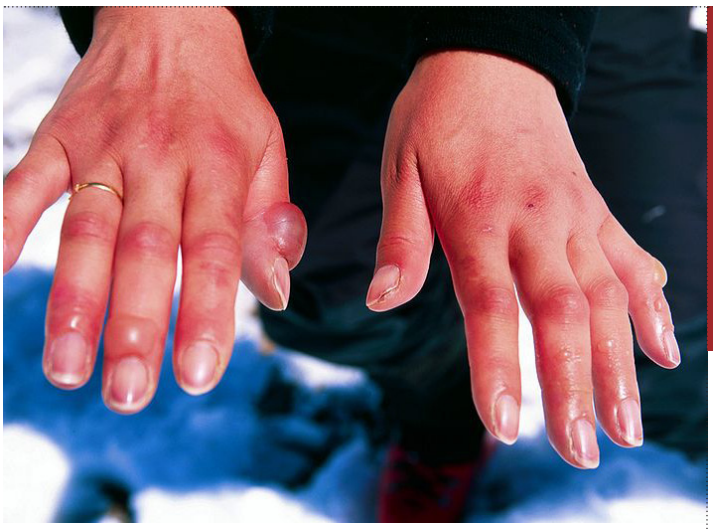

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Transfusion reactions

The other question is, could the worsening dyspnoea in our patient be due to an acute transfusion reaction?

Transfusion reaction can be acute (if it develops during or < 24 hours after transfusion) or delayed (> 24 hours). Therefore, it is good practice to inform all patients to report any symptoms, related to a transfusion reaction even more than 24 hours from the end of transfusion. There is a wide spectrum of symptoms including febrile or allergic reactions (most common), hypotensive episodes and respiratory distress.

If the reaction is mild, then continuation of blood transfusion is possible with appropriate measures. Mild reactions include a temperature ≥ 38°C and a rise between 1 and 2°C from pre transfusion values or transient flushing, urticaria or rash. Moderate reactions include a rise in temperature of ≥ 2°C, or fever ≥ 39°C and/or rigors, chills, other inflammatory symptoms/signs such as myalgia or nausea which precipitate stopping the transfusion. Also, wheeze or angioedema and a systolic blood pressure < 80 mm with a fall > 30mm from baseline during or within one hour from transfusion. Hypotension leading to shock, anaphylaxis and any reaction that prolongs admission or results in an unstable situation, are severe reactions.

Overall the most common adverse incidents are caused by errors, resulting in the transfusion of an incorrect component(17). It is worth mentioning that many reactions are probably preventable by improved practice and monitoring. For example, transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI) and haemolytic reactions. However, others are unpreventable, including transfusion-transmitted infection, transfusion-associated dyspnoea or acute transfusion reactions as described above.

Verbal consent for transfusion must be obtained and documented prior to transfusion, including discussion of the risks, benefits and alternatives to transfusion. Written information should also be provided.

See table 4 for a summary of the management of common transfusion reactions (15). (BCSH guideline - http://onlinelibrary.wiley.com/doi/10.1111/bjh.12017/pdf). If moderate or severe reactions always discuss with a blood transfusion specialist as further investigations and reporting of the reaction will be necessary.

Mild reactions (no or limited change in vital signs)	Isolated fever > 38°C **AND** rise of 1-2°C from baseline and/or pruritus or rash but **without** other features	May be treated with paracetamol +/- antihistamine. In these cases it is reasonable to restart the transfusion with direct observation.
Moderate reactions (may also include angioedema and dyspnoea, but not sufficiently severe to be lifethreatening)	Temperature > 39°C **OR** a rise of > 2°C from baseline **AND/OR** systemic symptoms such as chills, rigors, myalgia, nausea or vomiting), bacterial contamination or a haemolytic reaction should be considered.	Stop transfusion, monitor closely, consider antihistamines, steroids, nebulizers and discuss with specialist. Do not discard impilicated unit.
Severe reactions	•Severe hypotension associated with wheeze or stridor (consider anaphylaxis – follow local/ national guidelines) •Severe hypotension without clinical signs of anaphylaxis or fluid overload (ABO incompatibility or bacterial contamination) •Severe dyspnoea without shock (Consider TRALI or TACO) Senior advice is necessary	

Table 4: Management of ATR (as adapted from the British Committee for Standards in Haematology guideline)

Management of HVS

In our case of HVS we urgently need to remove and decrease the levels of IgM paraprotein. For this, we use a technique called plasmapheresis (apheresesis means removal) or theuraputic plasma exchange (TPE). It is very effective in rapidly relieving many clinical symptoms of HVS in patients presenting with neurological complaints or those with uncontrollable or recurrent epistaxis.

The efficiency of TPE in eliminating plasma IgM is excellent, but IgA or IgG related syndromes may require greater volumes and repeat exchanges, given that a large percentage of these smaller immunoglobulins are extravascular. TPE is even more important in patients with anaemia that require transfusion as plasmapheresis can 'make room' for the transfused blood(3,14).

CAUTIONS & HAZARDS OF BLOOD TRANSFUSION - A CASE OF HYPERVISCOSITY SYNDROME

I Koutsavlis

Test yourself section

1) This patient becomes pyrexial, 38.2°C, following the first unit of red cells. What is your next action?

a) Continue transfusion. No need for further investigations.

b) Stop transfusion. Patient has an allergic reaction. Inform blood transfusion service (BTS).

c) Stop transfusion, give paracetamol and then restart.

d) Stop transfusion, check patient's identity, observation chart and perform clinical examination. Give paracetamol and restart if rise in temperature is less than 2 degress from baseline and no signs of allergic reaction.

e) As d) Also inform BTS and investigate as likely severe allergic reaction.

2) A 70 year old patient presents with new unexplained back pain, mild normocytic anaemia and severe renal impairment. Which one of the following investigations is the most important?

a) Iron studies

b) X ray of the lumbar spine

c) Serum electrophoresis

d) Ultra sound scan of the kidneys

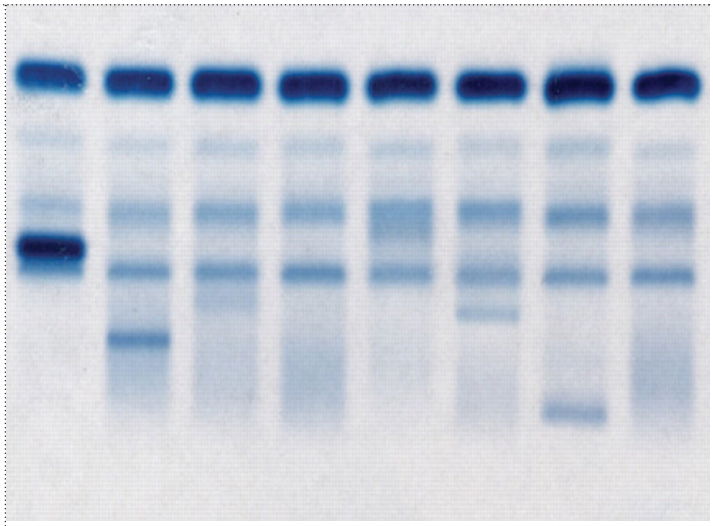
e) B12/Folate levels

Answers

1. Answer d) stop transfusion

The British Committee for Standards in Haematology (BCSH) transfusion guidelines are clear for the above matter. These are highlighted here. If a patient develops new symptoms or signs during a transfusion, this should be stopped temporarily, but venous access maintained. Identification details should be checked between the patient, their identity band and the compatibility label of the blood component.

Perform visual inspection of the component and assess the patient with standard observations. For patients with mild reactions, such as pyrexia (temperature of >38°C AND rise of 1-2°C from baseline), and/or pruritus or rash but WITHOUT other features, the transfusion may be continued with appropriate treatment and direct observation.



Patients with mild isolated febrile reactions may be treated with oral paracetamol (500-1000 mg in adults). Patients with mild allergic reactions may be managed by slowing the transfusion and treatment with an antihistamine. Isolated rise in temperature with the above features does not need to be investigated as a severe allergic reaction.

2. Answer: c) serum electrophoresis

In this scenario with unexplained anaemia, renal impairment and back pain, multiple myeloma must be considered. A simple test is to check for a monoclonal band (immunoglobulin arising from the same clone of plasma cells) in the blood.

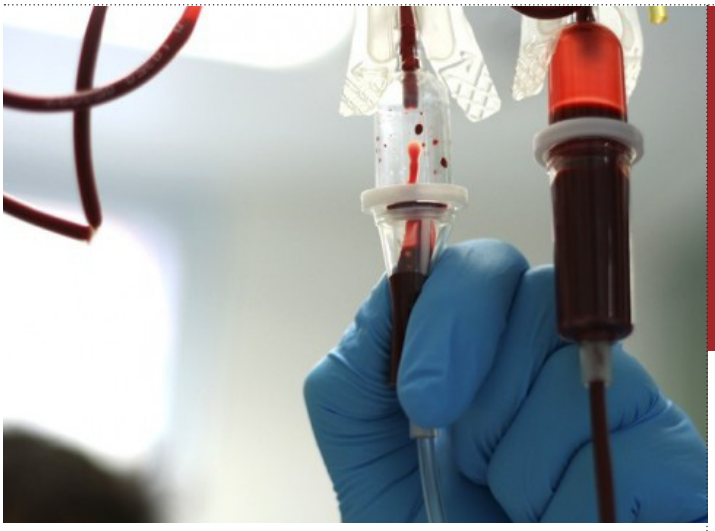
Therefore, from the above answers, serum electrophoresis is the right answer, however, a full workup of these patients should include a bone profile to exclude hypercalcaemia, a urine sample to check for bence jones protein, a skeletal survey to rule out any lytic lesions and a bone marrow aspirate and trephine(biopsy) to identify any plasma cells in the bone marrow. Watch out for cauda equina in these patients, which is a medical emergency.

Conclusion

Anaemia is very common amongst hospitalized patients and junior doctors often encounter complex cases. However, it is essential to elicit the underlying cause of the anaemia in order to make an individualized treatment plan. Not all anaemic patients require transfusion of blood components and in some cases blood transfusion could be hazardous. Therefore, it is important to weigh up the risks and benefits in all cases. Acute transfusion reactions should be classified according to symptoms and severity, which guide treatment and appropriate investigations where necessary.

CAUTIONS & HAZARDS OF BLOOD TRANSFUSION - A CASE OF HYPERVISCOSITY SYNDROME

I Koutsavlis



Cautions & hazards of blood transfusion - a case of hyperviscosity syndrome
Patient Management

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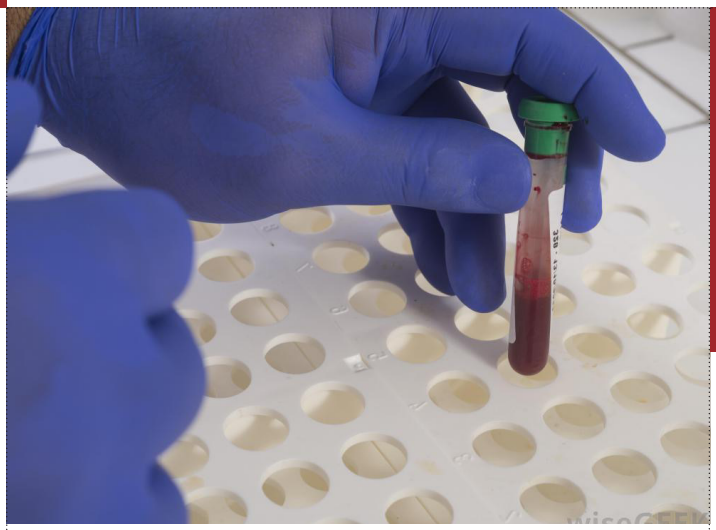
PANCYTOPENIA - A CLINICAL CASE OF HAIRY CELL LEUKAEMIA

ISL Lo & AE Milne



Pancytopenia - a clinical case of hairy cell leukaemia
Patient Management

Abstract

Pancytopenia is a common presentation to our day-to-day clinical practice. The causes of pancytopenia are diverse and severe pancytopenia can be life threatening therefore warrant urgent assessment and treatment. In this article, we described a case of pancytopenia caused by a rare form of leukaemia, hairy cell leukaemia, and illustrated a step-to-step approach leading to the diagnosis.

Case history

A 58 year old gentleman presented in the haematology department with lethargy, fever, recurrent sore throat and cough for the past 5 weeks. There had been no improvement despite multiple courses of antibiotics. Abdominal examination revealed splenomegaly 12cm below the costal margin without hepatomegaly or ascites. There was no evidence of peripheral lymphadenopathy, cutaneous rashes or purpura. Chest and cardiovascular examination were unremarkable.

Haematological investigations showed a haemoglobin 87 g/dl, total white cell count $0.9x10^9$/L, platelets $21x10^9$/L, no monocytes and the absolute neutrophil count was $0.14x10^9$/L, i.e. this showed pancytopenia. Biochemical parameters were normal. There was no paraprotein. CT abdomen confirmed splenomegaly but no additional lymphadenopathy.

This patient has no significant past medical history and not on any regular medication. He has no family history of haematological disease. He was an IT worker and lived a healthy lifestyle.

Blood film showed marked pancytopenia with monocytopenia and abnormal lymphocytes present with hairy projections. The bone marrow aspirate was dry and trephine showed markedly reduced haematopoiesis with a heavy infiltration of hairy cells and increased reticulin fibrosis.

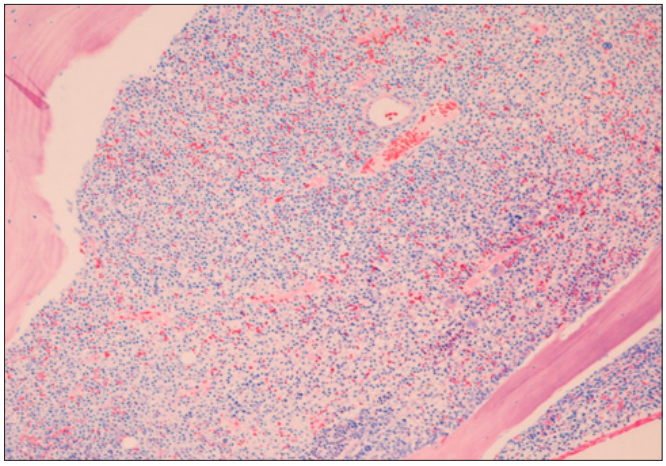


Figure 1: A bone marrow trephine stained Giemsa at low power showing diffuse, interstitial infiltrate of hairy cells.

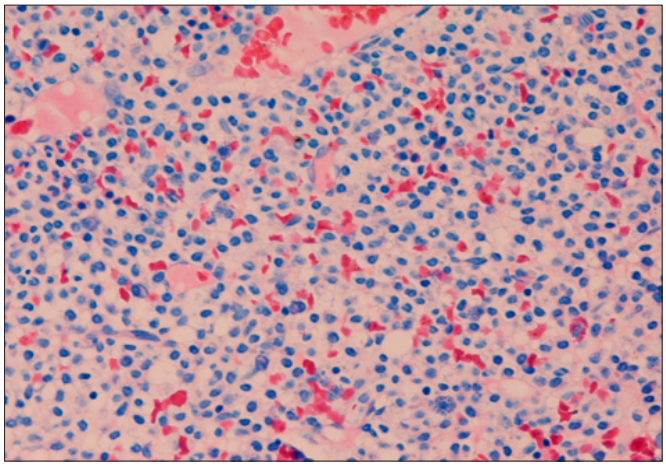
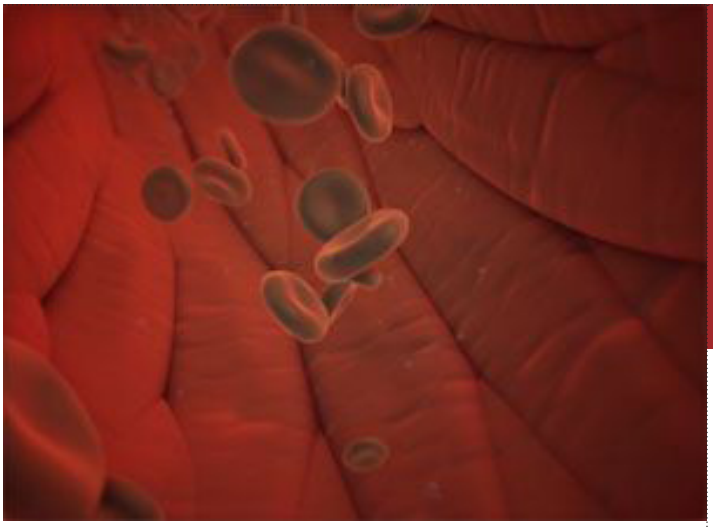


Figure 2: A bone marrow trephine stained Giemsa at high power showing hairy cells with a fried egg appearance with oval nuclei.

PANCYTOPENIA - A CLINICAL CASE OF HAIRY CELL LEUKAEMIA

ISL Lo & AE Milne



Pancytopenia - a clinical case of hairy cell leukaemia
Patient Management

Immunocytochemistry showed strongly positive for CD20, CD22, CD79b, CD25, CD103, and CD11 which confirmed the presence of hairy cells. The somatic acquired V600E mutation of the BRAF gene was identified in molecular studies which is highly specific to hairy cell leukaemia (1). He was thus diagnosed with hairy cell leukaemia (2). His management was discussed in the haematological MDT and the patient was commenced on supportive care including allopurinol, antibiotics and cladribine chemotherapy treatment as an inpatient. Cladribine is a purine based analogue and therefore irradiated blood products are indicated to avoid the risk of transfusion related graft versus host disease.

Discussion

Pancytopenia describes the reduction of all 3 types of cellular components of the blood leading to anaemia, neutropenia and thrombocytopenia. The causes of pancytopenia can be divided into bone marrow failure and increased peripheral destruction or consumption (Table 1).

Congenital/Familial	Alcohol
Drugs – cytotoxics, NSAIDS, anti-epileptics	Viral infection/ Mycobacterial infections
Malignant infiltration	Autoimmune disorders
Diet, B12 and folate deficiency	Paroxysmal nocturnal haemoglobinuria

Table 1: Causes of pancytopenia.

The presence of pancytopenia always warrants investigations by the haematologist unless the underlying cause is known. The cause of pancytopenia is diverse and the diagnosis is mainly based on a detail history, examination and standard blood test.

The symptoms of the pancytopenia relate to the affected blood cell linage and the severity of pancytopenia. The patients with mild pancytopenia are often asymptomatic and detected incidentally when blood is taken for another reason. In severe pancytopenia, spontaneously mucosal bleeding from gum and gastrointestinal tract, bruising, petechial and purpura secondary to thrombocytopenia are usually the first symptoms to develop, followed by symptomatic anaemia and bacterial infection secondary to neutropenia.

A detail history of drugs, previous or current chemotherapy and radiotherapy treatment should be obtained. A dietary history, including alcohol, may raise the possibility of B12 and folate deficiency. Previous transfusion, intravenous drug use and sexual history may indicate probable viral hepatitis or HIV infection. A medical history of solid tumours, haematological and autoimmune disorders are also important.

A thorough clinical examination of each organ system is required. Particular attention should be given to splenomegaly, lymphadenopathy and signs of vasculitis. Other important examinations include an eye examination to look for jaundice sclera (PNH and liver disease), and retinal haemorrhage (thrombocytopenia); and an oral examination for mucosal petechia (thrombocytopenia), stomatitis (B12 deficiency), and gingival hyperplasia (leukaemia infiltration).

Severe pancytopenia is medically important and the patient requires immediate support and investigation. Early involvement with a haematologist is recommended. If the initial blood result showed pancytopenia, consider repeating a full blood count to confirm the result.

The following investigations are required to confirm the diagnosis and exclude other causes of pancytopenia; a full blood count, reticulocytes, LFT, folate, B12, ferritin, viral screen (EBV, CMV, hepatitis screen), autoantibody screen and a blood film to assess morphological changes. In all unexplained pancytopenia, a bone marrow aspirate and trephine are mandatory to look for a primary haematological disorder.

PANCYTOPENIA - A CLINICAL CASE OF HAIRY CELL LEUKAEMIA

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A multi-disciplinary team approach is recommended to collate the relevant results and develop a management plan. The management of patients with pancytopenia includes treating the underlying cause, supportive care and prevention of infection. Support with red cell and platelet transfusion may be needed to maintain a safe blood count.

Symptomatic anaemia should be corrected by red blood cell transfusion to maintain haemoglobin level above 8 gm/dl. Red cells should be administered cautiously to avoid circulatory overload. It is recommended to give prophylactic platelet transfusion when the platelet count is less than $10x10^9$/L or $20x10^9$/L in the presence of infection. Fatal haemorrhage is more common with severe thrombocytopenia.

The risk of bacterial and fungal infection depends on the individual's neutrophil and monocyte counts. Patients who are severely neutropenic ($<0.5x10^9$/L) with a fever, should be nursed in isolation in a hospital, and received filtered water and food with low bacterial content. Some centres recommend prophylactic antivirals, antifungals, regular aseptic mouthwash, such as chlorhexidine, and prophylactic antibiotic against Pnumocystis jirovecii. Patients have the responsibility to pay particular attention to personal hygiene, including oral and skin care.

All neutropenic patients who develop a fever require urgent assessment and treatment. A full septic screen should include blood cultures, urine dip and chest X-ray. The choice of antibiotics for neutropenic sepsis is based on your local hospital guidelines. For persistent fevers despite ongoing treatment, further investigations for atypical bacterial and fungal infection are crucial.

All patients with pancytopenia should be carefully assessed. A systematic approach including a comprehensive history and examination should direct us to the diagnosis. Prompt investigations and treatment can avoid life threatening conditions.

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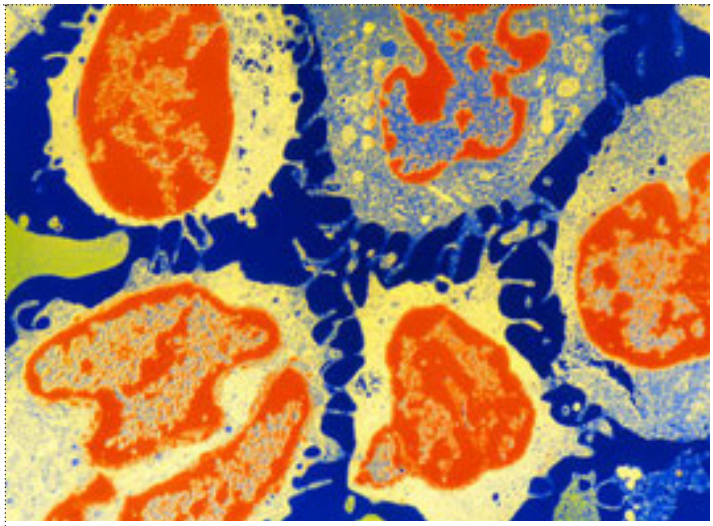

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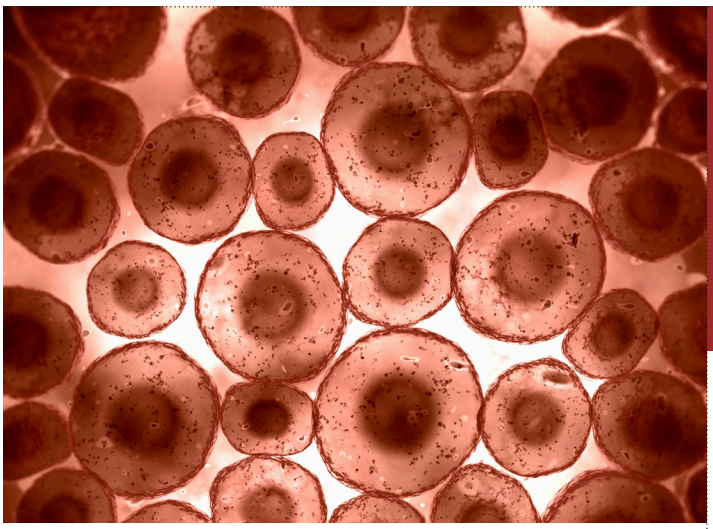
THE SPECTRUM OF COMPLICATIONS IN MYELOMA: A CASE BASED DISCUSSION

G Marron & J Rutherford



Abstract

Myeloma is a plasma cell neoplasm accounting for 10-15% of all haematological malignancies (1, 2). A disease of the elderly, the median age at presentation is 65 (1).

Plasma cells are derived from B-lymphocytes whose usual role is to produce immunoglobulins (antibodies). In myeloma a genetic insult results in development of a malignant plasma cell clone in the bone marrow with impaired production of normal blood cells. Characteristically a monoclonal immunoglobulin known as a paraprotein is produced, (1,2) which aids diagnosis and monitoring response to treatment. Sometimes only immunoglobulin light chains are produced. These are detectable in urine as Bence-Jones protein and blood as serum free light chains (3).

Myeloma is almost always preceded by a pre-malignant state called monoclonal gammopathy of unknown significance (MGUS), although this often goes unnoticed due to the absence of symptoms (3). The risk of progression from MGUS to myeloma is low at around 1% per annum.

This article will focus on Ms J, a 56 year old lady, who presented with a very aggressive form of myeloma. Acute management of myeloma complications will be discussed with a particular emphasis on sepsis and renal failure.

Presenting complaint

Ms J presented with a three week history of progressive back pain, myalgia and fatigue. Her General Practitioner noted mild renal impairment (creatinine 120mmol/l NR 46-92), anaemia (haemoglobin 117g/l NR 130-175) and hypercalcaemia (calcium 2.77mmol/l NR 2.10-2.55) on routine bloods.

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Plasma viscosity was elevated at 1.84mPA.s (NR 1.50-1.72) and she was commenced on prednisolone 15mg /day for suspected polymyalgia rheumatica. A myeloma screen was sent. Subsequently Bence-Jones protein was detected at 1.9g/l prompting urgent referral to Haematology.

On admission she was pale and tired. Chest and abdominal examinations were normal, she was haemodynamically stable and appeared euvolaemic. There was tenderness on palpation over her left chest wall.

Repeat bloods showed a dramatic deterioration in the ten days since seeing her GP with a urea of 23.5mmol/l and Creatinine of 318mmol/l.

Past medical history comprised only partial thyroidectomy for toxic multinodular goitre. She is a non-smoker and avoids alcohol. She had been self-medicating with Co-Codamol and Ibuprofen. Her only other medication was Levothyroxine. Her blood film showed rouleaux and circulating plasma cells.

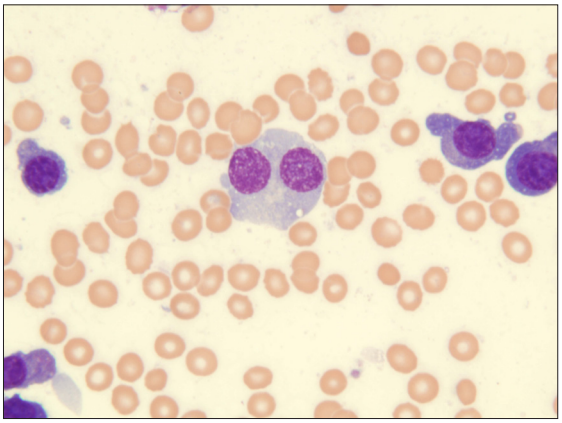

Figure 1: Plasma cells are not usually present in peripheral blood but may be seen in severe sepsis or in myeloma where they confer a poorer prognosis.

THE SPECTRUM OF COMPLICATIONS IN MYELOMA: A CASE BASED DISCUSSION

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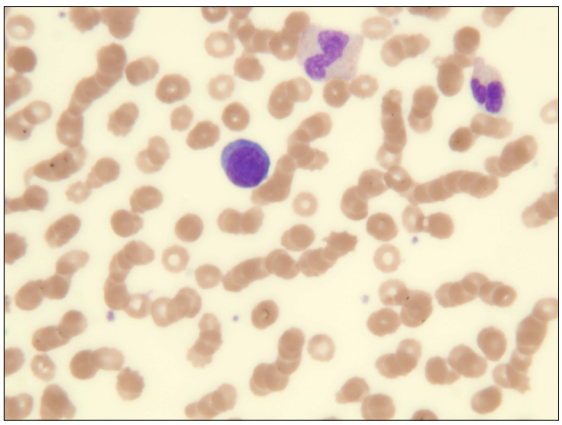

Figure 2: Red cell rouleaux may indicate a raised level of protein in the plasma.

Ms J underwent a bone marrow aspirate and trephine for staging and prognostic information. This demonstrated extensive replacement of normal haematopoiesis by plasma cells.

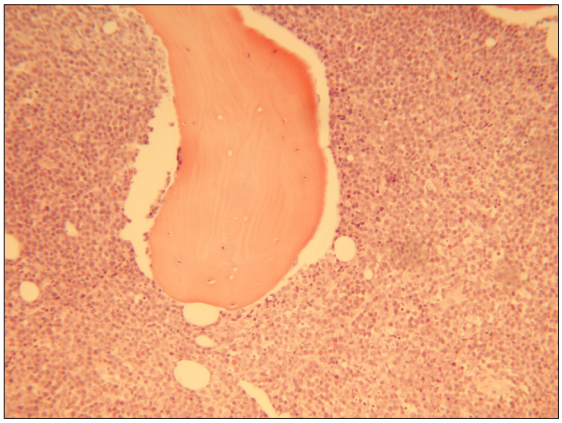

Figure 3: Bone marrow trephine showing loss of normal marrow architecture and replacement by a monotonous infiltrate of plasma cells.

Immunohistochemistry on the trephine showed the plasma cells expressed CD138 (found on normal and malignant plasma cells) and were Kappa light chain restricted with no expression of Lambda (indicating clonality) (3). Genetic analysis by fluorescence in situ hybridisation (FISH) showed deletion of chromosome 17p. This leads to the loss of a key tumour suppressor gene, TP53, as in many other cancers, and carries a poor prognosis in myeloma (4).

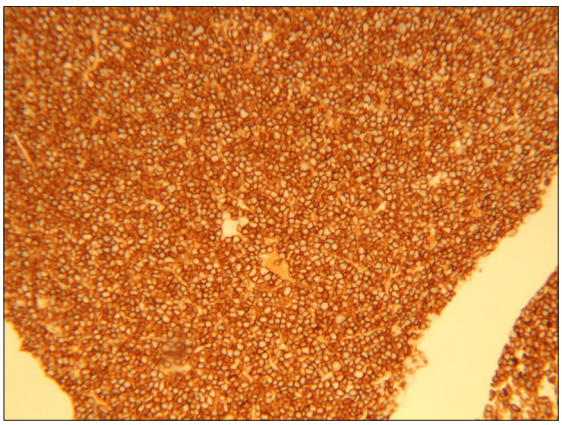

Figure 4: Immunohistochemistry uses stains conjugated to antibodies to highlight and characterise cells of interest, in this case CD138 which is expressed on plasma cells.

Skeletal survey showed lytic bone lesions in the skull but none elsewhere. An MRI of the spine revealed diffusely abnormal marrow signal in keeping with the bone marrow findings, but no bone destruction.

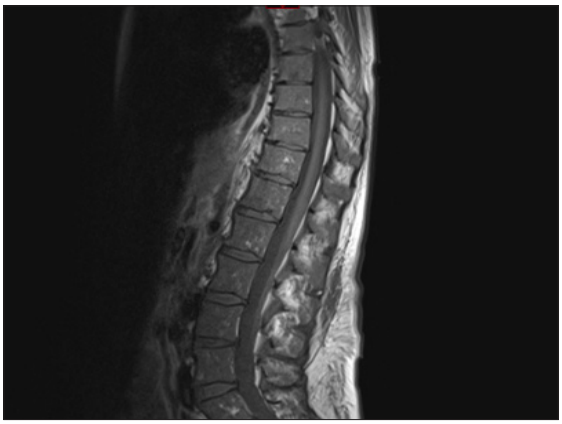

Figure 5: MRI of thoracic and lumbar spine (sagittal view) shows no focal bone lesions but diffusely abnormal marrow signal.

Ms J met the diagnostic criteria for myeloma by having clonal plasma cells in her bone marrow, monoclonal protein in her urine and the presence of at least one so called CRAB criteria for myeloma related organ dysfunction; elevated Calcium, Renal insufficiency, Anaemia and Bone damage (3).

She was given IV fluids and IV Pamidronate to correct her hypercalcaemia. A four day pulse of high dose Dexamethasone was prescribed as initial treatment. Corticosteroids are toxic to malignant plasma cells and also ameliorate hypercalcaemia.

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Given her aggressive presentation and renal failure she was then started on combination chemotherapy (Bortezomib (Velcade), Thalidomide and Dexamethasone, VTD) as a rapid reduction in myeloma protein burden was necessary to prevent further deterioration in renal function (5-7).

A week after admission she became breathless, febrile and hypotensive. She was diagnosed with septic shock (8), commenced on IV Tazocin and resuscitated appropriately. Unfortunately the next day she developed pulmonary oedema and required transfer to the Medical High Dependency Unit (HDU).

Although she recovered from her sepsis and pulmonary oedema, she became anuric and required haemodialysis. However with VTD her serum Kappa light chain level fell from 25,000mg/l to 25mg/l within four weeks. After three weeks on dialysis her urine output improved and she became dialysis independent. Her GFR is now stable around 30mls/minute.

Unfortunately Ms J developed sensory peripheral neuropathy during her first cycle of chemotherapy. This is a well-recognised side effect of both Bortezomib and Thalidomide but is usually mild (3). Despite withdrawal of Thalidomide and less frequent Bortezomib dosing it progressed, requiring discontinuation of VTD. She is now on second line Lenalidomide (a Thalidomide derivative which causes less neuropathy 3) chemotherapy and is responding well. Although her quality of life is still significantly affected by her neuropathy she is delighted to be dialysis free.

Discussion

Patients with haematological malignancies are at increased risk of sepsis for many reasons. Myelosuppresive chemotherapy induces neutropenia and immunosuppressive drugs like corticosteroids impair neutrophil function (9).

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Replacement of normal marrow by malignant cells results in reduced production of immune cells. In addition myeloma patients have secondary hypogammaglobulinaemia due to impaired production of functional antibodies (3). Unsurprisingly sepsis is a leading cause of early death in myeloma patients. Sepsis is time critical, therefore early recognition and management are essential.

Ms J had sepsis as defined by the Systemic Inflammatory Response Syndrome (SIRS) criteria (8) with a white cell count of $16.0x10^9$/l (NR 3.6-11.0), tachycardia, tachypnoea and fever. On examination she had bronchial breathing and bibasal crepitations. Once identified it is important that the Sepsis 6 protocol is implemented immediately.

- Take blood cultures
- Take bloods including a FBC, U &Es, LFTs, bone group, CRP, glucose and lactate. Consider a coagulation screen.
- Monitor urine output
- Give antibiotics
- Give fluids
- Give oxygen

Table 1: The Sepsis 6 Protocol (10).

Severe sepsis is classed as sepsis with resultant organ dysfunction, (8) such as acute kidney injury (as in the case of Ms J), liver derangement, lactic acidosis and disseminated intravascular coagulopathy. Complications can also occur due to treatment; Ms J was aggressively rehydrated, which although necessary to treat her hypovolaemia, may have provoked her pulmonary oedema.

In septic shock there is hypotension despite adequate fluid resuscitation (8). Therefore vasopressors may be needed to maintain blood pressure. Transfer to a High Dependency or Intensive Care Unit is then essential. Early involvement of Senior Medical Staff should always be sought.

As thrombocytopenia is common in haematology patients, the platelet count and coagulation should be checked if possible prior to carrying out any invasive procedure such as an arterial blood gas (11). Severe thrombocytopenia is a relative contraindication and platelet transfusion may be needed if the procedure is essential (11).

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A key difference in the management of septic haematology patients is the choice of antibiotic therapy. They are at a higher risk of opportunistic infections and can be profoundly neutropenic, making it difficult to identify the source of infection as local signs such as erythema or pus may be absent (12).

They may also have central lines in situ to facilitate treatment which can act as a source of infection. Therefore it is important to take both central and peripheral blood cultures (12). A broad-spectrum antibiotic such as Tazocin is started immediately after cultures are taken if neutropenic sepsis is suspected (12). This should cover the majority of likely microorganisms pending culture results.

Central lines may require removal if there are signs of infection around the exit site, particularly if not improving clinically or the line is colonised (as suggested by pyrexia or rigors with line access). Severe neutropenia is rare in myeloma patients, but infection should be treated aggressively as per neutropenic sepsis due to their immunocompromised state.

Other antibiotics may need to be added into the treatment plan to ensure appropriate cover, such as Gentamicin for Gram negatives, Teicoplanin in suspected line infections or Meropenem in patients with previous ESBL (12).

Microbiology advice should be sought as local resistance patterns may vary. Invasive fungal infections (eg pulmonary aspergillosis) should be considered in haematology patients undergoing intensive chemotherapy who are neutropenic for long periods. However they are rare in myeloma and their incidence is further reduced by the routine use of prophylactic agents such as Fluconazole and Co-trimoxazole (12).

Myeloma patients may develop acute renal impairment for many reasons, and this is present in 30% of patients at diagnosis (3).

Use of NSAIDs for bone and back pain
Hypercalcaemia
Dehydration
Hyperuricaemia
Sepsis
Cast nephropathy

Table 2: Common Causes of Acute Kidney Injury in Multiple Myeloma Patients (3)

Bone pain due to pathological fractures or lytic bone lesions is common in myeloma. Frequently patients or their doctors use NSAIDs for symptom control before the diagnosis is known. These have an adverse effect on renal perfusion which is exacerbated by dehydration (3). NSAIDs are generally contraindicated in myeloma.

Hypercalcaemia is frequent in patients with extensive bone disease and is nephrotoxic (3). In patients with a high disease burden and more rapid cell turnover such as Ms J, there is the risk of hyperuricaemia leading to the formation of urate crystals in the renal tubules (3). However tumour lysis syndrome rarely occurs in myeloma.

Acute tubular necrosis (ATN) may occur secondary to sepsis, nephrotoxic drugs or hypotension as in any other acutely ill patient. Therefore nephrotoxic antibiotics like Gentamicin must be used judiciously in myeloma (13).

Malignant plasma cells produce excess amounts of monoclonal immunoglobulin light chains which are filtered by the glomeruli, pass into the renal tubules and into the urine as Bence-Jones protein. Depending on their particular structure and charge, these light chains can precipitate in and obstruct the renal tubules forming tubular 'casts' (3) which may be visible in the urine. Treatment of cast nephropathy requires optimizing hydration and reducing light chain burden as quickly as possible by treating the myeloma (3). 'Novel agents' for myeloma such as Bortezomib and Thalidomide produce rapid responses in most patients (3, 5-7).

A renal biopsy can be useful to determine the cause of renal failure and predict the likelihood of recovery. However it is invasive and may not alter management. A biopsy was considered for Ms J whilst she was on dialysis, but prior to this her renal function began to recover. It is likely her renal failure was due to a combination of sepsis induced ATN and cast nephropathy.

Hopefully Ms J will continue to respond to Lenalidomide for some time. It is probable her neuropathy will gradually improve. Whilst the prognosis of myeloma has improved dramatically, with median survival in younger patients like Ms J of over five years, relapse and eventual chemotherapy refractoriness remain inevitable. Unfortunately due to her adverse genetics and aggressive presentation Ms J's remission duration is likely to be below average.

Questions

1. What percentage of MGUS patients transform into myeloma ever year?

a) 0.1%
b) 0.5%
c) 1% (correct)
d) 2%
e) 5%

THE SPECTRUM OF COMPLICATIONS IN MYELOMA: A CASE BASED DISCUSSION

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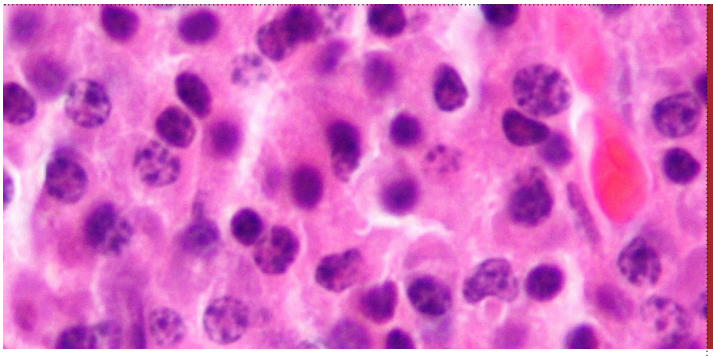

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2. Which two of these tests can be used to monitor myeloma response to treatment (3)?

a) Protein electrophoresis (correct)
b) Blood film
c) Skeletal survey
d) MRI of the spine
e) Urine Bence-Jones protein and serum free light chains (correct)

Learning notes

Question 1

Average risk of progression is 1% although some risk factors such as IgA MGUS, a larger paraprotein and the presence of an abnormal serum free light chain ratio are associated with a higher risk (3).

Question 2

The majority of myelomas produce either a paraprotein, urine BJP and/ or,have abnormal serum free light chain levels, providing an inbuilt marker of response which should fall with treatment (3).

Serum free light chains are particularly helpful in patients without an intact paraprotein or measurable BJP, or those with renal impairment and anuria where BJP testing is infeasible. In rare patients with 'non-secretory' myeloma, assessment is based on clinical response (eg improving Hb/renal function) with repeat bone marrows if unsure.

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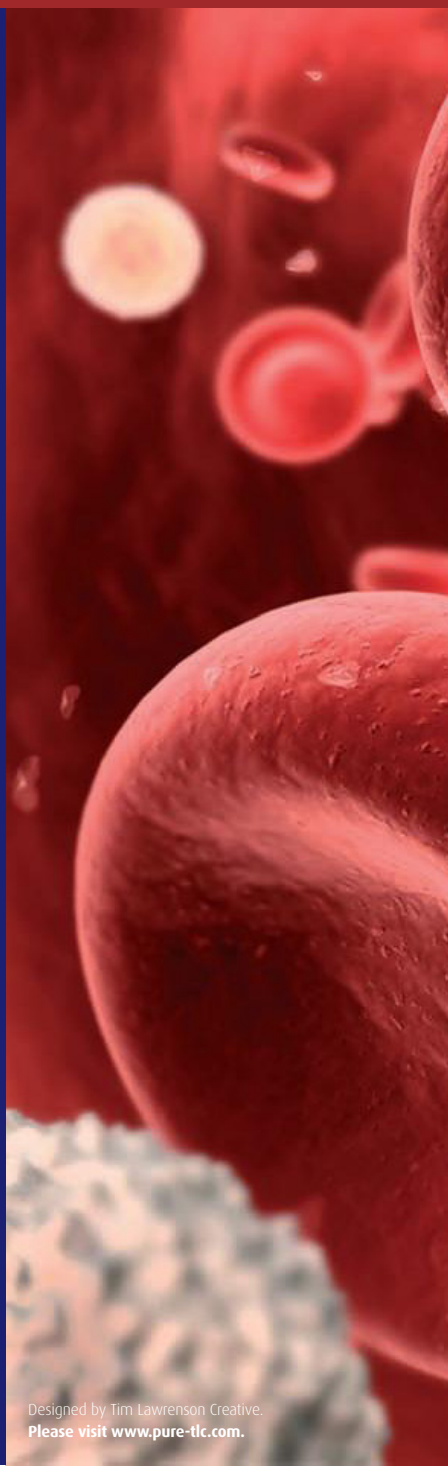

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