ABC of clinical haematology

Haematological emergencies

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Patients with both malignant and non-malignant haematological disease may present with dramatic and often life threatening complications of their diseases. This article deals with five of the most common emergencies encountered by haematologists. Although these conditions are not seen commonly in day to day clinical practice, recognition of the underlying pathological processes is important in determining the likely cause of the abnormalities and is helpful in determining the specific treatment needed.

Hyperviscosity syndrome

This may be caused by several haematological conditions. Blood viscosity is a function of the concentration and composition of its components. A marked increase in plasma proteins (for example, monoclonal immunoglobulin in myeloma) or cellular constituents (for example, white blood cells in acute leukaemia) will raise the overall blood viscosity. This leads to sludging of the microcirculation and a variety of clinical manifestations. Hyperviscosity may present insidiously or acutely with neurological symptoms and signs.

Fundal changes in patient with hyperviscosity (newly diagnosed myeloma with IgA concentration of 50 g/l).

Blood viscosity will often be more than four times the normal viscosity before symptoms occur. Patients with chronic disorders such as polycythaemia and myeloma are often physiologically well compensated for the degree of hyperviscosity and may complain only of mild headaches. In contrast, patients with acute leukaemia and a high white cell count may present in extremis; they become hypoxic from pulmonary involvement and are often obtunded, with a variety of neurological signs. Prompt treatment is needed to prevent permanent deficits. Elderly patients with impaired left ventricular function may experience decompensation due to their hyperviscosity, resulting in increasing congestive cardiac failure.

The definitive treatment of patients with hyperviscosity is dependent on the underlying pathology. For patients presenting with acute leukaemia vigorous intravenous hydration and intensive chemotherapy often results in a rapid reduction in the white cell count. Leukapheresis may be used as

General physicians must be able to recognise and start basic treatment, which may be life saving, in patients presenting with haematological emergencies

Causes of hyperviscosity

- Myeloma (especially IgA)
- Waldenström's macroglobulinaemia (IgM paraprotein)
- Polycythaemia
- High white cell count (hyperleucocytosis)

Symptoms and signs of hyperviscosity

- Mild headache
- Neurological disturbance
 - Ataxia
 - Nystagmus
 - Vertigo
 - Confusion
 - Changes in mental state
 - Coma
- Visual disturbance
 - Blurring of vision
 - Dilatation and segmentation of retinal veins
 - "Sausage" appearance of retinal veins
 - Risk of central retinal vein occlusion
- Genitourinary or gastrointestinal bleeding

Symptoms occur when the viscosity of the blood is more than four times that of water

Blood film in patient with hyperviscosity due to hyperleucocytosis (4 year old child with newly diagnosed acute lymphoblastic leukaemia (white cell count $200 \times 10^9/l$)).

an interim measure until chemotherapy exerts its full effect. For patients with myeloma or Waldenström's macroglobulinaemia (a low grade lymphoma characterised by production of monoclonal IgM, most of which is intravascular) plasmapheresis effectively reduces the paraprotein concentration.

Plasmapheresis may be used both for acute attacks and long term—for example, as palliative treatment for patients resistant to, or unable to tolerate, chemotherapy

Sickle cell crisis

The sickling disorders (Hb SS, Hb SC, Hb S/ β thalassaemia, and Hb SD) are inherited structural haemoglobin variants. Homozygous Hb SS in particular is associated with several complications, including recurrent vaso-occlusive crises, leg ulcers, renal impairment, hyposplenism, and retinopathy.

Sickle cell crises include vaso-occlusive, aplastic, sequestration, and haemolytic episodes. The chest syndrome and the girdle syndrome are more severe forms of crisis associated with higher morbidity and mortality.

Crises may be precipitated by dehydration or infection; in many cases no obvious precipitant is found.

The aim of treatment is to break the vicious cycle of sickling: sickling results in hypoxia and acidosis, which in turn precipitate further sickling. This is exacerbated by dehydration, and a high fluid intake (70 ml/kg/24 h) is the cornerstone of management.

Also imperative in managing sickle cell crises is adequate pain relief—opiates, by continuous subcutaneous or intravenous infusions, may be needed. Arterial blood gas pressures should be performed and oxygen therapy prescribed if hypoxia is confirmed. It should be remembered that sickle cell patients are functionally asplenic and that infection is a common precipitant of crises. Broad spectrum antibiotics should be started while waiting for the results of blood and urine cultures.

It is important to recognise the patients who need urgent exchange transfusion to reduce the level of Hb S to below 30%. Transfusion should be started promptly if the patient has a severe chest syndrome (with pronounced hypoxia), has had a cardiovascular accident, or has priapism.

Sickle cell crises

Vaso-occlusive—In any tissue but especially bones, chest, and abdomen (eg splenic infarcts); in cerebral vessels, leading to stroke

Aplastic—In parvovirus B19 infection

Sequestration—Particularly in infants and young children; massive pooling of red cells in spleen and other organs, leading to precipitous drop in haemoglobin

Haemolytic—Further reduction in life span of red cells, leading to worsening anaemia and features of haemolysis

Chest syndrome—Pleuritic pain and fever may mimic pneumonia or pulmonary embolism; progressive respiratory failure

Treatment of sickle cell crises

- Vigorous intravenous hydration
- Adequate analgesia—for example, intravenous opiates
- Broad spectrum antibiotics
- Oxygen therapy
- Consider exchange blood transfusion

Vicious cycle in sickle cell crisis.

Spinal cord compression

Some patients may present at the haematology clinic with metastatic tumour deposits—for example, lymphoma or plasmacytoma—resulting in cord compression. Commonly, overt cord compression is preceded by signs consistent with root compression, with pain in the affected dermatome. Most patients with cord compression complain of pain—it is often constant and easily confused with that of pain due to degenerative disease. Often it is not until more overt neurological signs are manifested that a diagnosis of cord compression is considered.

The neurological signs accompanying cord compression vary according to both the rapidity of development of compression and the area of cord affected. Acute lesions often result in hypotonia and weakness, whereas chronic lesions are more often associated with the classic upper motor neurone signs of hypertonia and hyper-reflexia. The associated sensory loss is defined by the site of the lesion, but hyperaesthesia may be seen in the dermatome at the level of the lesion. More lateral lesions may result in a dissociative sensory loss—that is, ipsilateral loss of joint position sense and proprioception with contralateral loss of pain and temperature. Bladder and bowel disturbances often occur late, with the exception of the cauda equina compression syndrome, in which they are an early feature.

Symptoms and signs of cord compression

- Back pain
- Weakness in legs
- Upper motor neurone and sensory signs
- Loss of sphincter control (bowels/bladder)

Magnetic resonance image showing spinal cord compression.

If cord compression is suspected the patient should be investigated with plain spinal radiography, which may show evidence of lytic lesions (as, for example, in myeloma). The definitive investigation is magnetic resonance imaging to delineate the level of the lesion and to help plan further treatment.

In a patient presenting de novo with cord compression further investigations (protein electrophoresis, measurement of prostatic specific antigen and other tumour markers, and chest radiography) are needed to elucidate the underlying cause. A formal biopsy of the lesion may be needed to determine the underlying pathology.

In an acute presentation high dose dexamethasone (for example, 4 mg four times daily) is given. Further management depends on the underlying cause, but often a combination of chemotherapy and radiotherapy is given.

Disseminated intravascular coagulation

Disseminated intravascular coagulation describes the syndrome of widespread intravascular coagulation induced by blood procoagulants either introduced into or produced in the bloodstream. These coagulant proteins overcome the normal physiological anticoagulant mechanisms. The overall result, irrespective of cause, is widespread tissue ischaemia (due to clot formation, thrombi) and bleeding (due to consumption of clotting factors, platelets, and the production of breakdown products that further inhibit the coagulation pathway).

The diagnosis of disseminated intravascular coagulation is initially clinical and is confirmed by various blood tests. There are many causes of disseminated intravascular coagulation, including obstetric emergencies, infections, neoplasms, trauma, and vascular disorders.

Treatment is primarily directed at the underlying cause—for example, the use of antibiotics when infection is suspected, or removal of fetus and placenta with placental abruption or retained dead fetus syndrome. Disseminated intravascular coagulation generally resolves fairly quickly after removal of the underlying cause.

Interim supportive measures, such as intravenous hydration and oxygen therapy, are important. Correction of the coagulopathy entails the use of fresh frozen plasma, cryoprecipitate, and platelet transfusion. No uniform protocol exists for transfusing blood and blood products. Instead, for each patient the quantity of blood product used is decided after clinical evaluation and serial coagulation assays.

The use of intravenous heparin to treat disseminated intravascular coagulation remains controversial. Some evidence supports the value of heparin in the management of acute promyelocytic leukaemia, the dead fetus syndrome, and aortic aneurysm before resection. For other causes of disseminated intravascular coagulation the use of heparin is more uncertain and may actually worsen the bleeding.

Causes of acute disseminated intravascular coagulation

Infection—Especially Gram negative infections, endotoxic shock

Obstetric—Placental abruption, intrauterine fetal death, severe pre-eclampsia or eclampsia, amniotic fluid embolism

Trauma—Especially head injury, burns

Malignancy—Carcinoma of prostate, lung, pancreas, ovary, and gastrointestinal tract

Miscellaneous—Transfusion with incompatible blood group, drug reactions, hypothermia, venomous snake bite, transplant rejection

Vascular—Aortic aneurysm, giant haemangioma

Neurosurgical advice should be obtained as in some cases surgical decompression may allow recovery of function

Clinical features of disseminated intravascular coagulation

Bleeding

- Spontaneous bruising
- Petechiae
- Prolonged bleeding from venepuncture sites, arterial lines, etc
- Bleeding into gastrointestinal tract or lungs
- Secondary bleeding after surgery
- Coma (intracerebral bleeding)

Clotting

- Acute renal failure (ischaemia of renal cortex)
- Venous thromboembolism
- Skin necrosis or gangrene
- Liver failure (due to infection and hypotension)
- Coma (cerebral infarction)

Shock

- Due to underlying disease together with disseminated intravascular coagulation

Central nervous system

- Transient neurological symptoms and signs
- Coma
- Delirium

Lungs

- Transient hypoxaemia
- Pulmonary haemorrhage
- Adult respiratory distress syndrome

Main investigations* for disseminated intravascular coagulation

<i>Investigation</i>	<i>Positive result</i>
Full blood count	Decreased platelet count
Prothrombin time	Increased
Activated partial thromboplastin time	Increased
Fibrinogen	Decreased
Fibrin degradation products/D dimers	Increased

*Other investigations: urea and electrolytes, liver function tests, blood cultures, pulse oximetry (oxygen saturation)

Initial management of disseminated intravascular coagulation

- Treat as for severe bleeding/shock
- Establish intravenous access (large bore cannula)
- Restore circulating volume—with, for example, crystalloids
- Administer fresh frozen plasma and cryoprecipitate and regularly monitor full blood count, prothrombin time, and activated partial thromboplastin time
- Consider giving platelet transfusion
- Remove the underlying cause

Infection in patients with impaired immunity

Patients with a variety of haematological diseases are immunocompromised due to either their underlying disease or the treatment required for the condition. For example, patients with myeloma often present with recurrent infection as a result of the reduction in normal immunoglobulin concentrations associated with the paraproteinaemia. This susceptibility is compounded by the use of combination chemotherapy, which may render them neutropenic.

Several haematological disorders are now routinely treated in outpatient clinics with aggressive chemotherapy, so some patients in the community may be neutropenic as a result of this. Patients are educated to seek medical advice immediately if they develop any infection since Gram negative septicaemia may lead rapidly to death. For patients receiving intensive chemotherapy presenting with fever while neutropenic, broad spectrum antibiotics should be started immediately. The choice of antibiotics depends on local microbiological advice in the light of the sensitivities of the micro-organisms in the region.

Patients with chronic lymphocytic leukaemia often have recurrent infection in the absence of neutropenia, because of the accompanying hypogammaglobulinaemia seen in this disorder. Frequent courses of antibiotics are often required. The role of regular intravenous immunoglobulin infusions to "boost" their immunity is debatable. Patients with chronic lymphocytic leukaemia may develop severe recurrent herpes zoster infections. Prompt treatment with aciclovir should always be given at the first suspicion of any herpetic lesions developing, and hospital referral for intravenous antibiotics and aciclovir should be considered if the lesions are not confined to a single dermatome or are in a delicate area—for example, ophthalmic division of trigeminal nerve.

Patients who are functionally or anatomically asplenic are at high risk of infection with encapsulated organisms, especially *Streptococcus pneumoniae*.

Penicillin prophylaxis and immunisation reduces the incidence of these infections but does not abolish the risk completely. If any of these patients becomes acutely unwell the prompt administration of 1200 mg benzylpenicillin (if no history of allergy to penicillin) and prompt referral for further treatment may be life saving.

Recommendations for patients with no spleen or hypofunctioning spleen*

- Pneumococcal vaccine (Pneumovax II) 0.5 ml—two weeks before splenectomy or as soon as possible after splenectomy (for example, if emergency splenectomy is performed); reimmunise every 5-10 years
- *H influenzae* type b (Hib) vaccine 0.5 ml
- Meningococcal polysaccharide vaccine for *N meningitidis* type A and C 0.5 ml
- Penicillin as prophylaxis (250 mg twice daily—for life)

The three vaccines (subcutaneous or intramuscular) may be given at same time, but different sites should be used

*Based on the guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen, *BMJ* 1996;312:430-4

Herpes zoster virus affecting the ophthalmic division of the trigeminal nerve in patient with chronic lymphocytic leukaemia.

Risks of infection in patients with no spleen or hypofunctioning spleen

- With encapsulated organisms—for example, *Streptococcus pneumoniae* (60%), *Haemophilus influenzae* type b, *Neisseria meningitidis*
- Less commonly—*Escherichia coli*, malaria, babesiosis, *Capnocytophaga canimorsus*

Name _____		
Address _____		
GP _____	Tel: _____	
Hospital _____	Tel: _____	
IMMUNISATIONS:	DATE GIVEN:	BOOSTER:
Pneumococcal _____		
Hib _____		
Meningococcal A and C _____		

Card carried by patients with no spleen or hypofunctioning spleen.

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The ABC of clinical haematology is edited by Drew Provan, consultant haematologist and honorary senior lecturer at the Southampton University Hospitals NHS Trust, and Andrew Henson, clinical research fellow, university department of primary care, Royal South Hants Hospital, Southampton.

Dr Ken Tung, consultant radiologist, Southampton University Hospitals Trust, provided the magnetic resonance image. The photograph showing herpes zoster virus is published with permission from *Clinical Haematology—a Postgraduate Exam Companion* (Provan D, Amos TA, Smith AG, Oxford: Butterworth-Heinemann, in press).