Clinical presentations of haematological disease

Few clinical symptoms and signs point immediately to haematological disease and many affected patients are diagnosed by chance on routine laboratory testing. However, as definitive treatment exists for most haematological disease, it is important that the underlying pathology be identified before irreparable end organ damage occurs.

JAMES P. ISBISTER
BSc(Med), MB BS, FRACP, FRCPA

Professor Isbister is Honorary Consultant Haematologist at Royal North Shore Hospital, St Leonards; Clinical Professor of Medicine, University of Sydney; Adjunct Professor, University of Technology, Sydney, NSW.

Haematology has a role on a daily basis in most disciplines of medicine as virtually all laboratory investigations include a full blood count as a routine starting point. Although there are specific haematological diseases – such as leukaemia and haemophilia – the specialty is increasingly becoming one of pathophysiology, being concerned with diseases manifesting as, for example, arterial thrombosis, venous thromboembolism, autoimmune disorders or infection. Few clinical symptoms and signs point immediately to haematological disease. When laboratory results appear to suggest such disease, it is appropriate to consider whether they indicate a serious blood disorder where time is of the essence or whether they are clues to underlying nonhaematological disease.

Many patients with primary haematological disease are diagnosed by chance now that tests are so readily available and are relatively cheap. The preoperative work up is the classic setting in which chance diagnoses are made; such diagnoses may or may not be relevant to the presenting disease or its therapy and include particularly chronic lymphocytic leukaemia and the myelodysplastic syndromes.

The increasing role of molecular genetics in understanding disease is introducing complexity to medical diagnosis and challenges in interpreting the clinical relevance of results. Patients who have been informed after diagnostic testing, screening or family studies that they have a genetic 'abnormality' are increasingly asking clinicians about such abnormalities. It is beyond the scope of this review to venture into this difficult area, but clearly patients' concerns need to be addressed appropriately and referral may be necessary.

A wide range of presentations

Haematological disease may present in a plethora of different guises and it is only with constant awareness of possibilities and probabilities, and an open mind for subtle clues, that early

IN SUMMARY

- **Apparent organ or system specific disease may be the initial presentation in patients with underlying primary haematological disease.**
- **A full blood count and basic biochemical analysis are cost effective investigations to diagnose or exclude a wide range of serious haematological disorders.**
- **A medication history is of central importance in the investigation of patients with abnormal haematology laboratory results.**
- **A patient's history is the best guide to a haemostatic defect. Haemostatic screening tests in the absence of a positive clinical history have poor predictive value for diagnosing a bleeding disorder.**
- **Many patients with primary haematological disease are diagnosed by chance. The preoperative work up is the classic setting for this.**

diagnosis will be made (Table).

A full blood count, including a differential leucocyte count and blood film, in conjunction with basic biochemical analysis will help swing the probabilities towards or against an underlying haematological disorder. The biochemical tests should include electrolytes, renal function (urea and creatinine), liver function (aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, serum alkaline phosphatase), lactate dehydrogenase, calcium, protein electrophoresis and urinalysis. Modern blood cell counters and biochemical analysers have revolutionised the determination of the basic cellular and plasma components of blood into a rapid, accurate and cost effective procedure. In contrast to the pre-automation era, blood film examination is now a focused and context-dependent analysis. Figure 1 shows an example of a blood film of acute lympho - blastic leukaemia.

Table. Possible clinical and laboratory presentations of haematological disease

Haemopoietic failure presentations

Failure of oxygen transport

- Symptomatic anaemia
- Microcirculatory failure
- Diseases complicated by anaemia
- Anaemia detected on blood test

Haemostatic failure

- Generalised bleeding, bruising or purpura
- Inappropriate local bleeding
- Primary diseases associated with haemostatic defects
- Screening prior to surgery or a procedure
- Abnormal APTT and INR*
- Past history or family history of inappropriate bleeding

Host defence failure

- Unusual or opportunistic organism
- Infection slow to resolve
- Atypical behaviour of an infection
- Host defence defect(s) that are associated with primary disease
- Abnormal laboratory results (white cell count or differential)

Other presentations

Organ enlargement

- Hepatosplenomegaly
- Lymphadenopathy

Focal manifestations of haemopoietic failure

- Tissue infarction/ ischaemia and loss of organ function
- Anaemia in conjunction with local vascular disease
- Primary haematological vascular occlusive disorder (red cell, platelet, coagulation, leucocyte disease)

Focal deposits or infiltration

- May present in any system of the body; requires identification and pathological diagnosis

High cellular counts in the blood

- Leukaemias and some lymphomas
- Polycythaemia
- Thrombocytosis/ thrombocythaemia

Biochemical presentations

- Abnormalities in any of the following may be a manifestation of haematological disease
  - elevations: calcium, lactate dehydrogenase, bilirubin, liver function tests, serum iron, urea/ creatinine, globulins, uric acid
  - reductions: serum iron, globulins, sodium

*APTT = activated partial thromboplastin time; INR = international normalised ratio.

Clinicians now have the dilemma of how to process the increasing volume of laboratory data to determine what is relevant and its implications. Having an abnormal result on a blood test does not mean disease. The statistical methods used to establish a reference range deem that 5% of normal people have an 'abnormal' result. The more tests that are performed, the lower the chance that they will all be statistically normal in a healthy person.

There are several general explanations for the wide spectrum of clinical presentations in disorders of the haemopoietic system. It is not surprising that neither the patient nor the doctor may consider a haematological disorder as there are few symptoms or signs of haemotological disease that immediately direct the patient or the doctor of initial contact to consider a disorder concerning the formation of blood cells. Some explanations are listed below.

- The haemopoietic system is disseminated throughout the body and disease may present in any other system.
- The initial presentation of disease of the haemopoietic system may be manifest by haemopoietic failure, such as anaemia, bleeding and infection, and the clinician may be distracted towards the organ system of initial involvement.
- Incidental abnormalities may be detected on a routine blood test or on tests done with other diagnoses in mind.

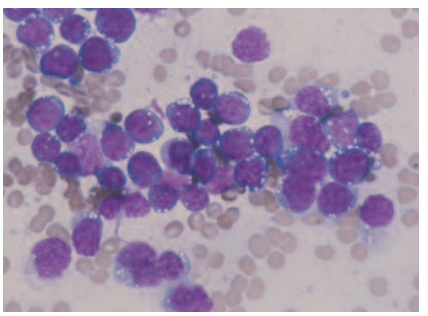

Figure 1. Acute lymphoblastic leukaemia.

Primary haematological disease should be considered, however, in certain patients, including the following:

- those with disseminated purpura/bruising, generalised lymphadenopathy or profound pallor – these symptoms will clearly alert the clinicians to underlying haematological disease
- those in whom blood test results may be diagnostic of a haematological disorder
- those who present with multiple

Case study: anaemia of chronic disease or iron deficiency?

History

A 65-year-old woman has a three-month history of gradual weight loss and increasing fatigue and lethargy. In the past month she has also experienced occasional night sweats and intermittent headaches. Her only medication is an NSAID, which she takes for arthritis in her hands and knees. She has deteriorated such that she is unable to care for herself at home; this precipitates her hospital admission.

Examination

On examination, the woman is afebrile, slightly wasted and only just able to walk. There are signs of osteoarthritis in her hands and knees, but no other abnormalities are found.

Initial investigations

(Normal ranges in parentheses.)

Full blood count:

- Haemoglobin, 98 g/L (115 to 150 g/L); mean corpuscular volume, 77 fL (77 to 98 fL); mean corpuscular haemoglobin, 29 pg (27 to 34 pg)
- White cell count, 14.3 x 10^9/L (4.0 to 10.0 x 10^9/L); neutrophils, 11.9 x 10^9/L (2.0 to 7.5 x 10^9/L); lymphocytes, 0.9 x 10^9/L (1.0 to 3.5 x 10^9/L); monocytes, 1.2 x 10^9/L (0.2 to 1.0 x 10^9/L); eosinophils, 0.3 x 10^9/L (0.02 to 0.5 x 10^9/L)
- Platelets, 540 x 10^9/L (150 to 400 x 10^9/L).

Biochemistry:

- Urea, 7 mmol/L (2.0 to 7.0 mmol/L); creatinine, 0.10 mmol/L (0.05 to 0.11 mmol/L)
- Total protein, 84 g/L (60 to 80 g/L); albumin 35 g/L (40 to 55 g/L).

What are the possible mechanisms of this patient's anaemia?

This woman presents with a nonspecific history. She has a normochromic normocytic anaemia, neutrophilia, lymphopenia and thrombocytosis, which suggests that her anaemia is secondary to chronic disease. Nonetheless, iron deficiency needs to be considered because in the early stages it may manifest with a normochromic normocytic anaemia, and in this case the mean corpuscular volume is at the lower limit of normal and the woman has a history of NSAID use.

Further investigations

Iron studies: serum iron, 8 µmol/L (10 to 38 µmol/L); transferrin saturation, 14% (15 to 58%); ferritin, 350 µg/L (20 to 200 µg/L).

Is this the anaemia of chronic disease or iron deficiency?

In this case, iron studies are consistent with the anaemia of chronic disease. Anaemia of chronic disease typically occurs despite adequate iron stores and is characterised by reduced serum iron, transferrin and total iron binding capacity; normal or raised ferritin; and high C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR). (Assays for CRP have become more sensitive and are usually recommended instead of measuring the ESR.)

The red cells are usually normochromic normocytic, but may show hypochromic microcytic indices similar to iron deficiency (especially when chronic disease has been present for a prolonged period of time, such as in rheumatoid arthritis and Crohn's disease.)

Thus, the anaemia of chronic disease may be difficult to distinguish from iron deficiency anaemia and, moreover, both may be present in the individual patient. The anaemia of chronic disease will not respond to iron therapy and identification and treatment of the underlying cause is paramount.

What are the next steps?

Clearly this woman has undiagnosed disease and persistence is required until a diagnosis is made. In most cases, the underlying disease will be identified. Further investigations should aim at identifying or excluding underlying infection, inflammation or malignancy.

Appropriate tests include:

- CRP
- urinalysis
- a chest x-ray
- serum electrophoretogram (EPG) and immunoelectrophoretogram.

If after these tests no cause is found, a CT scan of the abdomen may be considered. If no intra-abdominal pathology is identified, immunological disorders such as arteritis should be considered and it is generally best to refer the patient to a general physician or clinical haematologist.

What was the diagnosis in this woman?

In this case, consistent with the anaemia of chronic disease, there was an elevation in the CRP. The woman's total protein level was slightly increased but albumin was reduced suggesting an increase in globulins. On serum EPG, a polyclonal hypergammaglobulinaemia was identified. The patient was ultimately diagnosed as having a systemic arteritis.

problems disseminated in time (for example, recurrent infections, haemorrhagic episodes) and/or place (for example, different organs of the body) – suspicions for primary haematological disease should be high in these patients.

For example, multiple myeloma would not generally be suspected in an elderly patient presenting with a common problem such as pneumonia, but the possibility would arise if the patient had been complaining also of progressive lethargy and back pain and was found to have osteoporosis in association with a vertebral crush fracture.

Haemopoietic disorders

Failure of oxygen transport

Clinical features of systemic or local oxygen transport failure may be a manifestation of primary haemopoietic disease.

Anaemia

Anaemia may present with the classic symptoms and signs of pallor, lethargy, poor exercise tolerance, dyspnoea, faintness, nausea and anorexia. However, it may compound another condition with defective oxygen transport (such as angina or chronic obstructive pulmonary disease), exacerbating symptoms. Furthermore, one of the most common presentations of anaemia is via a routine blood count. It is important to note when considering all patients presenting with fatigue or pallor that most do not have anaemia or primary haematological disease.

Patients with vascular disease associated with anaemia may present with symptoms relating to the vascular bed in question, such as angina, intermittent claudication and transient cerebral ischaemic attacks. Patients with impaired cardiac reserve and anaemia may present in congestive cardiac failure.

In patients with respiratory disease and impaired pulmonary gas exchange, a higher haemoglobin level is required to ensure the delivery of adequate oxygen for the reduced haemoglobin oxygen saturation. If iron levels are low, failure of anaemia or fatigue to respond to iron therapy usually rules out iron deficiency. Depletion of iron stores in the absence of anaemia is unlikely to be a cause of fatigue. When the cause of anaemia is unclear, the case should be discussed with a haematologist and the blood film reviewed (see the case study on page 29).

Vascular occlusion

There is a wide range of diseases in which organ ischaemia or infarction occurs due to abnormalities in the blood or in the interactions between the blood and the blood vessel walls. Some of these are

the most common disorders afflicting Western society, such as coronary artery disease, cerebrovascular disease and peripheral vascular disease. Others are rare, such as hyperviscosity, microangiopathy, vasculitis, antiphospholipid syndrome, disseminated intravascular coagulation and thrombophilias.

Failure of haemostasis

Defects in the haemostatic system may manifest as underactivity (haemorrhage) or overactivity (thrombosis). In most patients, the initial clinical and laboratory assessment will determine whether further investigation or referral is indicated. Diagnostic dilemmas may arise with haemostatic failure when it is not obvious that the underlying problem is haemorrhagic or thrombotic in nature. Occult bleeding (for example, retroperitoneal haemorrhage and intramural bowel bleed) may produce a clinical picture that would not lead the clinician to suspect an underlying haemorrhage. Atypical vascular thrombotic events (such as mesenteric, cerebral sinus and portal vein thromboses) can also be problematic to diagnose.

Haemostatic disorders may present in the following ways:

- in relation to an acute haemorrhagic setting where inappropriate bleeding is occurring for which there is no obvious mechanical cause
- when surgery or an invasive procedure is contemplated in patients with a potential for bleeding and the likelihood of haemorrhage is investigated (this would apply particularly to patients with liver or renal disease and those on antithrombotic medications)
- in a patient initially presenting with symptoms or signs of unexplained bleeding, bruising or purpura
- by abnormalities detected on laboratory screening tests (abnormal coagulation test results on unselected patients are a poor predictor for the presence of a bleeding disorder)
- where there is a family history of haemostatic failure and investigation of an asymptomatic relative is requested
- during genetic counselling or antenatal diagnosis in a family with a known defect.

The presence of certain clinical features improves the pretest probability of detecting a haematological disorder. These features include:

- a history of haemorrhagic episodes in relation to minor trauma and surgery
- inappropriate local haemorrhage
- bleeding from multiple sites
- unexplained bruising
- purpura, ecchymoses, or buccal or

retinal haemorrhages (Figures 2 and 3)
- oozing from wounds or venepuncture sites.

Mucocutaneous haemorrhage, purpura and cutaneous ecchymoses, and excessive intraoperative or early postoperative bleeding are suggestive of a defect in primary haemostasis (that is, platelet numbers or function). Failure of the coagulation phases of haemostasis is suggested by deep haemorrhage in muscles and/or joints, and delayed excess surgical bleeding.

Thrombophilic and microvascular disorders

Thrombophilic disorders are receiving more attention as haemostatic control is becoming better understood. The same is occurring with microvascular disease, because of the remarkable recent insights into the role of the endothelial cell and its interactions with blood components. Although this evolving area of haematological knowledge is beyond the scope of this review, doctors at the frontline should consider thrombophilic and microvascular disorders in any patient presenting with atypical venous or arterial thrombosis, multisystem disease or familial thrombotic disorders.

Failure of host defences

The body has a limited number of ways of responding to exogenous stimuli and there tend to be common final pathways for the various types of insult. An underactive (immunocompromised) or over-active (autoaggressive) host defence system may be responsible, in whole or in part, for disease.

Cellular or humoral defects in both the nonspecific (innate) haemopoietic defences or the adaptive immunological defence system may be responsible for one or more of the following:
- infection, especially atypical opportunistic infections
- allergies and intolerances
- autoimmune disorders
- malignancies.

Immunocompromised patients may be identified by considering the following questions:
- If there is an infectious organism, what is it and what is the nature of the infection?
- Is the patient already in a risk group for having a host defence defect?
- Are there any clinical or simple laboratory findings that suggest an underlying disease?

Infectious organism and nature of infection

A single infection with a common organism is likely to be a unifactorial disease that will follow an expected natural history. Common infections may arouse suspicion of host defence failure if there are recurrent episodes, delayed resolution, unexpected natural history, multiple sites of infection, unusual sites of involvement, incomplete clearance of infection or systemic spread. Unusual organisms should arouse suspicion of an opportunistic infection, and multiple infections with different organisms should be a matter for concern.

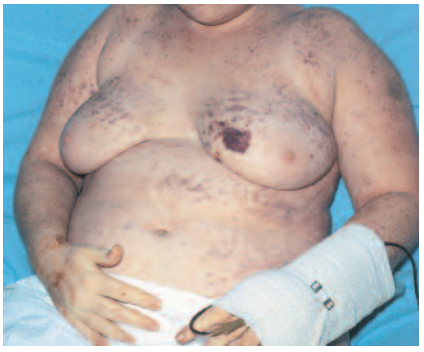

Figure 2. Extensive purpura in a patient with thrombocytopenia due to aplastic anaemia.

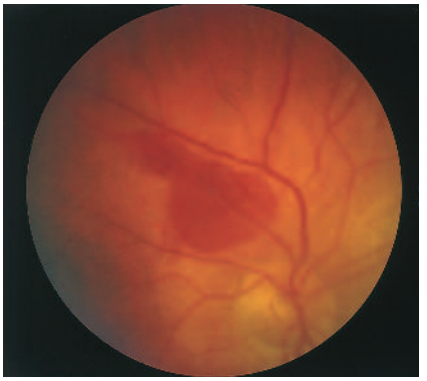

Figure 3. Retinal haemorhage in a patient with thrombocytopenia.

Risk groups for host defence defects

The patient's past or present medical history may be relevant to the likelihood of a host defence defect being present. Nonhaematological conditions that should be considered include diabetes, uraemia, liver disease, malnutrition, alcoholism, drug addiction, prematurity, malignancy and rheumatoid arthritis (Figure 4). Haematological disorders include postsplenectomy, haematological malignancy, known host defence defects, HIV/AIDS and chronic atypical mononucleosis syndromes. Age is also a factor.

A family history of immunodeficiency, allergy, autoimmune diseases or malignancy may indicate a high risk for having a host defence defect. Medications such as immunosuppressive therapy, cytotoxic therapy, corticosteroids and antibiotics predispose patients to host defence failure.

It is possible that a patient will be in a high risk group for host defence failure but problems have not yet manifested clinically. Thus diagnosed or undiagnosed haematological disease (chronic lymphocytic leukaemia or neutropenia) or medications may be responsible (Figure 5). The myelodysplastic syndromes are being more frequently recognised and may be on the increase (especially in the elderly). Their diagnosis requires good clinical acumen and careful analysis of laboratory parameters. Relying on automated full blood counts being 'flagged' by the computer can be unreliable. Preoperative diagnosis is important as unexpected bleeding or infectious complications should be avoided.

Findings suggesting underlying disease

If the patient has previously been well and there has been a change in susceptibility

to infection, an acquired defect is likely. A history of allergies, unexplained transfusion reactions, autoimmune disease, recurrent infections or chronic diarrhoea may be suggestive of immune deficiency or defective immunoregulation.

Findings on examination and investigation that suggest haematological or other disease include:

- physical findings of lymphadenopathy, organomegaly, skin rash, retarded growth or autoimmunity (Figure 6)
- clinical evidence of bone marrow failure such as associated haemostatic failure or anaemia
- anaemia, leucocyte abnormalities, thrombocytopenia on initial or routine full blood count and film.

Primary immune deficiency disease should not be assumed until primary underlying disease has been excluded.

Other presentations

Many reactive and malignant disorders of the haemopoietic system may present with organ enlargement or extra haemopoietic system mass lesions. These are colloquially known as the 'lumps and bumps' presentations. Organomegaly may present overtly as palpable masses or after detailed investigations. Generalised lymphadenopathy and hepatosplenomegaly would obviously direct the clinician towards the haemopoietic system. In contrast, an extra haemopoietic mass presenting in the nervous system may take some time for its true nature to be revealed. Haematological disease, especially neoplastic disorders, may have various direct and indirect manifestations, as summarised in the Table.

Mass haemopoietic disease may present in the following ways:

- lymphadenopathy or splenomegaly
- an obstruction to veins, bronchi, gut, renal tract or lymphatics
- an extranodal mass lesion, such as spinal cord compression, proptosis, skin lesions
- an incidental finding from an organ imaging investigation such as chest or abdomen x-ray or CT scan (Figure 7)
- haematomas or abscesses (obvious or occult sites).

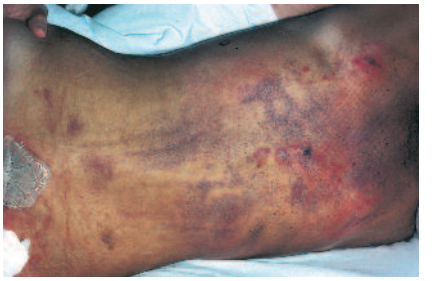

Figure 4. Scurvy.

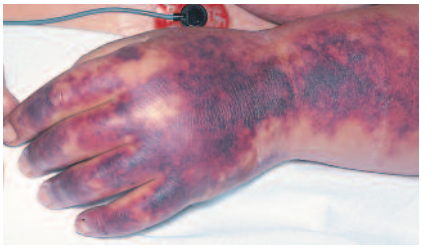

Figure 5. Vasculitis secondary to a drug reaction.

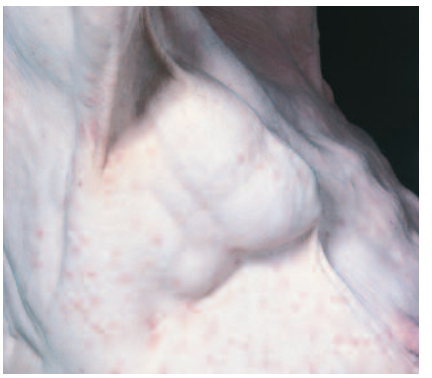

Figure 6. Axillary lymph nodes in a patient with chronic lymphocytic leukaemia.

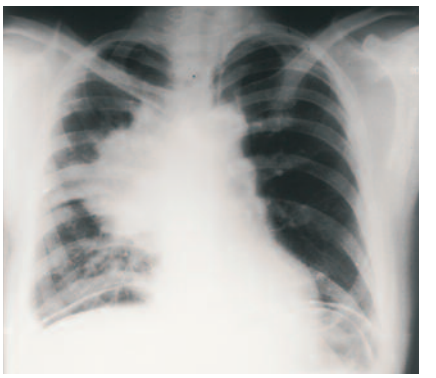

Figure 7. Mediastinal mass on chest x-ray in a patient with lymphoma.

If the lymphadenopathy is localised to a single nodal region, the drainage areas should be carefully examined for evidence of infection or malignancy. With generalised lymphadenopathy, systemic disease or haematological malignancy is more likely. Painful nodes are usually due to an infectious or inflammatory cause. The same principle applies to splenomegaly unless there has been a splenic infarct or haematoma. As a generalisation, the larger and firmer the organomegaly, the more likely it is to be due to malignancy. Fixation of lymph nodes to underlying tissues is highly suggestive of metastatic malignancy.

Knowledge of the length of history, the presence of systemic symptoms (for example, malaise, weight loss, fever, sweats and pruritus), contact with infectious diseases, historical or physical findings in other systems, recent travel and drug history will aid diagnosis. Clinical features of anaemia, haemostatic failure or immune deficiency may be important.

Conclusion

Primary haematological disease may present in virtually any system of the body. In most cases, the diagnostic process dictates initial localisation of the pathology and subsequent tissue diagnosis. If the diagnosis is pursued to its logical conclusion, the presence of an underlying haematological disorder will eventually be established. This diagnostic route, however, can be excessively devious and, at times, treacherous. As there is definitive treatment for most haematological disease, it is important that the underlying pathology be identified before irreparable end organ damage (such as spinal cord compression) has occurred. MT

DECLARATION OF INTEREST: None.