

## Case 6

# A 70-year-old man who was no longer able to take his dog for a walk

Hilliard Atler, a 70-year-old Caucasian man, went to his family doctor. He had a Jack Russell terrier for 10 years and usually walked him for 30–40 minutes in the evening. For the last few weeks he has noticed he was short of breath after about 10 minutes. This symptom had been getting worse to the point that he no longer feels he can walk his dog.

### Can his symptoms be accounted for by his age or do they suggest an underlying illness?

A change in work or recreation patterns is always suggestive of disease.

### What question(s) might define when the symptoms began? When were you last feeling well?

Were you well before... (use a well-known public holiday, e.g. Christmas, or national event)?

### What associated symptoms should be enquired about?

Symptoms relating to the respiratory or cardiovascular systems. A history of previous episodes of shortness of breath, a cough productive of sputum or blood (haemoptysis), wheeze or chest tightness or discomfort on exertion. Symptoms such as ankle swelling or waking suddenly from sleep with shortness of breath suggest a cardiac cause.

Ask Hilliard if he has ever been treated for high blood pressure, angina, asthma or chronic bronchitis. Review his medications and his smoking habits.

Hilliard said that he had been well all his life and 'never goes near a doctor'. He denies a history of the symptoms about which he has been questioned. He is a non-smoker.

### What should be done next?

Take a full history, including a family and personal history of tuberculosis. A positive family history or contact with a person with tuberculosis could put him at risk. Travel to areas where unusual infections are present should be noted.

Hilliard has always taken holidays in Europe and has no known contact with tuberculosis.

### What should be done next?

A full physical examination.

His blood pressure was 125/80 mmHg and his respiratory rate was 20/minute. His sclerae were jaundiced (icteric) and he was pale. His pulse was regular but slightly fast at 100 beats/minute. His heart size was normal and no murmurs were present but he had fine crackles at both his lung bases on inspiration. Hilliard had no lymphadenopathy but his spleen was palpable 3 cm below his left costal margin. He had bilateral pitting ankle oedema.

### What is your differential diagnosis?

His pallor and jaundice suggest anaemia and liver disease, haemolysis or ineffective erythropoiesis (cells dying prematurely in the marrow). His rapid pulse, inspiratory crackles and ankle swelling suggest mild heart failure and his large spleen, an unexpected finding, suggests a haematological or infectious component to his symptoms.

### What investigations should be carried out?

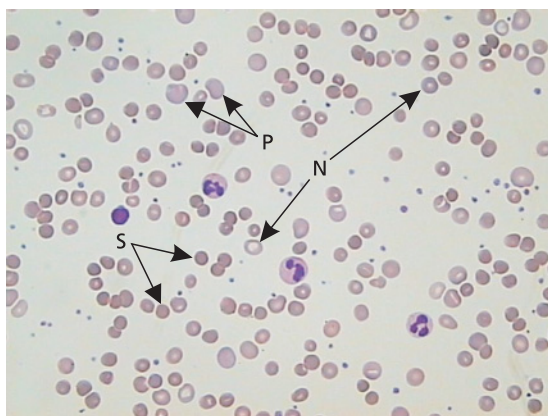
A full blood count, reticulocyte count (Table 19), blood film (Fig. 45) and biochemical screen should be performed.

*Haematology: Clinical Cases Uncovered.* By S. McCann, R. Foà, O. Smith and E. Conneally. Published 2009 by Blackwell Publishing, ISBN: 978-1-4051-8322-2

**Table 19** Results of the full blood count.

|                | Patient's results              | Normal range (male)  |
|----------------|--------------------------------|--|
| Hb             | 5.8 g/dL                       | 13.5–18.0 g/dL   |
| MCV            | 121 fL                         | 83.0–99.0 fL ( $\mu\text{m}^3$ )                                 |
| WBC            | $7.9 \times 10^9/\text{L}$     | $4.0\text{--}11.0 \times 10^9/\text{L}$ ( $10^3/\mu\text{L}$ )   |
| Platelets      | $450 \times 10^9/\text{L}$     | $140\text{--}450 \times 10^9/\text{L}$ ( $10^3/\mu\text{L}$ )    |
| Red cell count | $1.58 \times 10^{12}/\text{L}$ | $4.60\text{--}5.70 \times 10^{12}/\text{L}$ ( $10^6/\text{mL}$ ) |
| Reticulocytes  | $320 \times 10^9/\text{L}$     | $50\text{--}100 \times 10^9/\text{L}$ (0.5–1.5%)                 |

Hb, haemoglobin; MCV, mean corpuscular volume; WBC, white blood cell count.



**Figure 45** A blood film showing normal red cells (N), spherocytes (S) and polychromasia (P).

Red cells are biconcave discs and on blood film appear to have an area of central pallor. Most of the haemoglobin is around the edge of the cell and not in the middle, hence the appearance. Spherocytes are almost completely spherical but in a two-dimensional view will appear as a small dense cell without central pallor. The haemoglobin is equally distributed throughout the cell. The polychromasia or blue–grey colour of the red cells reflects the presence of ribosomes and haemoglobin synthesis. These young red cells are called reticulocytes. They are present in the peripheral blood in small numbers ( $50\text{--}100 \times 10^9/\text{L}$ ). Premature removal of red cells from

the circulation (from haemolysis or bleeding) will be reflected by an increase in the number of reticulocytes found in the peripheral blood as a compensatory measure.

### How do the blood results alter your differential diagnosis?

The low haemoglobin means the patient is anaemic and the low red cell count suggests there are production problems in the marrow or that red cells have a shortened lifespan in the peripheral blood. The elevated MCV reflect the presence of an increased number of reticulocytes, which are large. This would indicate bleeding or haemolysis.

### What is the significance of spherocytes in the blood?

Spherocytes indicate a congenital or acquired alteration in the surface area to volume ratio of the red cells.

Loss of red cell membrane alters the ratio of cell surface area to volume which results in the shape change. Red cells are normally very plastic and the biconcave shape facilitates reversible shape change as the cells traverse small blood vessels and the cords of the spleen. Spherocytes are inherently less plastic and have much more difficulty traversing apertures  $<8.0 \mu\text{m}$  in diameter.

### By what mechanisms can normal red cell biconcave discs change into spherocytes?

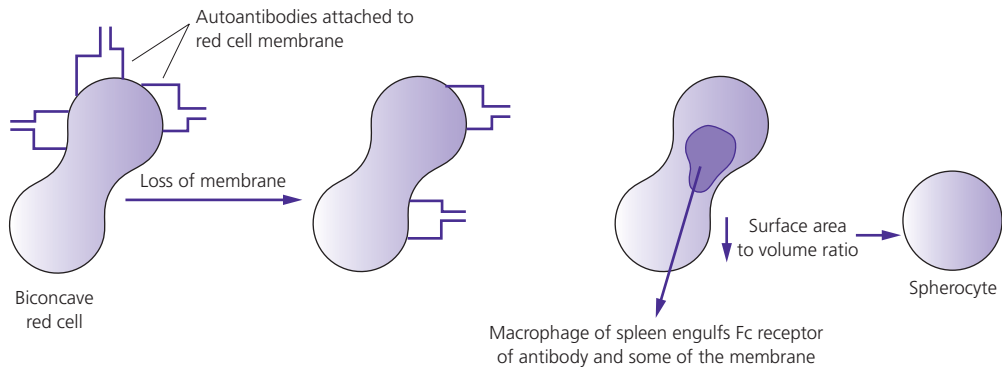
Inherited abnormalities of red cell membrane, which interfere with the structure or function of the spectrin–actin complex (cytoskeleton), give rise to spherocytes, the so-called hereditary spherocytosis syndrome. Attachment of autoantibodies, with or without complement, to the red cell membrane results in phagocytosis of the attached antibody and/or complement by macrophages with subsequent loss of red cell membrane (Fig. 46).

#### KEY POINT

The mechanism of spherocyte formation cannot be ascertained from the blood film appearances.

### What tests can differentiate the mechanism of spherocyte formation?

The direct antiglobulin test, also known as the Coombs' test (DCT).



**Figure 46** Diagram showing autoantibodies attached to the red cell membrane. Thus autoantibodies and endothelial cells in the spleen engulf some of the red cell membrane. Membrane is lost and a spherocyte is formed.

### How does the DCT differentiate between the mechanisms?

The DCT detects the presence of autoantibodies (usually IgG) or complement (usually C3d) on the red cell membrane.

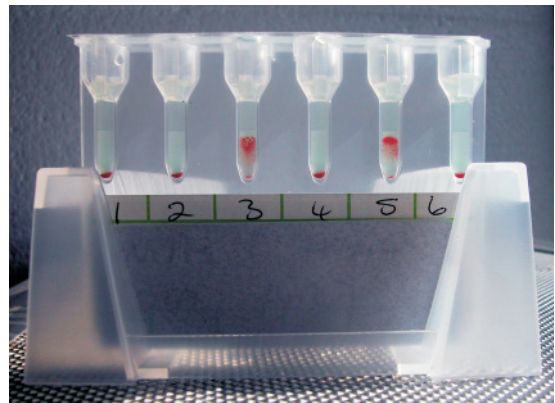
A reagent called the Coombs' reagent is used. This reagent is made by immunizing rabbits with human serum. The rabbit responds by making antibodies.

### What components of serum does the rabbit make antibodies against?

IgG and complement.

### How is the test performed?

Coombs' reagent is added to the red cells (Fig. 47) and the cells are centrifuged.



**Figure 47** The Coombs' test (DCT). Tubes 1, 2, 4 and 6 contain normal red cells and the Coombs' reagent. After centrifugation in a gel phase, the red cells fall to the bottom. Tubes 3 and 5 contain red cells with IgG and complement on their surface. The cells clump together and appear to be suspended in the tube.

#### KEY POINT

If there are molecules of autoantibody (IgG or C3d) on the red cell membrane, the Coombs' reagent will bind to these molecules and bridges will be formed between the red cells. The result is that the red cells will clump together (agglutinate).

### What other tests confirm a diagnosis of haemolysis?

Plasma bilirubin, haptoglobins and lactic dehydrogenase (LDH) (Table 20).

**Table 20** Results of confirmatory tests of haemolysis.

|              | Patient's results        | Normal range                           |
|--------------|--------------------------|--|
| Bilirubin    | 56 $\mu\text{mol/L}$     | 0–17 $\mu\text{mol/L}$ (0.3–1.1 mg/dL) |
| Haptoglobins | Undetectable             | 0.45–2.05 g/L (mg/dL)                  |
| LDH          | 1404 IU/L                | 230–450 IU/L                           |
| DCT          | Positive for IgG and C3d |  |

DCT, direct antiglobulin test (Coombs'); Ig, immunoglobulin; LDH, lactic dehydrogenase.

### Now what is the diagnosis?

The raised plasma bilirubin (predominantly indirect) indicates destruction of red cells and causes the jaundice. Plasma haptoglobins are decreased or absent. The LDH is elevated as a result of red cell destruction. The DCT is positive, indicating autoantibody on the red cell surface.

Haptoglobin binds to haemoglobin, which has been released from the haemolysed red cell, and reticuloendothelial cells phagocytose the complex, thus haptoglobin disappears from the plasma. The diagnosis therefore is acquired autoimmune haemolytic anaemia (AIHA).

### How should the patient be managed and why?

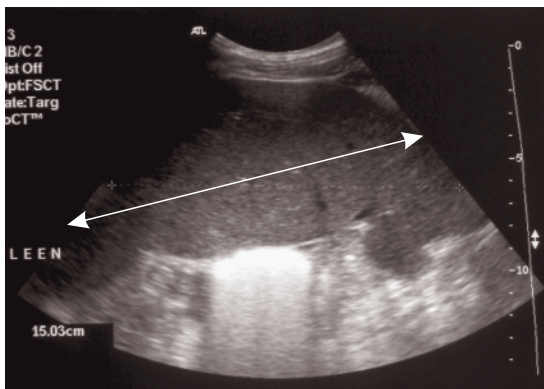
Mr Adler should be referred to a specialist. AIHA can be severe and life-threatening.

#### KEY POINT

The ability of the patient to withstand the effects of haemolysis will depend on the general state of health and any other illness that might be present such as heart disease.

### What further tests will the specialist do?

Repeat the blood tests to see if the haemoglobin has fallen further. Carry out an ultrasound examination of the abdomen to assess the spleen size (Fig. 48).



**Figure 48** Ultrasound scan of the left upper quadrant of the abdomen demonstrating a large spleen indicated by the arrows.

Other diseases may be associated with haemolysis, e.g. systemic lupus erythematosus (SLE) or chronic lymphocytic leukaemia. Drugs such as penicillin, quinidine or methyldopa may cause AIHA.

### What are the principles of treatment?

Give corticosteroids and monitor the response. Avoid red cell transfusion if possible.

### Why should blood transfusion be avoided?

The antigens on the transfused red cells may stimulate further production of antibody in the recipient's plasma and increase the rate of haemolysis.

#### KEY POINT

Give folic acid orally. Patients who have haemolysis may become deficient in folic acid because of the excessive demand by the bone marrow to make new red cells leading to a worsening of the anaemia. A falling reticulocyte count with a further fall in the haemoglobin is suggestive of folate deficiency.

### Which other types of autoantibodies can cause haemolysis?

Antibodies of the IgM class, so-called cold antibodies, can bind to the red cell surface and always bind complement.

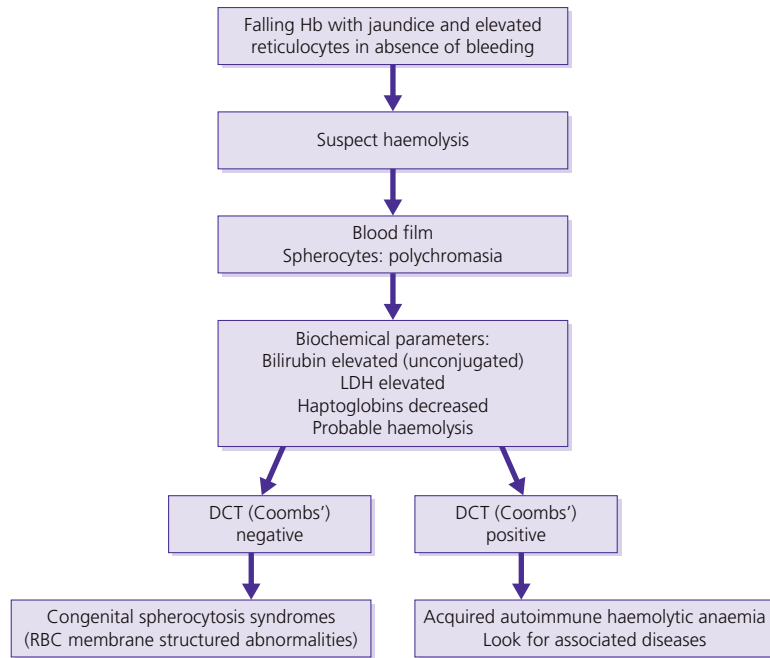
The patient may experience acrocyanosis (purple discoloration of the extremities) in cold weather because of clumping of red cells in the circulation.

#### KEY POINT

Recently, patients with chronic haemolytic anaemia that fails to respond to corticosteroids have been successfully treated with anti-CD20 antibody (rituximab).

### Can you construct an algorithm when you suspect haemolysis?

Yes.



*Outcome.* Mr Adler was given oral corticosteroids and folic acid supplements. Antifungal prophylaxis and proton pump inhibitors were prescribed to counteract the major toxicities

of corticosteroids and his blood glucose was monitored carefully. No underlying disease was detected and his haemoglobin returned to normal in 4 weeks.

## CASE REVIEW

An elderly man complains of shortness of breath on exertion. He was icteric and had evidence of mild heart failure. The initial symptoms and signs could point to a number of diagnoses including cancer, ischaemic heart disease and liver disease. A critical finding is that of a large spleen. This raises the possibility of a haematological disorder and the icterus, pallor and heart failure suggest a form of anaemia.

The blood result is crucial, revealing severe anaemia with a high MCV and a reticulocytosis. This implies haemolysis and in a man of this age is likely to be acquired.

The blood film is diagnostic of haemolysis, revealing spherocytes and polychromasia. The direct antiglobulin test (Coombs' test) is positive. This clinches a diagnosis of

autoimmune haemolytic anaemia and the loss of membrane accounts for the spherocytes in the blood film. The only way to distinguish spherocytes resulting from autoantibody formation from congenital membrane defect is by the direct antiglobulin test.

A diagnosis of acquired autoimmune haemolytic anaemia should always prompt a search for an underlying disease; however, as in this case, nothing else was discovered. Treatment is usually with corticosteroids and folic acid, but splenectomy may be required in resistant cases. Treatment of any underlying disease is indicated (e.g. chronic lymphocytic leukaemia; Case 11) and monoclonal antibodies to CD20 may be useful in switching off antibody production and reducing haemolysis.

## KEY POINTS

- An elderly man presents with jaundice, evidence of heart failure and splenomegaly
- The blood findings suggest haemolytic anaemia
- Inspection of the blood film is crucial in revealing the diagnosis
- Spherocytes are present and the direct antiglobulin (Coombs') test is positive
- Although there may be an underlying disease many patients appear to have isolated autoimmune haemolysis
- The usual treatment is with corticosteroids but the precise mechanism of action is debated. It probably is a combination of uncoupling of antibody from the red cell membrane, Fc receptor blockade and a gradual reduction in antibody production by B lymphocytes
- Response to steroids is usually brisk but often incomplete. Treatment with immunosuppressive agents is commonly required in order to allow a reduction in the dosage of corticosteroids
- Patients may respond, have a prolonged disease-free period without treatment and then relapse for unknown reasons
- Folate deficiency, secondary to increased requirement of the marrow to produce 'new' erythrocytes, may compound the anaemia. This will inevitably be accompanied by a fall in the haemoglobin and the reticulocyte count

## Further reading

Cunningham MJ, Silberstein LE. Autoimmune hemolytic anemia. In: Hoffman R, Benz EJ Jr, Shattil SJ, Furie B, Cohen HJ, Silberstein LE, *et al.* eds. *Hematology: Basic Principles and Practice*, 4th edn. Churchill Livingstone, 2005: 693–707.

Dacie J. *The Haemolytic Anaemias*, Vol. 4. *Secondary or Symptomatic Haemolytic Anaemias*, 3rd edn. Churchill Livingstone, 1995.

Hoffbrand AV, Moss PAH & Pettit JE. *Essential Haematology*, 5th edn. Blackwell Science, Oxford, 2006: 58–71.

Hoffman PC. *Immune Hemolytic Anemia*. *asheducationbook*. [hematologylibrary.org/cgi/content/full/2006/1/13](http://hematologylibrary.org/cgi/content/full/2006/1/13) Accessed in 2006.