Case 16.1 Primary autoimmune haemolytic anaemia

A 32-year-old man gradually noticed that he had ‘yellow eyes’ and dark urine, felt continually tired and was short of breath when climbing stairs. He had no other symptoms; in particular, there was no itching, fever or bleeding; he was not taking any drugs. On examination, he was anaemic and jaundiced but afebrile, with no palpable lymphadenopathy, hepatosplenomegaly, rash or arthropathy.

On investigation, his haemoglobin was very low at 54 g/l. The white cell count appeared raised (40 x 10^9/l), but this was due to nucleated red cells being counted as leucocytes by the automated counter. The blood film showed gross polychromasia with nucleated red cells and spherocytes; the reticulocyte count in the blood was 9%. His serum bilirubin (47 mmol/l), aspartate transaminase (90 IU/l) and lactate dehydrogenase levels (5721 IU/l) were raised. Further tests showed that his red cells had IgG and C3 on their surfaces by the direct Coombs’ test. Serum contained warm non-specific autoantibodies (i.e. reactive with all the red cells in the test panel). Antinuclear antibodies and rheumatoid factor tests were negative and immunoglobulin levels were normal; there were no paraprotein bands in his serum or urine. Large amounts of urinary haemosiderin were detected.

A laboratory diagnosis of primary AIHA due to warm antibodies (leading to haemolysis and jaundice) was made. He failed to respond to high-dose corticosteroids and had a splenectomy 3 weeks later. Although impalpable, the spleen was twice the normal size; histology did not reveal a malignancy. He made a good post-operative recovery; his haemoglobin rose rapidly and the reticulocyte count fell. He took prophylactic penicillin for at least 2 years after surgery to prevent severe Strep. pneumoniae infection.

Case Figure 16.1a Mild jaundice in autoimmune haemolytic anaemia – note yellow sclera, though skin as yet unchanged.
**Case Figure 16.1b** Warm AHA – blood film – note spherocytes and polychromasia, i.e. grey tint to some red cells indicating they are reticulocytes.

**Case Figure 16.1c** Increased reticulocytes in warm AHA – the blood film has been stained with brilliant cresyl blue to show the ribosomal RNA in the immature red cells.
A 77-year-old man presented one winter with malaise and very cold hands and feet. He admitted to a tendency to bruise easily, and to passing dark urine in cold weather. He was not on any medication and was a non-smoker. On examination, he had some bruising on the shins and was mildly jaundiced. His fingers and toes were cold, but not ischaemic. He had small but palpable lymph nodes in both axillae and groins but no hepatosplenomegaly.

His haemoglobin was low (100 g/l) and the blood film showed rouleaux formation (autoagglutination) and polychromasia; neutrophil, lymphocyte and platelet counts were normal. He had raised serum bilirubin and lactate dehydrogenase levels; serum iron, folate and vitamin B<sub>12</sub> measurements were normal. He had normal IgG (8.3 g/l) and IgA (1.2 g/l) levels and a slightly raised IgM (4.2 g/l); electrophoresis of serum and urine showed no paraprotein bands. He had a normal level of serum β<sub>2</sub>-microglobulin. There were cold antibodies in his serum that agglutinated red cells of ‘I’ specificity. A laboratory diagnosis of cold haemagglutinin disease leading to haemolysis and mild jaundice was made. He was advised to keep as warm as possible at all times. He has been seen regularly over the last 8 years but has not required active treatment or developed an overt lymphoid malignancy.
Case Figure 16.2 Red cell agglutination in blood film of patient with cold AHA; in contrast to rouleaux in multiple myeloma, there is no background staining due to very high serum protein levels.

Case 16.3 Cephalosporin-induced haemolytic anaemia

A 72-year-old woman with osteoarthritis suffered acute haemolysis after her right hip was replaced. She had no evidence of splenomegaly and no lymphadenopathy to suggest an underlying malignancy. No explanation was found for the episode; warm and cold antibody tests were negative. She remained well until she had the other hip replaced 2 years later, when she again developed haemolysis soon after the anaesthetic, as well as after the revision 7 months later. Her serum was found to react with red cells coated with the cephalosporin used at the time of anaesthetic induction. She was advised that she had cephalosporin-induced haemolytic anaemia and to avoid this antibiotic in the future. She invested in a MediAlert bracelet to ensure that she was not given cephalosporins even if unconscious and was tested for cross-reactivity to penicillin.

Case Figure 16.3 Antibody-mediated mechanisms for drug-induced haemolysis.
Case 16.4 Autoimmune immune thrombocytopenia

A 29-year-old man presented with spontaneous bruising of his legs and arms. He had had three recent epistaxes but no other bleeding. He was not taking any drugs and had no risk factors for HIV. There were no physical signs apart from bruises and scattered petechiae on the legs. The spleen was not palpable. On investigation, he had a normal haemoglobin (138 g/l) and white cell count, but a low platelet count of \(10 \times 10^9/l\) (normal \(>150 \times 10^9/l\)). His serum CRP and immunoglobulin levels were normal; direct Coombs’ test was negative; antinuclear and DNA-binding antibodies and rheumatoid factor were absent. His bone marrow contained an increased number of normal megakaryocytes but was otherwise normal. A diagnosis of immune thrombocytopenia was made and he was started on a high dose of prednisolone. His platelet count rose rapidly over the next few days and the steroids were tailed off over 4 weeks. He relapsed 10 months later with further bruising, but again responded to a short course of oral steroids.

Case Figure 16.4a Bruising and purpura in hand and arm of an elderly patient due to poor vasculature – distinct from a purpuric rash.

Case Figure 16.4b Immune Thrombocytopenia in another patient to show acute purpuric rash – note tiny lesions (petechiae), small purple spots (purpura) and larger coalescences.
Case 16.5 Neonatal alloimmune diseases

A 32-year-old woman undergoing a twin pregnancy had been given a blood transfusion for a post-partum haemorrhage in her first pregnancy 3 years earlier. The current pregnancy and delivery were normal and non-identical twin boys were born, both with Apgar scores of 10. Four hours later, both infants had extensive purpura on their abdomens, arms and legs but neither was jaundiced.

Twin 1 had a platelet count of $30 \times 10^9/l$ and his haemoglobin was 176 g/l. He did not become jaundiced and his platelet count gradually rose without treatment over several weeks. His platelet count was normal ($400 \times 10^9/l$) at 2 months.

Twin 2 had a platelet count of $46 \times 10^9/l$ and a normal haemoglobin (190 g/l). However, he rapidly developed anaemia (Hb 84 g/l) and jaundice (bilirubin 300 mmol/l) at 48 h. A Coombs’ test was positive and his red cells were found to be group A, whereas his mother’s cells were group O. In view of the rising serum bilirubin, an exchange transfusion was performed. Following this, his haemoglobin and platelet count returned to normal and he was discharged 6 days later with a platelet count of $213 \times 10^9/l$ and a haemoglobin of 132 g/l.

The mother’s serum was found to contain IgG antibodies to the father’s platelets and to some, but not all, of a panel of platelets from normal, unrelated donors. These antibodies were typed as specific anti-HPA-1a antibodies and had been provoked by the previous pregnancy and transfusion. These antibodies crossed the placenta to cause alloimmune thrombocytopenia in both twins. Twin 2 also had a red cell incompatibility and so needed an exchange transfusion to compensate for haemolysis. It is unusual for an ABO incompatibility to require an exchange transfusion (see section 18.4.5). His platelet count returned to normal more quickly than that of twin 1 because the antibodies to platelets were removed by the exchange.
Case 16.6 Primary antiphospholipid antibody syndrome

A 28-year-old woman was admitted with a stroke due to a cerebral vascular thrombosis. She had had four spontaneous abortions in the past. She was a non-smoker. Cerebral angiography confirmed the thrombosis but showed normal vasculature otherwise. Haemoglobin, platelet and white cell counts were normal, as were her serum immunoglobulins, C3 and C4 levels. Antibodies to nuclei, extractable nuclear antigens and double-stranded DNA were negative, but she did have high-titre antiphospholipid antibodies. Coagulation tests showed a prolonged kaolin–cephalin clotting time which did not correct with normal plasma, i.e. lupus anticoagulant. A diagnosis of primary antiphospholipid antibody syndrome was made, so she received long-term anticoagulant therapy. She made a good recovery from the stroke.

Case 16.7 Transmission of hepatitis C by a blood product in early 1990s

David was diagnosed as having a common variable immune deficiency disorder aged 28 years, after developing bronchiectasis over the preceding 5 years. He had also suffered from episodes of urethritis, eventually found to be due to Ureaplasma urealytica (a common organism known to cause significant infections in antibody-deficient patients). He received 25 g of intravenous immunoglobulin at 3-week intervals, with regular monitoring of his liver function tests (6-weekly). After 3 years of uneventful infusions, he developed raised alanine transaminase levels and rapidly became jaundiced. His serum was now positive for hepatitis C virus by polymerase chain reaction (HCV-PCR). He had iatrogenic hepatitis C.

He was admitted for assessment and the jaundice and liver enzyme levels reversed spontaneously; he received 6 million units of interferon (IFN)-α subcutaneously three times a week for 6 months. The PCR became negative within 4 weeks and has remained so over the next 20 years, as have his liver function tests.

This type of transmission of hepatitis C is thankfully very rare nowadays, since blood products are treated routinely with solvent:detergent or other methods to inactivate lipid-coated viruses. Such a patient would now receive Ribavirin with IFN-α, as the results of such treatment in blood transfusion-transmitted disease are superior.