Case 3.1 X-linked agammaglobulinaemia (Bruton's disease)

Peter was born after an uneventful pregnancy, weighing 3.1 kg. At 3 months, he developed otitis media; at the ages of 5 months and 11 months, he was admitted to hospital with untypable Haemophilus influenzae pneumonia. These infections responded promptly to appropriate antibiotics on each occasion. He is the fourth child of unrelated parents: his three sisters showed no predisposition to infection.

Examination at the age of 18 months showed a pale, thin child whose height and weight were below the third centile. There were no other abnormal features. He had been fully immunized as an infant (at 2, 3 and 4 months) with tetanus and diphtheria toxoids, acellular pertussis, Hib and Mening. C conjugate vaccines and polio (Salk). In addition, he had received measles, mumps and rubella vaccine at 15 months. All immunizations were uneventful.

Immunological investigations (Table 3.4) into the cause of his recurrent infections showed severe reduction in all three classes of serum immunoglobulins and no specific antibody production. Although there was no family history of agammaglobulinaemia, the lack of mature B lymphocytes in his peripheral blood suggested a failure of B-cell differentiation and strongly supported a diagnosis of infantile X-linked agammaglobulinaemia (Bruton's disease). This was confirmed by detection of a disease-causing mutation in the Btk gene. The antibody deficiency was treated by 2-weekly intravenous infusions of human normal IgG in a dose of 400 mg/kg body weight/month. Over the following 7 years, his health steadily improved, weight and height are now on the 30th centile, and he has had only one episode of otitis media in the last 4 years. He is now 12 years and able to treat himself with the same dose of subcutaneous replacement immunoglobulin at home.

Table 3.4 Immunological investigations* in Case 3.1. XLA

Quantitative serum immunoglobulins (g/L):		
IgG	0.17	(5.5–10.0)
IgA	Not detected	(0.3–0.8)
IgM	0.07	(0.4–1.8)
Antibody activity		
Immunization responses – no detectable IgG antibodies to:		
Tetanus toxoid (post Imx)		
Haemophilus type b polysaccharides (post Imx)		
Polio (post Imx)		
Measles (post Imx)		
Rubella (post Imx)		
Isohaemagglutinins (IgM) not detected (blood group A Rh+)		
Blood lymphocyte subpopulations ($\times 10^9$/L):		
Total lymphocyte count	3.5	NR* (2.5–5.0)
T lymphocytes (CD3)	3.02	NR (1.5–3.0)
B lymphocytes (CD19)	<0.1	NR (0.3–1.0)

*Normal range for age 18 months shown in parentheses.
Imx = immunisation

Essentials of Clinical Immunology, Sixth Edition. Helen Chapel, Mansel Haeney, Siraj Misbah, and Neil Snowden.

Case 3.2 CD40 ligand deficiency

Michael was seen in OPD at the age of 4 years with a history of painful mouth ulcers, abdominal pain over 7 weeks but persistent diarrhoea in the last 2 weeks. He had suffered multiple episodes of ear and chest infections, starting with pneumonia at the age of 9 months, when he had been noted to have neutropenia but this had appeared to be transient. He has three healthy sisters. On examination he had multiple oral ulcers, enlarged tonsils, purulent nasal discharge, scarred tympanic membranes, abdominal distension and hepatomegaly.

He was investigated for an early presentation of inflammatory bowel disease, including stool microscopy. In addition, liver function tests and hepatitis serology were done to determine the cause of the enlarged liver, T-lymphocyte enumeration to exclude severe combined immunodeficiency (SCID) and immunoglobulin levels to exclude a CVID. Cryptosporidia were found in the stools and liver enzyme levels were raised. Serum IgG and IgA levels were very low but B and T-cell numbers were normal (see Table 3.5). Since C-reactive protein (CRP) and albumin serum levels were normal, an intestinal biopsy was not indicated. A diagnosis of primary antibody deficiency with cryptosporidiosis was made.. Abdominal ultrasound showed a diffusely enlarged liver with a dilated common bile duct.

This was most likely to be due to a hyper-IgM syndrome as the serum IgM was raised and cryptosporidia is a particular feature of this condition. Peripheral blood lymphocytes were separated and stimulated in culture; activation markers, including CD40 ligand, were then detected by flow cytometry. CD69 and CD72 were present but there was no CD40 ligand on activated T lymphocytes. Mutation analysis confirmed a deletion in the CD40 ligand gene on the X chromosome and a substantive diagnosis of CD40 ligand deficiency was made. He was treated initially with replacement immunoglobulin, co-trimoxazole to prevent Pneumocystis infection and specific antibiotics for Cryptosporidiosis; if this organism can be controlled, human stem cell transplantation, with or without liver transplantation, will be considered. His mother was tested for carrier status, as will his sisters when they reach the age of consent.

Table 3.5 Immunological investigations in Case 3.2, CD40 ligand deficiency

Serum proteins			
Albumin		39 g/l	
C-reactive protein		8 mg/l	
Immunoglobulins	IgG	0.9 g/l	NR* (5.8–10.0)
	IgA	<0.07 g/l	NR (0.6–2.0)
	IgM	3.2 g/l	NR (0.5–1.8)
There were no detectable IgG antibodies to immunization or exposure antigens			
Blood lymphocyte subpopulations (10^9/l):			
Total lymphocyte count		2.1	(1.5–3.50)
T lymphocytes			
CD3		1.5	(0.9–2.8)
CD4		0.8	(0.6–1.2)
CD8		0.7	(0.4–1.0)
B lymphocytes			
CD19		0.4	(0.2–0.4)
NK lymphocytes			
CD16:CD56		0.2	(0.2–0.4)

Lymphocyte stimulation assays (with phytohaemagglutinin)

	Prestimulation*			**Post-stimulation**		
	CD69	**CD71**	**CD40 ligand**	**CD69**	**CD71**	**CD40 ligand**
Control	3%	5%	<1%	73%	49%	62%
Patient	1%	2%	<1%	72%	63%	<1%

*NR Normal range for age 4 years
**Percentage of CD3 cells with relevant activation marker on surface.

Case 3.3 Common variable immunodeficiency disorder (CVID)

A 34-year-old woman developed herpes zoster and lobar pneumonia; over the previous 5 years she had been admitted to hospital with pneumonia on two previous occasions and made a full recovery. There had been no history of recurrent chest infections during childhood. Non-encapsulated Haemophilus influenza and Streptococcus pneumoniae were isolated. At the age of 35, she developed a non-erosive seronegative arthritis. On direct questioning, she gave a history of intermittent diarrhoea since her late teens. These episodes lasted from 2 days to 2 weeks and she passed five to six partly formed stools a day. There was no family history of recurrent infections: she had two sons, aged 10 and 7, both of whom were well. Physical examination was normal, although she was thin.

Investigations showed a haemoglobin of 115 g/l, with normal neutrophil and lymphocyte counts. Immunological studies (Table 3.6) showed very low levels of serum immunoglobulins, and no detectable specific antibodies despite culture-proven Streptococcus pneumoniae and a tetanus toxoid boost 1 year earlier. She had normal numbers of circulating T and B lymphocytes. No infective cause of the intermittent diarrhoea was found; barium enema and colonoscopy were normal.

She was diagnosed as having a common variable immunodeficiency disorder, a diagnosis of exclusion, as no underlying cause was found. She was given fortnightly intravenous infusions of human normal IgG (400 mg/kg body weight/month) for the antibody deficiency. However three years later she developed pain, bloating and further diarrhoea. Duodenal biopsies showed flat villi without pathogens. A gluten-free diet (to which she adhered rigidly) was not successful in reducing the abdominal symptoms. Ultimately she failed to absorb fat soluble vitamins A, D and E and lost 6 kg in weight. She had the enteropathy associated with CVID, the pathogenesis of which is uncertain. She died suddenly of an unrelated pulmonary embolus.

Table 3.6 Immunological investigations* in Case 3.3, a CVID

Quantitative serum immunoglobulins (g/l):		
IgG	3.15	NR (7.2–19.0)
IgA	0.11	NR (0.8–5.0)
IgM	0.66	NR (0.5–2.0)
Antibody activity		
Post-immunization IgG to:		
Tetanus toxoid		Negative (>0.85 IU/ml)
Diphtheria toxoid		Negative (>0.2 IU/ml)
Pneumococcal polysaccharides		Negative (>80 U/ml)
Blood lymphocyte subpopulations ($\times 10^9$/l):		
Total lymphocyte count	1.6	(1.5–3.5)
T lymphocytes		
CD3	1.31	(0.9–2.8)
CD4	0.89	(0.6–1.2)
CD8	0.41	(0.4–1.0)
B lymphocytes		
CD19	0.2	(0.2–0.4)
NK lymphocytes		
CD16: CD56	0.2	(0.2–0.4)

*Normal adult ranges shown in parentheses.

Case 3.4 IgA with IgG subclass deficiencies

A 48-year-old man was admitted for investigation of weight loss associated with intermittent diarrhoea; stool examinations had been unhelpful. He had a history of pneumonia as a child and again as a young man working abroad. At the age of 33 he had developed chronic sinusitis, with persistent headaches. On examination, he was thin but had no signs of malignancy. There was no clubbing, lymphadenopathy or hepatosplenomegaly and his chest was clear on auscultation. Haemoglobin, serum albumin, liver function tests and urine electrophoresis were normal. Immunological tests are shown in Table 3.7. Investigations into the cause of the recurrent diarrhoea revealed Giardia lamblia on jejunal biopsy, even though microscopy was negative *even though microscopy was negative*. Endoscopic examination of his maxillary sinuses showed considerable inflammation and hypertrophy of the mucosa.

A diagnosis of IgA with IgG subclass deficiencies, with chronic sinusitis and intestinal giardiasis as secondary complications, was made. He was given a course of metronidazole for the giardia infestation and replacement immunoglobulin was started with weekly infusions initially and subsequently 3-weekly at a dose of 0.4 g/kg per month. The sinusitis gradually improved, the diarrhoea did not return and he remained infection free for many years.

Table 3.7 Immunological investigations* in Case 3.4, IgA with IgG subclass deficiency

Serum immunoglobulins (g/l):			
IgG	7.6		(6.5–12.0)
IgA	<0.1		(0.8–5.0)
IgM	1.2		(0.5–2.0)
IgG1	1.1		(3.6–7.3)
IgG2	3.8		(1.4–4.5)
IgG3	0.1		(0.3–1.1)
IgG4	2.6		(0.1–1.0)
Serum and urine electrophoresis – no monoclonal bands			
Antibody activity – post immunization:			
IgG	Tetanus toxoid Diphtheria toxoid Pneumococcal polysaccharides	Negative Negative Normal	(>0.85 IU/ml) (>0.2 IU/ml) (>80 U/ml)
Antibody activity – post exposure:			
IgG	Rubella Measles Varicella zoster	Not detectable Not detectable Not detectable	
Blood lymphocyte subpopulations (·10^9/l):			
Total lymphocyte count	2.8		(1.5–3.5)
T lymphocytes			
CD3	2.2		(0.9–2.8)
CD4	1.6		(0.6–1.2)
CD8	0.6		(0.4–1.0)
B lymphocytes			
CD19	0.3		(0.2–0.4)
NK lymphocytes			
CD16:CD56	0.2		(0.2–0.4)

**Normal adult ranges shown in parentheses.*

Case 3.5 Severe combined immunodeficiency

David was born at full term after a normal pregnancy; his parents were unrelated. He was not given Bacille Calmette–Guérin (BCG) at birth. He was well until 2 months, when he became 'chesty' and needed antibiotics. Routine immunizations were postponed until he had recovered, but he then developed 'antibiotic-related' diarrhoea, which did not settle after the antibiotics were stopped. After 3 months a further chest infection occurred, his weight fell from the 25th centile to below the third. He was admitted for investigation for failure to thrive and was found to have a silent atypical pneumonia on initial chest X-ray.

On examination, he was a thin, scrawny infant on the 25th centile for length. There were no rashes or lymphadenopathy, but his liver was palpable just below the right costal margin. He had slight tachycardia and tachypnoea; bronchoscopy to obtain a sample for microbiological tests revealed Pneumocystis jiroveci on staining of the fluid. Investigations (Table 3.8) showed a marked deficiency of T cells with normal numbers of B cells but no immunoglobulin production. He had a T–B^{++} NK^{-} form of SCID. He was treated with high dose co-trimoxazole for the Pneumocystis and referred promptly to a specialist unit for human stem cell transplantation, where he was put in isolation and given immunoglobulin therapy to prevent further infections. The diagnosis was investigated further by mutation analysis, starting with the commonest form of this type of SCID, X-linked common γ chain cytokine receptor deficiency, which was positive.

Table 3.8 Immunological investigations* in Case 3.5, severe combined immune deficiency

Full blood count		**Immunological results**	
Haemoglobin	108 g/l	IgG	0.9 g/l
Neutrophil count	3.5×10^9/l	IgA	<0.1 g/l
Lymphocyte count	0.5×10^9/l [NR for age (4–15)]	IgM	0.1 g/l
Microbiology results		**Lymphocytes**	
Blood	Negative for HIV & CMV by PCR	$CD3^+/CD4^+CD3^+/$ $CD8^+CD19^+CD3^+/$ $CD16^+56^+CD4^+/$ $CD25^+CD3^+/HLA\text{-}DR^+$	0.09×10^9/l 0.04×10^9/l 0.23×10^9/l 0.07×10^9/l 0.08×10^9/l 0.1×10^9/l
Urine	Negative for CMV antigen		
Nasopharyngeal swab	Rhinovirus		
Stool	Echovirus-22		
Sputum Lavage fluid	Negative for bacterial culture Pneumocystis: PCR +ve and staining		

*Normal range for 3 months shown in parentheses (see Fig. 3.9).
†Stimulation index.
‡Percentage of $CD3^+$ cells expressing CD69 after 6 hours.

Case 3.6 IRAK-4 deficiency

A 9-year-old girl was admitted with meningitis due to Shigella; previously she had been in hospital with septic arthritis due to Streptococcus pneumoniae as well as several deep-seated abscesses caused by Staphylococci or Streptococcus pyogenes. On each occasion, full blood counts were normal, including lymphocyte and neutrophil counts. Curiously, her CRP had also been low despite severe infections, never higher than 35 mg/l. Other screening tests such as liver function tests, functional complement (CH_{50} and AP_{50}) were normal, as were serum immunoglobulin levels and antibody production (Table 3.12). The only abnormality was failure to reduce dihydrorhodamine on stimulation with lipopolysaccharide in vitro, the significance of which was unknown at the time. Years later, when more was known about the innate immune system, peripheral blood mononuclear cells were isolated from her blood and tested in vitro for IL-6 production following stimulation with a variety of agents including lipopolysaccharide; poor production of IL-6 was seen. It was thought that she might have a defect in the NF-κB pathway; on sequencing of her IRAK-4 gene, this was found to be the case.

Table 3.12 Immunological investigations in case 3.6, IRAK-4 deficiency

Investigation	Patient	Normal ranges
Dihydrorhodamine reduction test:		
Medium only	2%	8.7 ± 7.3%
Phorbol myristate acid	99%	99.2 ± 0.9%
Lipopolysaccharide	7%	>60%
Serum immunoglobulin concentrations:		
IgG *(g/l)*	16.7	6.0–13.0 g/l
IgA *(g/l)*	1.1	0.8–3.0 g/l
IgM *(g/l)*	1.9	0.4–2.5 g/l
IgE (KU/l)	400	<125 kU/l
Post-immunization IgG antibodies to:		
Tetanus	0.06	>0.01 IU/ml
Diphtheria	0.18	>0.01 IU/ml
23 valency Pneumovax	>100	>50 IU/ml
Haemophilus influenzae type b	1.36	>1 μg/ml

Case 3.7 Chronic granulomatous disease

Mark was born by Caesarean section and weighed 3.1 kg. He is the sixth child of unrelated white parents. At the age of 4 weeks, he developed an axillary abscess that healed spontaneously, followed by a staphylococcal abscess of the chest wall, requiring surgical incision and a course of flucloxacillin. He had a total white-cell count of 45×10^9/l, of which 90% were neutrophils, giving an unusually high neutrophil count.

At the ages of 3 and 7 months, he was readmitted to hospital with large staphylococcal abscesses, first on his face and then on his right buttock; both abscesses were treated by surgical incision and systemic antibiotics for 10 days. By the age of 2 years, he had been admitted to hospital five times with staphylococcal abscesses. The family history was remarkable: three elder brothers had died of infections at ages ranging from 7 months to 3 years, but his parents and two sisters were healthy.

On examination, he was pale and persistently pyrexial. His height and weight were below the third centile. He had bilateral axillary and inguinal lymphadenopathy with marked hepatosplenomegaly.

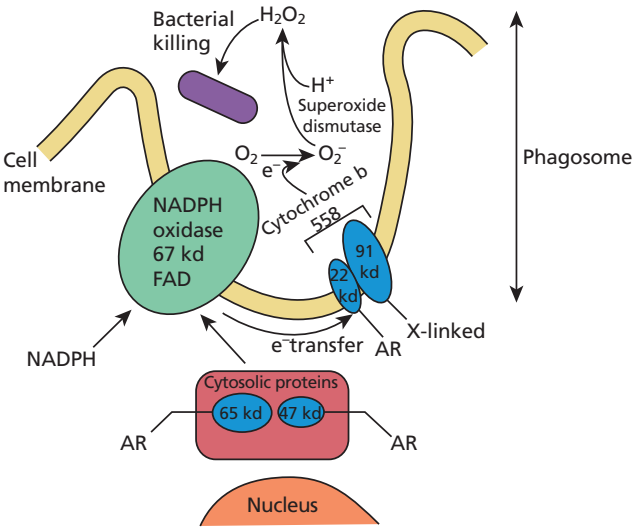
Laboratory tests showed mild anaemia (Hb 104 g/l) with marked polymorphonuclear leucocytosis. His immunological investigations are summarized in Table 3.14. There was gross polyclonal elevation of all immunoglobulin classes, particularly IgG and IgA. Dihydrorhodamine test on this boy showed that his polymorphs failed to reduce the dye and that his mother had two populations of neutrophils, one normal and one also unable to reduce dihydrorhodamine. These findings, and the X-linked nature of the condition, are diagnostic of chronic granulomatous disease (CGD).

Now aged 7 years, Mark continues to have periodic abscesses despite long-term co-trimoxazole. Since most antibiotics fail to penetrate cells effectively, treatment of acute infections is continued for at least 8 weeks. He has not had a major infection necessitating therapy with IFN-γ but is on a prophylactic antifungal agent. He will be considered for human stem cell transplantation when a matched donor can be found.

Table 3.14 Immunological tests* in Case 3.7, chronic granulomatous disease

Quantitative serum immunoglobulins (g/l):		
IgG	17.8	(5.5–10.0)
IgA	4.8	(0.3–0.8)
IgM	2.0	(0.4–1.8)
Antibody activity		
IgG antibodies: post immunization		
Tetanus toxoid	89	(>1.0 IU/ml)
Diphtheria toxoid	3.0	(>0.6 IU/ml)
Nitroblue tetrazolium (NBT) test†		
Unstimulated	2	(normal <10)
Stimulated	4	(normal >30)
Dihydrorhodamine test‡		
Control		90% cells positive
Patient		0% cells positive

*Normal range for age (or value for healthy control studied in parallel) is shown in parentheses.
†Percentage of neutrophils showing reduction of NBT before and after stimulation with endotoxin (see Chapter 19).
‡(see Chapter 19 section 19.8).



Case Figure 3.7 Diagrammatic representation of components of the NADPH oxidase system within a phagosome, depicting bacterial killing and site of abnormalities in chronic granulomatous disease. AR, autosomal recessive; NADPH, nicotinamide adenine dinucleotide phosphate; FAD, flavin adenine dinucleotide. (Modified from JAMA 1990; 263: 1533–1537.)

Case 3.8 IL-12 receptor deficiency

A 3-year-old girl, Sophia, born to consanguineous parents, came to OPD with a newly enlarged and persistent single lymph node in the supraclavicular region. Her parents were extremely anxious about leukaemia, although the child was well and a full blood count done in advance was normal. She had not been exposed to Mycobacteria tuberculosis, nor had she received BCG. She had had a few episodes of otitis media after an upper respiratory tract infection but no infections elsewhere. Biopsy of the lymph node was performed under general anaesthetic; histology showed a granuloma and the presence of a few acid-fast bacilli; an atypical (environmental) mycobacterium was grown on culture.

In order to be sure that this was not due to HIV disease, the child and her parents were tested after parental consent was given; the results were negative. Analysis of T, B and NK cells was normal, excluding a late presentation of SCID or another combined defect. IFN-γ and IL-12 production by monocytes and T cells were shown to be normal by Elispot. However a markedly reduced expression of IL-12 receptors on the surface of activated T cells was found and a diagnosis of complete IL-12 receptor deficiency was confirmed on mutation analysis. She has three healthy older siblings who were found to be heterozygous for the defect, as were her healthy parents.

Case 3.9 Isolated deficiency of complement component

A 26-year-old West Indian man presented with a 24-h history of occipital headache and vomiting. He was pyrexial (temperature 38.3°C), confused, irritable and had marked neck stiffness with a positive Kernig's sign. There was no other history of serious infections. His immediate family were healthy.

Lumbar puncture produced turbid cerebrospinal fluid (CSF) with a protein concentration of 4.5 g/l (NR 0.1–0.4), glucose content of <0.1 mmol/l (NR 2.5–4.0) and a leucocyte count of 8000/mm^3 (97% neutrophils). Neisseria meningitidis was cultured from the CSF. The patient was treated with intravenous penicillin and oral chloramphenicol and made a rapid recovery over the following 2 weeks.

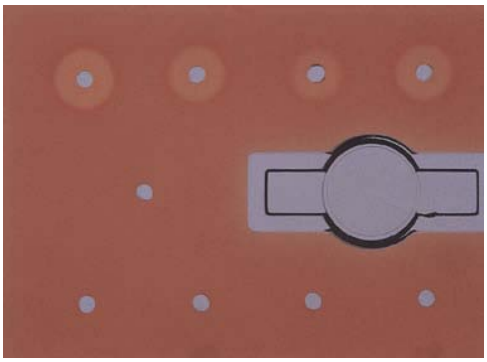
A search was made for an underlying cause of his meningitis. X-rays of the skull and sinuses showed no abnormal communication with the CSF. The possibility of an underlying immune defect was then considered and the results of immunological tests are shown in Table 3.16. Antibody production to a variety of bacterial and viral antigens was normal. However, total classical pathway haemolytic complement activity (CH_{50}) and alternate pathway (AP_{50}) were consistently undetectable in his serum during convalescence, indicating a complete functional absence of one or more complement components of the terminal lytic pathway. Eventually, he was shown to have an isolated deficiency of C6, with normal levels of all other components. Half normal levels of C6 were found in the sera of his parents and in three of his four siblings: the other sibling had a normal level.

Unlike immunoglobulin deficiency, long-term replacement of missing complement components is not feasible at present because their half-lives are so short (<1 day). Nasopharyngeal carriage of Neisseria meningitidis by the patient and his close contacts can be eradicated by antibiotics but at the risk of inducing resistant strains. Prophylactic penicillin is used in those patients with symptomatic complement deficiencies along with immunisation to the locally prevalent types of neisseria for which vaccines are available.

Table 3.16 Immunological investigations* in Case 3.9, complement deficiency

Quantitative serum immunoglobulins (g/l):		
IgG	15.0	(7.2–19.0)
IgA	3.2	(0.8–5.0)
IgM	1.2	(0.5–2.0)
Antibody activity		
Normal titres of antibodies to tetanus toxoid, diphtheria toxoid and pneumococci		
Detectable antibodies to herpes simplex, measles, influenza A and adenovirus		
Complement activity		
CH_{50}	No detectable activity	
AP_{50}	No detectable activity	

**Normal ranges shown in parentheses.*



Case Figure 3.9 Classical pathway, haemolytic complement screening test for complement deficiency. This test measures the ability of complement in the patient's serum to lyse antibody-coated erythrocytes via the classical pathway. The coated erthrocytes are embedded in a gel. Control and test sera are placed in wells and left overnight. Normal sera containing complement components C1-9 lyse the erythrocytes – seen as a ring around the well (top wells). Sera that are completely deficient in one or more complement components do not cause lysis (middle and bottom rows).

Case 3.10 Acquired immune deficiency syndrome: Persistent generalized lymphadenopathy

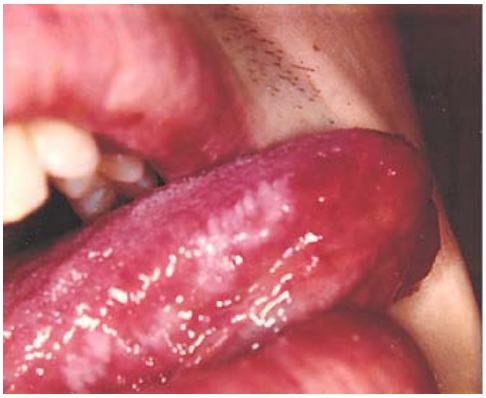
A 29-year-old man had a history of fatigue, night sweats, diarrhoea and axillary lymphadenopathy for 6 months. Fine-needle lymph-node biopsy suggested a reactive cause rather than malignancy. At a follow-up visit 2 months later he was found to have palpable, non-tender cervical and inguinal nodes and considerable weight loss (8.5 kg) associated with colitis. Further investigations were done to exclude a lymphoma. Computed tomography scan of his chest and abdomen showed no lymph-node enlargement and no organomegaly (Box 3.5).

Immunological investigations are shown in Table 3.17. Full blood counts were normal, as was the CRP level. In view of these findings, he was asked about previous blood transfusions (none) and high-risk activity for HIV infection (three heterosexual partners), counselled and tested for HIV antibody. He was HIV-antibody positive. A clinical diagnosis of AIDS was made, on the basis of a positive HIV antibody test and weight loss of more than 10% in 12 months.

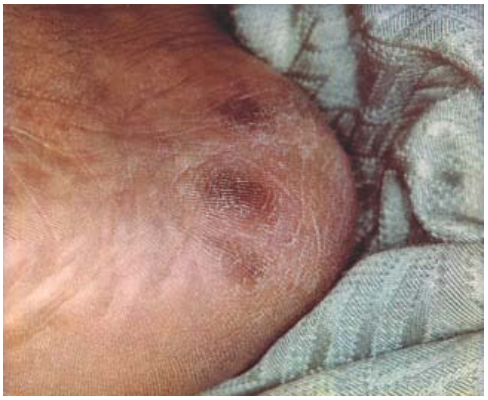
Viral load measurement showed 46×10^3 copies of HIV-RNA per millilitre and he was positive for cytomegalovirus infection by PCR. In view of the low CD4 count he was started on prophylactic co-trimoxozole and combination therapy. CMV colitis was treated with Ganciclovir. He was initially reviewed at 4-weekly intervals and monitored with regular viral load measurements, but became a poor attender and there was doubt about compliance with therapy. Four years later he complained of headaches, vomiting, a dry cough, sweats and profound breathlessness on minimal exertion. A chest X-ray showed bilateral lower-lobe shadowing and subsequently bronchial washings were positive for Pneumocystis jirovecii; rapid deterioration occurred and he died of respiratory failure.

At post-mortem examination, cytomegalovirus and Mycobacterium avium-intracellulare were also isolated from the lungs. A particular surprise was the presence of localized, unsuspected central nervous system lymphoma.

Table 3.17 Immunological investigations* in Case 3.10, HIV infection		
Quantitative serum immunoglobulins (g/l):		
IgG	16.00	(8.0–18.0)
IgA	7.90	(0.9–4.5)
IgM	1.65	(0.6–2.8)
Peripheral blood lymphocytes (·10^9/l):		
Total lymphocyte count	1.8	(1.5–3.5)
T lymphocytes (CD3)	1.51	(0.9–2.8)
$CD4^+$	0.20	(0.6–1.2)
$CD8^+$	1.26	(0.4–1.0)
B lymphocytes (CD19)	0.14	(0.2–0.4)
**Normal ranges shown in parentheses.*		



Case Figure 3.10a Oral hairy leucoplakia. Note the white area on the side of the tongue.



Case Figure 3.10b Lesions of Kaposi's sarcoma on the heel of the foot.

Case 3.11 Acquired immune deficiency syndrome: Kaposi's sarcoma

A 45-year-old man presented with a skin 'rash' of 2 months' duration. This had started as a single, small spot on his trunk, followed by widespread crops of similar lesions; they were painless and did not itch. He had no other symptoms; in particular, no cough, chest symptoms, fever, weight loss or lymphadenopathy. He was homosexual, with one regular sexual partner over the preceding 2 years, though he participated in casual, unprotected sexual intercourse whilst on holiday (Box 3.5). He had never used intravenous drugs.

He was apyrexial, with bilateral axillary and inguinal lymphadenopathy. About 20 purplish-red nodules were present on his trunk, face and palate as well as at the anal margin. His nose showed similar discoloration and swelling. White, wart-like projections of 'hairy leucoplakia' were present on the sides of his tongue.

Investigations showed a normal haemoglobin, a normal white-cell count (4.9×10^9/l) and normal absolute lymphocyte count (1.8×10^9/l). After counselling, blood was sent for an HIV antibody test; this was positive by enzyme-linked immunosorbent assay (ELISA) and confirmed by Western blotting (see Chapter 19). A second test was also positive. Immunological studies (Table 3.18) showed a raised serum IgA and analysis of lymphocyte subpopulations showed absolute depletion of $CD4^+$ cells.

Biopsy of one of his skin lesions showed the typical histological features of Kaposi's sarcoma, so the clinical diagnosis was that of the acquired immune deficiency syndrome, caused by HIV-1.

He was started initially on combination therapy and prophylactic co-trimoxazole and undertook regular monitoring. He remains well more than 18 years later, and is religiously compliant with HAART.

Table 3.18 Immunological investigations* in Case 3.11, HIV infection

Serum immunoglobulins (g/l):		
IgG	20.2	(8.0–18.0)
IgA	2.1	(0.9–4.5)
IgM	0.9	(0.6–2.8)
Electrophoresis – hypergammaglobulinaemia		
β_2-microglobulin	3.8 mg/l	(<3.5)
Lymphocyte subpopulations ($\cdot 10^9$/l):		
Total lymphocyte count	2.80	(1.5–3.5)
T lymphocytes		
$CD3^+$	2.35	(0.9–2.8)
$CD4^+$	0.23	(0.6–1.2)
$CD8^+$	2.04	(0.4–1.0)
B lymphocytes		
$CD19^+$	0.36	(0.2–0.4)

*Normal adult ranges shown in parentheses.

Case 3.12 Listeria monocytogenes meningitis after immunosuppression for SLE

A 24-year-old woman presented with a 3-week history of tiredness, a facial rash and progressive swelling of her ankles. There was no past medical or family history of note. On examination, she was pale and pyrexial (temperature 38.2°C) with a 'butterfly' rash on her face. There was gross oedema to the level of her sacrum and blood pressure was 180/100. Urinalysis showed haematuria (2+) and proteinuria (3+). The clinical diagnosis was nephrotic syndrome, probably due to systemic lupus erythematosus. This was supported by laboratory results: her haemoglobin was 91 g/l with a white-cell count of 3.2×10^9/l and an erythrocyte sedimentation rate (ESR) of 110 mm/h. CRP was normal. Her antinuclear antibody was strongly positive (titre >1/10 000) and she had serum antibodies to dsDNA (98% binding; normal <25%). There was marked complement consumption: C3 was 0.36 g/l (NR 0.8–1.4) and C4 0.08 g/l (NR 0.2–0.4). Her serum albumin was 27 g/l, with proteinuria of 7.5 g per day.

The renal lupus (see section 9.6.3) was treated aggressively with high-dose methylprednisolone, azathioprine and thrice-weekly plasma exchange. However, 4 weeks later, she suddenly became unusually agitated and disorientated, with mild neck stiffness. CSF showed a raised protein concentration of 0.85 g/l (NR 0.1–0.4) with 10^4 polymorphs/mm^3. Cultures of blood and CSF grew Listeria monocytogenes. The meningitis was treated with Ampicillin and her mental state rapidly returned to normal.