



Case 5.1 Is this rheumatoid arthritis?

A 43-year-old woman presented to her general practitioner with sudden onset of acute back pain while gardening, followed by more sustained but less severe pain over the next 2 weeks. The GP felt that this was mechanical back pain but performed some 'screening investigations' that included a normal CRP level and a positive test for rheumatoid factor at a titre of 1 in 256. She was then referred to her local rheumatology department with a possible diagnosis of 'rheumatoid arthritis'. This caused the patient considerable anxiety as her aunt had had severe rheumatoid arthritis, leading to a very high level of disability. When she was seen in the rheumatology clinic 3 months later she still had minor back pain, but this was overshadowed by her anxiety. She had no other musculoskeletal symptoms and examination was normal apart from mild restriction of the lumbar spine. The rheumatologist agreed with the initial diagnosis of mechanical back pain and explained that around 5% of healthy normal people have a positive test for rheumatoid factor. The presence of a *normal CRP level was reassuring and testing for rheumatoid factor not useful*; it is only used in patients with a clinical diagnosis of rheumatoid arthritis, when it is an helpful prognostic indicator.



Case 5.2 Myasthenia gravis and neonatal myasthenia gravis

A 21-year-old woman was referred to a neurology clinic with a 1-month history of double vision, difficulty swallowing and weakness in her upper arms. These symptoms were mild or absent in the morning and tended to worsen through the day. When she was seen towards the end of an afternoon neurology clinic, she was found to have a bilateral ptosis and disconjugate eye movements that could not be ascribed to a cranial nerve lesion. Her upper limb power was initially normal but deteriorated with repeated testing. An intravenous injection of edrophonium, a short-acting cholinesterase inhibitor, completely abolished the neurological signs but her eye movements deteriorated again 30 min after the injection. A clinical diagnosis was made of myasthenia gravis. Subsequent blood testing showed the presence of a high level of autoantibodies against the acetylcholine receptor.

She was treated with oral cholinesterase inhibitors with some improvement. However, 1 month later she deteriorated and corticosteroids were introduced without effect. A computed tomography scan of her thorax showed no evidence of a thymoma but she was nevertheless referred to a thoracic surgeon for thymectomy, as this can sometimes induce remission in myasthenia even in the absence of a thymoma. A small thymic remnant was removed and she recovered uneventfully and was able to withdraw from all medication without deterioration in her symptoms. Acetylcholine receptor antibody levels fell but remained detectable. One year later, she became pregnant and after an uneventful 41-week pregnancy she delivered a 4-kg male infant. There were immediate concerns about the baby, who failed to make adequate respiratory efforts and who appeared limp and hypotonic. The baby was intubated and ventilated on the neonatal intensive care unit. In view of mother's history, a provisional diagnosis of neonatal myasthenia gravis was made, although care was taken to exclude other causes of neonatal respiratory insufficiency such as maternal analgesia with pethidine, hypoglycaemia and sepsis. A cranial ultrasound showed no evidence of bleeding or other pathology. Subsequent testing of a blood sample taken from the umbilical cord showed low levels of acetylcholine receptor antibody. The baby needed ventilation and feeding via a nasogastric tube for 3 days, after which time the ventilation was successfully withdrawn. There were some initial feeding problems due to difficulty sucking and swallowing, but these resolved over the next 48 h. The child's subsequent development has been entirely normal. The mother also remains well.



Case 5.3 Fungal infections, fits and hypocalcaemia

A 14-year-old boy presented to a dermatologist with sore, cracked hypertrophic lips, chronic paronychia (tender, swollen nail beds with dystrophic nails) and curious horn-like lesions in the scalp. The dermatologist made a clinical diagnosis of chronic mucocutaneous candidiasis, and subsequently cultured the yeast, *Candida albicans*, from the boy's mouth and a dermatophyte fungus from the lesions on the scalp. The dermatologist noted a history of epilepsy starting at the age of 5. Subsequent investigation demonstrated profound hypocalcaemia with corrected serum calcium of 1.1 mmol/l (normal 2.2–2.6) with undetectable levels of parathyroid hormone. His 4-year-old sister had also recently developed epilepsy and was also found to be severely hypocalcaemic. The classical clinical picture allowed a confident diagnosis of autoimmune hypoparathyroidism (subsequently confirmed by positive autoantibodies against endocrine parathyroid tissue) as a feature of APECED (Autoimmune Polyendocrinopathy, Candidiasis and Ectodermal Dysplasia). The patient subsequently developed fatigue and vomiting and a short synacthen test revealed adrenal cortical failure as well and he was found to have autoantibodies to adrenal cortex confirming autoimmune adrenalitis. As yet there is no evidence of diabetes mellitus. Genetic analysis confirmed a disease causing mutation in the AIRE gene and the other family members were also screened.



Case 5.4 Lymphocyte-depleting monoclonal antibody treatment for multiple sclerosis (MS) results in Graves' disease

A 38-year-old woman with progressive MS underwent treatment with the monoclonal antibody Campath-1H (alemtuzumab) as part of a clinical trial. The treatment did not seem to slow the progress of her neurological disease, although she developed no new lesions on magnetic resonance imaging scanning of her brain over an 3 year period. About 2 years after treatment with Campath-1H she developed a fine tremor, 5 kg weight loss and heat intolerance. Examination revealed a tachycardia and mild exophthalmos. The clinical impression of thyrotoxicosis was confirmed by a low level of thyroid-stimulating hormone (TSH) at <0.03 mU/l (normal range 0.4–4 mU/ml) and raised free T4 elevated at 76 pmol/l (normal range 5–20). Antibodies binding to the TSH receptor were found in the patient's blood; a diagnosis of Graves' disease (autoimmune hyperthyroidism) was made.

Campath-1H targets the CD52 antigen, which is expressed on both T and B cells. Treatment with Campath-1H produces prolonged suppression of peripheral blood lymphocyte numbers. Clinical trials suggest that this form of treatment may slow clinical and radiological progression of MS. However, around 30% of patients treated for MS with Campath-1H subsequently develop Graves' disease or more rarely an autoimmune cytopenia. The precise mechanisms are unclear, though high levels of IL-21 were associated with the development of these autoimmune diseases. Alternatively Campath-1H depletes all circulating lymphocytes, including Tregs which would otherwise prevent the development of antithyroid autoimmunity.



Case 5.5 Guillain–Barré syndrome

A 23-year-old man developed flu-like symptoms, severe diarrhoea and abdominal pain 4 days after attending a dinner party at which he had eaten a chicken casserole. Three other guests at the same party developed gastrointestinal symptoms. These symptoms settled within a few days. Stool cultures taken from all four individuals grew *Campylobacter jejuni*. 10 days later, he developed diffuse aching around his shoulders and buttocks and pins and needles in his hands and feet. Over the next week the sensory changes worsened and spread to involve his arms and legs. His limbs became progressively weaker and 8 days after the onset of neurological symptoms, he could not hold a cup or stand unaided.

He was admitted to hospital and found to have severe symmetrical distal limb weakness and 'glove and stocking' sensory loss to the elbows and knees. Nerve conduction studies showed evidence of a mixed motor and sensory neuropathy and examination of his cerebrospinal fluid (CSF) showed a very high total protein level at 4g/l but no increase in the number of cells in the CSF. High titres of IgM and IgG antibodies to *Campylobacter jejuni* were found in his peripheral blood. A diagnosis was made of the Guillain–Barré syndrome (acute inflammatory polyneuropathy), probably triggered by *Campylobacter jejuni* infection.

He was treated with high-dose intravenous immunoglobulin but his condition deteriorated with respiratory muscle weakness and he required mechanical ventilation. His condition slowly improved and he was able to breathe spontaneously after 2 weeks. His strength and sensory symptoms slowly improved with vigorous physiotherapy, but 1 year after the initial illness he still had significant weakness in his hands and feet.



Case 5.6 Minocycline-induced systemic lupus erythematosus

A previously healthy 23-year-old woman was referred to a rheumatology clinic with a 4-month history of pain and swelling in the small joints of her hands associated with a blotchy rash over the bridge of her nose and over her knuckles. Examination revealed mild symmetrical synovitis in the hands and red scaly patches over her knuckles and face consistent with a photosensitive rash. Her blood pressure was normal and dipstick testing of her urine showed no blood or protein. Investigations showed a normal full blood count, urea and creatinine. Her erythrocyte sedimentation rate was significantly elevated at 43mm/h. Antinuclear antibodies were present at a titre of 1/1000 with a homogeneous pattern. Antibodies to double-stranded DNA and extractable nuclear antigens were absent. A diagnosis of mild SLE was made and she was treated with non-steroidal anti-inflammatory drugs and hydroxychloroquine. She was also given advice on protection from ultraviolet light.

Her symptoms failed to improve over the next 6 months and treatment with low-dose corticosteroids was considered. However, she refused to consider steroid treatment as she had read about side-effects and was concerned that this drug would cause her previously troublesome acne to return. At this point it transpired that she had been receiving treatment with daily low doses of the antibiotic minocycline for the last 4 years because of previously severe acne. She had not mentioned this previously as she had been taking this form of treatment for so long that she did not feel it could be relevant to her more recent problems. The minocycline was discontinued and the clinical and laboratory features of SLE disappeared over the next 6 months, confirming the revised diagnosis of minocycline-induced SLE. Her acne remained in remission without treatment.