How might tuberculosis chemotherapy induce hyperglycaemia? In patients taking rifampicin for tuberculosis Japanese investigators obtained normal results for intravenous glucose tolerance but hyperglycaemia after oral glucose.¹⁰ No such effect was seen with other agents including isoniazid, ethambutol and streptomycin. These workers suggested that rifampicin either augments intestinal absorption of glucose or reduces insulin sensitivity.

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Use of rituximab in two unusual antibody-mediated autoimmune disorders

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In immune disorders characterized by specific autoantibody production, conventional immunosuppressive therapy can be unsatisfactory. When the illness is life threatening, B-cell depletion with a monoclonal antibody offers an additional strategy.

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CASE HISTORIES

Case 1

A month after undergoing breast reduction surgery an Afro-Caribbean aged 17 experienced a widespread burning erythematous rash, arthralgias, fatigue, fevers, alopecia, anorexia and weight loss. There was no history of Raynaud's syndrome, mouth ulcers or photosensitivity; her mother had systemic lupus erythematosus. On examination there was a widespread urticarial vasculitis and her temperature was 39°C. Enlarged lymph nodes were present in the cervical and inguinal regions and she had knee effusions and synovitis.

Blood tests were as follows: antinuclear factor persistently negative, haemoglobin 10.8 g/dL, white blood cells $6.5 \times 10^6/L$, platelets $457 \times 10^9/L$, erythrocyte sedimentation rate (ESR) 57 mm/h, C-reactive protein 200 mg/dL, C3 186 mg/dL (reference range 70–165), C4 13 mg/dL (16–54), biochemical results normal apart from lactate dehydrogenase 1340 IU/L. On CT of the chest, abdomen and pelvis there was extensive lymphadenopathy, and biopsy of a node showed reactive lymphoid hyperplasia. On skin biopsy the presence of perivascular neutrophils with nuclear fragmentation was consistent with urticarial vasculitis. Further antibody testing showed positive anti-C1q antibody, 32 U/mL (0–15). With a diagnosis of hypocomplementaemic urticarial vasculitis syndrome (HUVS)¹ she was started on prednisolone 15 mg and hydroxychloroquine 200 mg daily but remained unwell with anaemia, ESR >90 mm/h, arthritis and worsening of the rash. C4 was persistently low despite treatment with high-dose methylprednisolone and immunosuppressive drugs including azathioprine and mycophenolate mofetil. She showed signs of respiratory involvement—a grave complication of HUVS¹—with exertional dyspnoea and a restrictive ventilatory deficit.

In view of the severity of her disease she was treated with four weekly infusions of the anti-CD20 monoclonal antibody rituximab at a dose of 375 mg/m². Her condition went into remission and the dose of prednisolone was tapered from 30 mg to 12.5 mg per day, in combination with mycophenolate mofetil 500 mg twice daily. At follow-up six months after rituximab treatment she was well, without rash or synovitis. Her C4 was now almost normal at 16 mg/dL and her anti-C1q had fallen to 23 U/mL.

Case 2

2 years after the onset of systemic lupus erythematosus an Afro-Caribbean woman of 41 experienced a severe flare of disease with synovitis, peripheral lymphadenopathy and a facial discoid rash. Blood tests showed pancytopenia and dsDNA antibodies (>500 IU/mL). She responded to intravenous methylprednisolone (1.5 g) and cyclophosphamide

(750 mg) but was then found to have a random blood glucose in the diabetic range (>20 mmol/L). This was initially attributed to the steroid therapy but over the next two weeks the diabetes became increasingly difficult to control, with plasma glucose 10–20 mmol/L despite insulin infusion of over 800 units/24 h. In addition there had been a change in physical appearance with complete loss of subcutaneous fat and hirsutism.

When found to have high titres of antibody to the insulin receptor but no antibodies to insulin she was diagnosed as having the syndrome of type B insulin resistance.² She then received four weekly intravenous doses of rituximab 580 mg. There were no obvious side effects and a month after the start of treatment her peripheral B-cell count had fallen by 94% (T-cell count unchanged). The ESR declined from 116 to 9 mm/h. Reduction of the insulin dosage was then begun. Two months after the treatment, daily insulin was about 300 units and blood glucose was 5–12 mmol/L. At three months her daily insulin requirement had fallen to 120 units and at five months she was able to stop insulin therapy. Over this period the fat atrophy resolved and her facial appearance returned to normal.

COMMENT

In these two patients, the production of well-defined autoantibodies led to severe life-threatening disease that proved resistant to strong immunosuppressive drugs. Originally used in the treatment of B cell lymphomas,³ rituximab has lately found a place in management of autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus.^{4,5} The B-cell-depleting effect results from complement and antibody dependent cell mediated cytotoxicity, inhibition of cell proliferation and induction of apoptosis of CD20 expressing cells of the B-cell lineage. Lack of expression of CD20 on progenitor cells means that rituximab can deplete peripheral B cells without robbing the bone marrow of progenitor cells. The agent is well tolerated: neutropenic sepsis has been described,⁶ but major infections seem uncommon after its use in rheumatic disease.⁴ Clinicians should consider rituximab therapy when faced with severe antibody-mediated autoimmune conditions resistant to conventional immunosuppressive drugs.

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Hearing loss treated with pamidronate

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Elderly patients who attend an audiology department for hearing loss are commonly found to have a treatable cause.¹

CASE HISTORY

A retired army quartermaster aged 72 sought advice because of hearing loss and tinnitus reminiscent of Morse code. He also reported an increase in regimental beret size from $6\frac{3}{4}$ inches to $7\frac{1}{2}$ inches. This classic detail of the history prompted measurement of serum alkaline phosphatase, which was high at 562 u/L (corrected calcium 2.35 mmol/L). The diagnosis of Paget's disease was confirmed by isotope bone scan.

MRI of his brain and internal acoustic meati confirmed skull vault thickening and showed no evidence of compression of the 8th cranial nerve on either side. The cochleas appeared normal. His audiogram showed the moderate mixed high-frequency sensorineural and low-frequency conductive hearing loss typical of Paget's disease. Tympanograms were normal, and loudness discomfort levels suggested a non-recruiting loss. He was treated with six intravenous pamidronate infusions at one-week intervals and was provided with a hearing aid. At reassessment six months later the conductive component of his hearing loss had completely resolved and in consequence air conduction thresholds had improved (Figure 1). He no longer required the hearing aid. His tinnitus had greatly improved, and the alkaline phosphatase was now 198 u/L.

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