Resolution of insulin-requiring diabetes after cessation of chemotherapy for tuberculosis

Mona Waterhouse MB MRCP Claire Wilson BSc RGN
Veronica L C White MD MRCP
Tahseen A Chowdhury MD FRCP

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Drugs that increase the risk of diabetes include corticosteroids, thiazides and beta blockers.¹ In addition certain antipsychotic² and antiretroviral drugs³ have been associated with hyperglycaemia and the metabolic syndrome. Such effects have not been reported with antituberculosis chemotherapy.

CASE HISTORY

A Somali woman of 38 was referred to the chest clinic in August 2001 because of cough, night sweats, haemoptysis and bilateral cervical lymphadenopathy. She had been living in the UK for 4 years. Her only medication was cyclical oestrogen for irregular periods. 2 years previously her general practitioner had noted a slightly raised random blood glucose (10.1 mmol/L) but an oral glucose tolerance test had been normal (fasting glucose 4.6 mmol/L; 2 hour, 6.7 mmol/L). A chest radiograph showed mild elevation of the left hilum suggestive of previous tuberculosis but no signs of active disease. The erythrocyte sedimentation rate was 14 mm/h, C-reactive protein slightly raised at 6 mg/L. All other blood results, including liver function tests, calcium and full blood count were within normal limits (fasting glucose 4.5 mmol/L). Sputum cultures were negative for *Mycobacterium tuberculosis* but excision biopsy of a cervical lymph node showed caseating granulomata highly suggestive of active tuberculosis.

In December 2001 she was started on Rifinah-300 (two tablets, each containing rifampicin 300 mg, isoniazid 150 mg), ethambutol 1200 mg, pyrazinamide 2 g and pyridoxine 10 mg, all daily. Pyrazinamide was stopped after two months and the other treatments were continued for a further four months. She improved symptomatically and her cervical lymphadenopathy lessened. The tuberculosis

nurses thought she had adhered well to the treatment, and chemotherapy was stopped in June 2002. A year later, she returned to the chest clinic because of increasing cervical lymphadenopathy, fever and sweats. The chest X-ray showed increased shadowing in the left upper zone, and sputum microscopy was positive for acid-fast bacilli. Treatment was resumed with Rifinah 300 and ethambutol in the previous dosage. Six months into treatment, in January 2004, she reported polyuria, polydipsia and weight loss. The antituberculosis treatment was her only medication. Random plasma glucose was 17.9 mmol/L and she had heavy ketonuria. On referral to the diabetes clinic she was started on subcutaneous mixed insulin twice daily; a dietitian found her diet to be good, with little excess refined carbohydrate or fat. On 30 units of mixed insulin daily good glycaemic control was achieved. Tests for glutamic acid decarboxylase and islet-cell antibodies were negative. Her tuberculosis chemotherapy was stopped three months later when she developed signs of ethambutol ocular toxicity, and soon afterwards she was troubled by frequent unpredictable hypoglycaemic symptoms. Under the guidance of the diabetes nurses, her insulin doses were reduced weekly. Within three weeks she was able to stop her insulin, and home glucose monitoring then showed preprandial values in the range 4–5 mmol/L, postprandial 6–7 mmol/L. In an oral glucose tolerance test, fasting glucose was 5.3 mmol/L, 2 hour glucose 4.9 mmol/L.

COMMENT

Abnormalities of glucose tolerance are found in around 20% of patients with active tuberculosis,^{4,5} and indeed patients with diabetes are thought to have a 6–7-fold excess risk of developing tuberculosis.⁶ Little has been published on hyperglycaemia due to antituberculosis drugs, though the *British National Formulary* does list this as a potential adverse effect of isoniazid. We have found no previous report of insulin-requiring diabetes developing during tuberculosis chemotherapy and resolving on cessation of treatment. In the present case, cause and effect seem likely, though other factors cannot be excluded. So far as we could ascertain, the patient's dietary habits did not change during or after treatment, and she was not taking any other therapy that might have influenced glucose metabolism (including 'alternative' therapies). There are case reports of rifampicin being associated with abnormalities of glucose tolerance. An increased requirement for oral hypoglycaemics^{7,8} has been reported, probably due to the effect of enzyme induction, which speeds the metabolism of these drugs. In one noteworthy case, a patient with type 1 diabetes required more insulin when treated with rifampicin and returned to previous dosage when rifampicin was stopped.⁹

Departments of Diabetes and Metabolism, and Respiratory Medicine, The Royal London Hospital, London, UK

Correspondence to: Dr T A Chowdhury, Consultant in Diabetes, 5th Floor, Alexandra Wing, The Royal London Hospital, Whitechapel, London E1 1BB, UK
E-mail: Tahseen.Chowdhury@bartsandthelondon.nhs.uk

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

Matthew Adler BSc MRCP Fotini Soliotis BSc MRCP
Sonali Thakrar BSc Richard Stratton MD FRCP

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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.

Rheumatology Department, Royal Free Hospital, London NW3 2QG, UK

Correspondence to Dr Richard Stratton

E-mail: r.stratton@medsch.ucl.ac.uk

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