Methotrexate toxicity induced by acute renal failure

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Methotrexate is one of the most widely prescribed disease-modifying drugs for rheumatoid arthritis. Since it is excreted largely unchanged via the kidney, renal impairment increases the concentration in blood.

CASE HISTORIES

Case 1

A woman of 46 with seropositive rheumatoid arthritis had been treated for 9 years with 10 mg methotrexate and 5 mg folic acid. She took the methotrexate on Fridays. On a Saturday she was admitted to hospital with right lower lobe pneumonia and proved to be in acute renal failure: urea 23.0 mmol/L, creatinine 377 μ mol/L, potassium 7.4 mmol/L. On previous routine testing these had been normal. Alanine aminotransferase was raised at 1861 IU/L (previously 7) but liver function tests were otherwise undisturbed. Haemoglobin was 11.1 g/dL, white cell count 29.0×10^9 /L (neutrophils 27.8), platelets 363×10^9 /L, C-reactive protein (CRP) 353 mg/L. She was treated with intravenous fluids, cefuroxime for two days, then cefuroxime plus gentamicin 3 mg/kg. She required invasive ventilation and renal dialysis for a few days. Renal biopsy showed acute tubular necrosis. By day 7 she had improved clinically, the CRP had dropped to 209 mg/L and the alanine aminotransferase was 160 U/L. Nevertheless, the haemoglobin fell to 10.4 g/dL, the white cell count to 0.4×10^9 /L (neutrophils 0.1×10^9 /L) and the platelet count to 27×10^9 /L. The lowest haemoglobin recorded was 7.7 g/dL, platelets 2×10^9 /L. She was treated with calcium folinate 15 mg four times daily for 48 hours, granulocyte-colony stimulating factor (G-CSF) and blood and platelet transfusions. Bone marrow biopsy showed hypocellular marrow. By discharge on day 19 the blood indices, liver function and renal function were normal. Methotrexate was restarted several months later without further incident.

Case 2

A woman aged 47 with seronegative rheumatoid arthritis had been taking 12.5 mg methotrexate and 5 mg folic acid weekly for 5 years (on Wednesdays). She was admitted on a Wednesday having taken the usual dose of methotrexate; she had had general malaise, cough and drowsiness for 48 hours. Coarse crackles were heard at both lung bases, and despite an essentially normal chest radiograph she was thought to have a lower respiratory tract infection. She proved to be in acute renal failure with urea 11.5 mmol/L and creatinine 281 μ mol/L (both of which had been within normal limits on previous routine follow-up). Haemoglobin was 9.7 g/dL, white cell count 30.1×10^9 /L (neutrophils 28.0×10^9 /L), platelets 272×10^9 /L, CRP 385 mg/L. Liver function was normal. She was treated with intravenous co-amoxiclav and intravenous fluids, and also with inotropes for a short spell. Renal physicians reviewed her regularly but she did not require dialysis. On day 8 she had improved clinically and CRP had dropped to 109 mg/L. However, the haemoglobin had fallen to 10.7 g/dL, the white cell count to 3.2×10^9 /L (neutrophils 1.3×10^9 /L) and the platelet count to 92×10^9 /L. Over the next few days the haemoglobin stabilized and the platelet count gradually improved but the white cell count dropped to a minimum of 2.7×10^9 /L (tough neutrophil count 0.1×10^9 /L). She was given calcium folinate 15 mg four times daily for 4 days. By discharge on day 20 the blood indices had returned to normal apart from the haemoglobin, which remained around 10 g/dL. Methotrexate was subsequently reintroduced.

COMMENT

Both patients had taken their weekly methotrexate shortly before admission but in neither case did the clinicians initially worry about accumulation of the drug when biochemical tests revealed acute renal failure. A possible explanation for the patients' pancytopenia is sepsis rather than methotrexate toxicity, but the time-course suggests otherwise: marrow suppression became evident only after the symptoms and signs of infection had improved and the CRP had fallen.

Methotrexate is excreted by glomerular filtration and active tubular secretion—hence the known requirement to stop the drug (or not to prescribe it) in patients with renal failure.^{1–3} In these circumstances, treatment with folinic acid deserves early consideration, especially if blood indices show unexpected declines. Methotrexate acts by inhibiting the formation of reduced folates; folinic acid is a fully reduced folate and can thus reverse the marrow toxicity. Patients taking the drug are already advised to consult a doctor about any symptom suggestive of infection. In our opinion, they should be warned also to stop the drug immediately if such symptoms develop.

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Cerebellar atrophy in systemic sclerosis

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Cerebellar atrophy has been recognized as an occasional feature of systemic lupus erythematosus (SLE)^{1,2} but not systemic sclerosis.

CASE HISTORY

The patient was a woman whose illness had begun at the age of 40 with Raynaud's phenomenon, progressing to distal necrosis and ulceration of fingertips, with sclerosis of the hands, feet and face. The results of investigation were consistent with systemic sclerosis (SS). Subsequently she reported heartburn and regurgitation, and oesophageal manometry revealed a defect compatible with SS. Findings on oesophagogastrosocopy and echocardiography were normal; respiratory function tests showed slight ventilatory dysfunction. At age 46 she sought advice after six months of progressive unsteadiness and ataxia. On examination her gait was broad-based and she had cephalic and intention tremors with bilateral dysmetria. Motor and sensory nerve function was normal. Tests for antinuclear, anticentromere and anti-SSA antibodies were positive; those for anti-SSB, anti-dsDNA, anti-Jo1, anti-Scl70 and anti-RNP were negative. She did not report dry eyes or dry mouth and Schirmer's test was negative. The echocardiogram and the respiratory function tests had not changed. Cranial CT (Figure 1) revealed severe diffuse symmetrical cerebellar atrophy without evidence of demyelination or infarction; no lacunae (basal or cortical) were present and the

Figure 1 Cranial CT showing cerebellar atrophy

supratentorial subarachnoid space was normal; there were no features suggestive of vascular disease and the carotid and vertebral arteries showed no calcifications. The patient did not use alcohol and did not recall any exposure to toxic substances; investigations for possible underlying occult neoplasia were negative. After methylprednisolone pulse therapy (1 g per day for three days) the cerebellar signs improved and she became able to walk without assistance, though the ataxia and unsteadiness did not resolve completely. A year later, pulmonary hypertension was diagnosed (pulmonary artery systolic pressure 58 mm Hg) with depression of right ventricular function, dilatation of the right atrium and tricuspid insufficiency. Helical thoracic CT showed no evidence of vascular thrombi or pulmonary fibrosis and the ventilation–perfusion scan did not support the diagnosis of pulmonary embolism. The pulmonary hypertension was interpreted as secondary to the pulmonary microvascular disease of systemic sclerosis. Intravenous Iloprost (a prostacyclin analogue) decreased the pulmonary systolic pressure to 41 mm Hg and she improved clinically. She was then switched to inhaled Iloprost and the improvement continued after discharge. The cerebellar ataxia was no worse than it had been a year before. A month after discharge, she was readmitted severely hypoxic with pneumonia and had an irreversible cardiorespiratory arrest.

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