Case reports

Fatal intrahepatic cholestasis and interstitial lung fibrosis following gold therapy for rheumatoid arthritis[1]

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Hepatic and pulmonary damage have often been reported as complications of gold therapy for rheumatoid arthritis. We believe this is the first case where both complications occurred and there was a fatal outcome.

Case report

Mrs B, aged 53, had had seropositive, erosive rheumatoid arthritis for four years. In spite of treatment with various non-steroidal anti-inflammatory drugs (including benoxaprofen, which she took for three months with no noticeable side effects) the arthritis steadily worsened. In July 1981 she was started on penicillamine 250 mg a day with significant improvement. However, a few months later her arthritis flared up again and her general condition deteriorated with loss of weight and marked tiredness, the haemoglobin dropping from 11 to 9.3 g/100 ml and the ESR increasing from 67 to 100 mm/hour.

On admission to the Rheumatology Unit she had severe polyarticular pain, prolonged morning stiffness and looked pale and unwell. Systemic examination showed no particular abnormality. Several joints showed active synovitis, but no structural deformities.

Investigations on admission showed Hb 9.1 g/100 ml (microcytic, hypochromic picture); WBC 8300/mm^3 (neutrophils 70%, lymphocytes 23%, monocytes 1%, no eosinophils); platelets abundant; ESR 95 in first hour; plasma proteins: total protein 71 g/l, albumin 36 g/l, globulin 37 g/l; liver function tests: bilirubin 6 μmol/l, aspartate transaminase (AST) 17 iu/l, alkaline phosphatase 70 iu/l. Blood urea, creatinine and electrolytes within normal limits. Serology: Rose positive 1 : 1000, ANA negative; urine: no abnormality; chest X-ray: no abnormality.

It was felt that penicillamine was no longer effective, so the drug was stopped and gold (sodium aurothiomalate) was commenced. After a test dose of 10 mg intramuscular sodium aurothiomalate she developed nausea for a few hours but remained apyrexial. There was no increase in eosinophils. A week later an injection of 20 mg sodium aurothiomalate was given: a few hours later she felt unwell, was shivering and complained of back pain. Her temperature was 39.0°C and there were widespread crepitations in the chest. The white cell count was 10 000/mm^3 (98% polymorphs, no eosinophilia). Although the chest X-ray appeared normal a provisional diagnosis of chest infection was made and she was started on amoxycillin 250 mg three times daily, following which she became apyrexial but remained short of breath; there was possible finger clubbing and persistent basal crepitations. Two days later the sclerae became yellow, then the jaundice progressively deepened. There was no itching or abdominal pain, the liver was not palpable and there were no abnormal abdominal masses. She passed pale stools and dark urine. Liver function tests then showed that the total bilirubin had risen to 111 μmol/l, conjugated bilirubin 110 mmol/l, alkaline phosphatase now 2080 iu/l and AST 198 iu/l. The blood count showed 8% eosinophils, with normal reticulocytes. Her condition rapidly deteriorated with increased jaundice, dyspnoea and dehydration and in spite of intravenous fluids and oxygen she died the next day.

At post-mortem the immediate cause of death was thought to be bronchopneumonia. Histologically the lungs showed changes previously reported as 'gold lung', similar to those seen in fibrosing alveolitis. The liver was of normal size and histologically showed mild centrizonal congestion, necrosis and bile stasis with periportal mixed inflammatory changes.

Discussion

It has become apparent that pulmonary and hepatic disease resulting from gold therapy are not as rare as was formerly thought. Since Savilahti in 1948 described pulmonary complications following 1.06 g gold successfully treated with dimercaprol, there have been several reports of pulmonary complications following gold therapy for rheumatoid arthritis (Winterbauer *et al.* 1976, Geddes & Brostoff 1976, Gould *et al.* 1977, James *et al.* 1978, Scharf *et al.* 1977, Weaver & Law 1978, Tala *et al.* 1979, Terho *et al.* 1979, Sepuya *et al.* 1978, Podell *et al.* 1980, Smith & Ball 1980, Daymond & Griffiths 1980, Cooke & Bamji 1981). No deaths were reported in any of these cases, all patients recovering completely, some after institution of corticosteroid therapy (James *et al.* 1978).

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Gold therapy for rheumatoid arthritis is equally well known to produce hepatic disorder. In 1973 Schenker *et al.* described 2 cases, both recovering completely: liver biopsy showed centrilobular cholestasis and swollen parenchymal cells in one case, cholestasis but no cell changes in the other. Favreau *et al.* (1977) reported 3 further cases where jaundice developed 3–7 days after the last gold injection: liver function tests indicated cholestatic jaundice in all cases, and biopsy showed ballooning of liver cells in one case. In 1979 Griffin reported a further case of cholestatic jaundice following 100 mg sodium aurothiomalate; jaundice was intense for 12 days, but liver function tests were normal in 3 weeks. Howrie & Carlton-Gartner (1982) described a three-year-old child who developed a rash, jaundice and laboratory evidence of hepatic dysfunction.

The mechanism of gold-induced hepatotoxicity and pulmonary disease is unknown, but it is probable that a type I hypersensitivity reaction is responsible, as suggested by Davis & Hughes (1974), who noted that eosinophilia and raised IgE levels were often found. It is notable that in our case eosinophilia only appeared several days after the second gold injection, by which time the patient had become seriously ill.

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Exertional angio-oedema[1]

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Angio-oedema is not commonly found in association with cholinergic urticaria. We report an unusual case in which angio-oedema confined to the periorbital region was precipitated by exertion but not by passive overheating or emotional stimuli.

Case report

For several years this 35-year-old French woman had developed periorbital oedema on such exertion as a brisk walk, swimming or 'keep fit' exercises. Her symptoms would begin within minutes of starting the exercise, reach a maximum after about half an hour and then take several days to subside. There was no accompanying itching or rash but she did experience a feeling of tightness in the chest with the exertion. She did not develop periorbital oedema following a hot bath or shower, or if she became nervous or embarrassed, but she had noticed some irritation of the skin and a blotchy rash on her chest after a hot bath. Between attacks the symptoms would subside completely and there was no residual periorbital oedema. However, the condition was so readily provoked and so unsightly for several days that she found her life severely restricted. She was otherwise well, with no personal or family history of atopy although her mother had also suffered from exertional angio-oedema for many years.

A brisk fifteen minute walk precipitated the periorbital oedema shown in Figure 1, and examination of her skin at this time showed marked dermographism but no cholinergic urticaria. However, later challenge with a hot shower did produce the lesions characteristic of cholinergic urticaria.

Routine blood investigations were normal, as was the C_1 esterase inhibitor level. Airways conductance, FEV_1, and inspiratory and expiratory flow volumes measured before and after cold air challenge were normal, so it is unlikely that the feeling of tightness in the chest was due to exercise-induced bronchospasm or to angio-oedema of the upper respiratory tract.

The patient was given a trial of antihistamines and of prophylactic sodium cromoglycate eye

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