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Case Report

The Three Week Sulphasalazine Syndrome

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Summary **We report a 53-year-old man with sero-negative rheumatoid arthritis who developed a fever, rash and hepatitis 3 weeks after starting sulphasalazine therapy. This was associated with a T cell lymphocytosis, eosinophilia and evidence of classical complement pathway activation. He responded to high dose corticosteroids. This is a rare but characteristic reaction which is likely to be encountered by rheumatologists more frequently with the increasing use of sulphasalazine. It should be recognized promptly as it may be fatal and can be confused with other systemic diseases.**

Key words **Sulphasalazine, Serum Sickness, Hypersensitivity, Rheumatoid Arthritis, Hepatitis, Adverse Drug Reaction.**

INTRODUCTION

Sulphasalazine is frequently used as a second line agent for patients with rheumatoid arthritis (RA) unresponsive to nonsteroidal anti-inflammatory drugs (1). Approximately 25% of RA patients have to stop sulphasalazine because of adverse effects and most of these occur in the first 3 months of therapy (2-4). Many of these adverse reactions, however, are mild and respond to withdrawal of the drug (2,3). Hepatotoxicity is rare but may be fatal (5,6). We report a rare but characteristic sulphasalazine-induced serum sickness with liver involvement that requires prompt recognition and drug withdrawal.

CASE REPORT

A 53-year-old white male with a 6-month history of seronegative rheumatoid arthritis was started on sulphasalazine 1 gram daily, increasing to 2 grams daily after 1 week. Apart from a raised plasma viscosity at 1.81 cp the full blood count, liver function tests and urea and electrolytes were normal. After 2 weeks he developed general malaise and headache, followed a week later by the development of an urticarial rash, nausea and central abdominal pain. He worked as a pest control officer but denied any contact with rats and there was no other relevant medical history. He had been taking naproxen 500 mg twice daily for 4 months but was on no other medication and had no known allergies or history of previous medication with sulpha drugs. On examination he was pyrexial and icteric with an urticarial rash on the face, trunk and limbs and urine testing was positive for blood and protein. He was admitted to hospital and the sulphasalazine was stopped.

Initial investigations showed a bilirubin of 103 umol/L (3-17 umol/L), alanine transaminase of 231 iu/L (2-53 iu/L), gamma glutaryl transferase of 209 iu/L (0-50 iu/L) and alkaline phosphatase of 706 iu/L (40-130 iu/L). Over the next week the bilirubin rose to a maximum of 153 umol/L, the gamma glutaryl transferase to 500 iu/L and alkaline phosphatase to 1088 iu/L. At the same time the haemoglobin dropped from 13.5 to 10 g/dl and the platelets rose from 135 to 331 * 10^9/L. The white cell count was 12.4 * 10^9/L on admission with 16% atypical lymphocytes and rose to 38.2 * 10^9/L with 44% cosinophils over the first week in hospital. There was a lymphocytosis of 7.08 * 10^9/L, 80% of which were T cells and most of these expressed activation markers (HLA Dr and/or IL-2 receptor). C-reactive protein was raised at 7.2 mg/dl (<1 mg/dl). C3 levels were normal but C4 was undetectable on admission, returning to normal 4 weeks later. A liver biopsy showed the portal tracts expanded by a mixed inflammatory infiltrate with plasma cells, lymphocytes, polymorphonuclear cells and eosinophils. There was mild cholestasis.

IgG anticardiolipin antibody was transiently positive in the second week of the illness antinuclear antibod-

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ies, direct Coombs test, C1 inhibitor, 4 blood cultures and clotting screen were normal or negative. There was no serological evidence of recent toxoplasmosis, infectious mononucleosis, leptospirosis, hepatitis A and B or cytomegalovirus infection. At the end of a week in hospital, with a persistent hectic fever and rising bilirubin he was started on prednisolone 60 mg daily. He improved clinically and the bilirubin fell to 29 umol/L after 2 weeks on steroids. He was discharged on 30 mg prednisolone daily but readmitted 1 week later with angio-oedema and widespread urticarial rash. This responded promptly to intravenous steroids and he was discharged on 60 mg prednisolone on alternate days. He remains well 3 months later on a reduced dose of 30 mg prednisolone on alternate days.

DISCUSSION

A syndrome of fever, lymphadenopathy, rash, arthralgia and proteinuria was first described in patients receiving horse serum antitoxins (7,8). Animal studies later showed that injection of foreign protein evoked an antibody response which resulted in no adverse effect until about day 9 when the antibody is in relative excess. Circulating immune complexes are then formed which deposit in the walls of small blood vessels. Local inflammation and complement consumption occurs leading to arthritis, carditis and glomerulonephritis (9,10). A detailed study of patients receiving antithymocyte globulin confirmed these events in man (11). Levels of predominantly IgM containing immune complexes start rising between 5 and 10 days after the initial antigenic stimulus, associated with falling C3 and particularly C4 levels indicating activation of the classical complement pathway. Skin biopsies reveal immune complex deposition in small blood vessels associated with an inflammatory cell infiltrate. Arthralgia and rashes follow on about day 15 and 20 respectively (11). This type III hypersensitivity reaction is now more commonly seen as a result of drug ingestion.

Our patient developed a high fever, rash and progressive hepatitis with a transient anaemia, thrombocytopaenia and evidence of renal involvement. He had a raised IgM level, evidence of classical complement pathway activation and large numbers of activated T lymphocytes. Since sulphasalazine is cleaved in the large bowel and only the sulphonamide moiety reaches significant serum levels (12), the latter is likely to be the initiating antigen. This syndrome was first described in patients with inflammatory bowel disease (13,14) and several deaths have been reported (5,6,15). The use of sulphasalazine in RA has increased markedly over the past decade but the first report of this reaction in an RA patient was in 1990 (16) and we are aware of only 1 other (17).

It is clearly rare and there was only 1 patient in a multi-centre study of 1382 RA patients treated with sulphasalazine who might have had a similar reaction although there were insufficient details in this report (4). It is, however, very characteristic. In all reported cases it begins between 2 and 3 weeks after starting treatment (in 1 case after increasing the dose) with a fever and widespread erythematous rash, followed by rising liver enzymes and bilirubin (5,6,13-18). Activated T lymphocytes, often noted as "atypical" on the blood film, and reduced C3 and C4 are usual. Rheumatologists and general physicians should be aware of this syndrome, not only because it can be fatal, but also because it can mimic other systemic diseases. The rash, hepatitis, lymphadenopathy and atypical lymphocytes suggest infectious mononucleosis and in our patient, a pest control officer, leptospirosis was a consideration.

Most cases have been treated with, and appear to respond to, high dose corticosteroids although all 3 reported deaths also received steroids (5,6,15). From the limited data available, the dose and duration of steroid treatment appears to depend on the severity of the reaction. Thus, milder cases without clinical jaundice respond adequately to drug withdrawal alone (14,18) while, in more severe cases, 30 mg prednisolone has proved insufficient (16) and there has been a fatal relapse following steroid withdrawal after 2 months (6). In severe cases with clinical jaundice we therefore suggest a starting dose of 60 mg prednisolone, maintained at a relatively high dose for 4 weeks and then tapering off over a further 3 to 5 months, given an adequate clinical response.

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