MILD HAEMOLYSIS ASSOCIATED WITH FLU-SYNDROME DURING DAILY RIFAMPICIN TREATMENT — A CASE REPORT

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ABSTRACT

We describe a woman with the 'flu' like syndrome and haemolysis whilst on a supervised daily rifampicin regimen for the treatment of pulmonary tuberculosis.

Although these are known complications of rifampicin therapy, they often occur when therapy is intermittent or interrupted. Hence the case we describe is unique and is the first of its kind to be reported in Singapore.

Key words: Daily Rifampicin, 'Flu'like Syndrome, Haemolysis

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INTRODUCTION

The 'flu' like syndrome, haemolysis, thrombocytopenia and acute renal failure are rare complications of rifampicin therapy. This is often described in intermittent or interrupted therapy with rifampicin. These complications are extremely rare during daily rifampicin therapy (1). Up to 1983, there were only five cases of reported instances of renal impairment following continuous rifampicin therapy. Some of these cases were preceded by the 'flu' like syndrome and intravascular haemolysis (2, 3). Thrombocytopenia is also rare on a well supervised daily therapy with rifampicin. A search of the literature revealed only two cases so far (4, 5).

Hence, the patient we describe illustrates a rare occurrence.

CASE REPORT

A 44 year old Malay woman was diagnosed to have pulmonary tuberculosis in April 1987, presenting then with a cough associated with haemoptysis. Pulmonary tuberculosis was diagnosed based on Chest X-ray finding of left upper lobar cavitated lesion (Fig 1) and a positive sputum culture. The patient's husband suffered from pulmonary tuberculosis 9 years ago. Treatment with daily Isoniazid 300 mg, Rifampicin 450 mg, Pyrazinamide 1.5 gm and intramuscular Streptomycin 0.75 gm was commenced in May 1987. Supervised therapy was enforced — that is, the patient had to consume medication daily at an outpatient clinic under the supervision of a nurse. The patient was compliant with treatment. The patient had no previous exposure to rifampicin.

The patient was seen at the hospital three weeks later, being referred from the outpatient clinic for jaundice. There were associated symptoms of daily myalgia, lethargy, and fever with chills one to two hours after each dose of anti-tuberculous drugs. This had commenced on the sixth day of anti-tuberculous therapy.

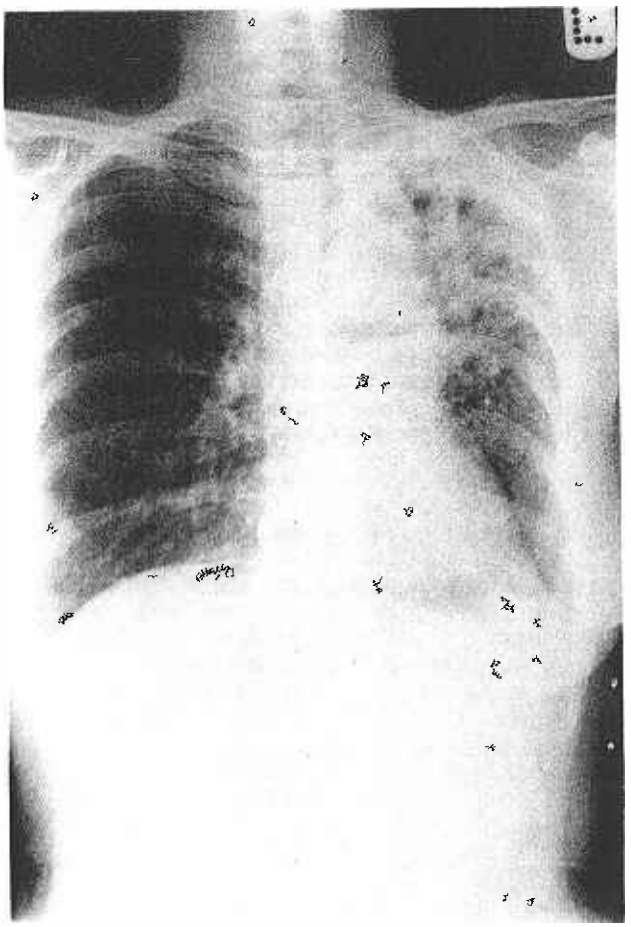

Fig. 1

Clinical examination revealed a woman of medium build. The patient was febrile, mildly jaundiced and pale. There was a tachycardia of 120/min. Blood pressure was 130/90 mmHg. No abnormalities were detected in the cardiovascular and central nervous system. Examination of the respiratory system revealed evidence of left upper

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lobar consolidation. The liver was palpable 2 cm from the right costal margin, with a normal span of 12 cm. The spleen was not palpable. There were no petechial haemorrhages noted in the skin.

Investigations on admission revealed a haemoglobin level of 11.8 g% with platelet and total white counts within normal limits. However, there was a significant drop in the haemoglobin level to 9.6 g% one week later. The reticulocyte count on admission was 5% and serum bilirubin level was 4.5%. Peripheral blood film showed mild macrocytosis with anisocytosis. Serum haptoglobulin done when jaundice had subsided two weeks post admission was not low (more than 100 mg%). The serum transaminases were mildly raised on admission, SGPT being 93 U/l and SGOT being 65 U/l. The direct Coomb's test was negative. G6PD level was normal. Haemoglobin electrophoresis was normal. The blood urea was 17 mg% and serum creatinine was 0.9%. Random blood sugar on admission was 249 mg%. Glucose tolerance test confirmed a diabetic pattern.

Anti-tuberculous therapy was withheld from the patient on admission. The patient's condition improved remarkably. The jaundice subsided and the diabetes was managed with glibenclamide 5 mg daily and dietary control. Anti-tuberculous therapy consisting of daily Isoniazid 300 mg, Ethambutol 600 mg, and intramuscular Streptomycin 0.75 gm was recommenced about two weeks after without side effects.

DISCUSSION

The clinical presentation and investigations of the patient described strongly suggest haemolysis. This is likely to be drug induced, possibly the result of administration of rifampicin.

Haemolysis is supported by the fact that the patient became clinically jaundiced and pale three weeks after starting anti-tuberculous therapy. Investigations demonstrated a definite fall in haemoglobin level; a pre-hepatic jaundice with a raised bilirubin level and only mildly raised transaminase levels; a high reticulocyte count; and an initial peripheral blood film of macrocytosis and anisocytosis. However, there was no demonstrable fall in haptoglobulin level as would have been expected in acute intravascular haemolysis. This is explained by the fact that haptoglobulin level was obtained only after the acute episode. The direct Coomb's test was also done after the acute episode, which may explain the negative result.

We believe that the reactions were rifampicin induced for the following reasons:

1. The patient was not anaemic prior to treatment, and had became so after commencing anti-tuberculous treatment.
2. Cessation of therapy resulted in marked improvement of the patient's condition.
3. The reaction is not likely to be due to Isoniazid or Streptomycin as these drugs were restarted subsequently with no ill effects.
4. The presentation of myalgia, lethargy and fever, associated with haemolysis is classical of rifampicin induced 'flu' – like syndrome and haemolysis (6).

In fact, the 'flu'syndrome may represent a first warning sign of intravascular haemolysis, which, if massive enough, could eventually lead to haemolytic crisis and renal failure (7). The mechanism of the 'flu'syndrome and haemolysis had been related to the presence of rifampicin dependent antibody. Poole et al followed 49 patients taking rifampicin biweekly and demonstrated rifampicin dependent antibody in the sera of 16 patients. These patients exhibited a variety of manifestations including pyrexia, thrombocytopenia and renal failure (8). The precise steps in the evolution of the drug induced antibodies are uncertain. It was postulated that rifampicin could act as a hapten, being bound to macromolecules in the plasma. These become antigenic and therefore stimulate antibody formation. These hapten-antibody complexes bind complement, either in the blood stream or on the surface of the blood cell (red cells, platelets) membrane, which then leads to cell destruction (6).

The 'flu'syndrome is uncommon during the first 3 months of chemotherapy (9). It often occurs with intermittent usage of high dose rifampicin, when the patient has been irregular in taking daily rifampicin, or when the drug has been resumed after an interval of 3 days to several months (10). It is not common during daily therapy. Its incidence and severity depends on individual dose size and on the interval between doses of rifampicin (7).

Hence the patient described is unusual, in that 'flu' syndrome and mild haemolysis occur whilst the patient is on a daily regimen of low dose rifampicin. Furthermore, the reactions had occurred within three weeks of anti-tuberculous therapy.

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