

Case Report**RIFAMPICIN-INDUCED ACUTE THROMBOCYTOPENIA**V V Banu Rekha¹, A R Adhilakshmi¹, M S Jawahar²**ABSTRACT**

Rifampicin is an essential component of the treatment regimen for tuberculosis. Extensive clinical experience has shown that the drug is well tolerated, but on rare occasions it can cause life threatening adverse reactions like acute renal failure and thrombocytopenia. At the Tuberculosis Research Centre, we have treated more than 8000 patients with pulmonary and extra-pulmonary tuberculosis with

rifampicin-containing regimens over the past 30 years and we are reporting a case of acute thrombocytopenia probably rifampicin induced, in a patient who was retreated for tuberculosis. The physician treating tuberculosis patients must be aware of this rare life threatening complication, which if detected early, is completely reversible.

Lung India 2005; 22: 122-124**Key words** : Tuberculosis, Treatment, Rifampicin, Thrombocytopenia**INTRODUCTION**

Rifampicin is a crucial drug in the treatment regimens for tuberculosis. Usually it is well tolerated. Apart from minor side effects like abdominal discomfort, nausea and vomiting, very rarely it can cause life threatening acute renal failure or thrombocytopenia¹. Rifampicin induced thrombocytopenia was first reported in 1970². It is usually reversible if detected early and treated appropriately. The Tuberculosis Research Centre (TRC), Chennai of the Indian Council of Medical Research has been conducting controlled clinical trials for treatment of tuberculosis since 1956. Since 1974, more than 8000 patients with pulmonary and extra-pulmonary tuberculosis have been treated with rifampicin-containing treatment regimens. We are reporting a case of acute thrombocytopenia, probably rifampicin induced, in a patient who was being retreated for pulmonary tuberculosis at our centre.

CLINICAL RECORDS

A 40-year-old female weighing 57 kg attended our centre in July 2002 with cough, fever, breathlessness and loss of appetite for 2 months. About a week earlier, she had completed treatment for sputum positive pulmonary tuberculosis at a government dispensary with 2 months of isoniazid 600 mg, rifampicin 450 mg, ethambutol 1200 mg and pyrazinamide 1500 mg followed by 4 months of isoniazid 600 mg and rifampicin 450 mg thrice weekly. She was referred to our centre as she had persistent positive sputum smears and cultures for tubercle bacilli. The bacilli were resistant to streptomycin, isoniazid

and ethambutol. The patient was a diabetic for the past 10 years and was on Inj. Mixact Bovine insulin 15 units twice daily.

On examination she had no anaemia, jaundice or pedal edema. She was normotensive and had crepitations in both lungs. X-ray chest showed infiltration of the right mid and lower zones. Two sputum smears were positive for tubercle bacilli by fluorescent microscopy, confirmed later by positive cultures. Hepatic and renal functions were normal.

Treatment for sputum positive pulmonary tuberculosis was re-started in July 2002 with inj. kanamycin 1 gm thrice weekly, ofloxacin 600 mg, rifampicin 600 mg and ethionamide 500 mg daily based on the drug susceptibility profile. During the supervised treatment of initial 5 months she had missed about 18 doses now and then. At the 6th month of treatment on request from the patient, we supplied the anti-tuberculosis drugs. During this period, she complained of fever with chills followed by a rash on the face, buccal mucosa, trunk and extremities. Anti-tuberculosis drugs were withheld and she was prescribed prednisolone tablets 5mg thrice daily. Two days later, the anti-tuberculosis drugs were re-introduced as the symptoms had subsided. The patient then developed hemorrhagic spots on the face, trunk and extremities and bleeding per vaginum three days later. On examination, she was well oriented, afebrile, not anaemic, or dyspnoeic. There were petechial eruptions over the face, trunk, extremities, buccal mucosa and bleeding per vaginum. Systemic

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examination and vital signs were normal. All anti-tuberculosis drugs were withheld. The patient was hospitalised. Investigations revealed a platelet count of 15000 cells/cmm and bleeding time of 7 minutes and clotting time of 13 minutes. Bone marrow aspiration showed megakaryocytosis. Liver and renal function tests were within normal limits. A diagnosis of acute thrombocytopenic purpura was made. The patient was treated with intravenous fluids, inj. hydrocortisone hemisuccinate 200 mg iv thrice daily. The bleeding subsided and her general condition improved with a gradual decline of purpuric spots. The steroid dose was gradually tapered and changed to oral prednisolone tablets 20 mg thrice daily and which was also later tapered. She was discharged in February 2003 with a normal platelet count of 2.1 lakhs/cmm and bleeding time of 2 min. and clotting time of 3 min.. As she had 6 months of treatment and since her sputum smears and cultures were negative for tubercle bacilli consistently after the 1st month of treatment, we decided to stop treatment and follow her up. Her sputum smears and cultures are negative for tubercle bacilli till date.

DISCUSSION

The causes of thrombocytopenia include viral infections, immune disorders, collagen vascular diseases, lymphoproliferative disorders and drugs³. Drug induced thrombocytopenia can be caused by quinidine, sulphonamides, chemotherapeutic agents, penicillin, barbiturates, heparin, digoxin and estrogen³. Thrombocytopenia attributed to rifampicin, though rare, has been reported in the treatment of pulmonary tuberculosis⁴⁻⁷. A literature search revealed a total of about 35 cases of rifampicin-induced thrombocytopenia which included 15 cases reports. Our patient was also receiving kanamycin, ofloxacin and ethionamide but damage to the platelets have not been reported with these drugs. Hence we concluded that the thrombocytopenia was probably rifampicin induced. This is consistent with a case reported by Ferguson in which the patient developed thrombocytopenia after 9 months of daily rifampicin therapy.⁸

Our patient had tolerated the initial treatment with intermittent rifampicin for 6 months without any complaints. But after a gap of 10 days when daily rifampicin treatment was re-started she developed thrombocytopenia after 6 months of treatment. As we had supplied the drugs during the 6th month we

were not sure whether the drugs were consumed daily or intermittently. Serious adverse reactions due to rifampicin, which are immune complex mediated, are mostly encountered during intermittent therapy or when there is a gap in treatment⁹⁻¹⁰. It has been postulated that with daily administration of rifampicin, there is neutralization of any antibody formed and the immune complexes are continuously removed without causing any allergic reaction¹¹. Rifampicin induced thrombocytopenia during daily administration though rare, has been reported. Unlike our patient, retreatment with a daily rifampicin regimen in the reported cases resulted in thrombocytopenia in a week's time of start of treatment^{6,7}. As we were unaware of the rhythm of drug intake in our patient, it is not certain that the thrombocytopenia had occurred due to daily or intermittent rifampicin intake.

Although we did not measure rifampicin dependent antibodies in our patient, the occurrence of thrombocytopenia is attributed to rifampicin dependent antibodies. The mechanism hypothesized is that, in the presence of the drug, the immune complexes non-specifically adsorb to the platelet membrane causing platelet damage and rapid removal from the circulation^{2,12}. The binding epitope of the IgG antibody was found in the glycoprotein Ib / IX complex which is the target in rifampicin induced immune thrombocytopenia¹³.

Serious adverse reactions during rifampicin therapy are usually reversible if detected early and treated appropriately. Our patient recovered completely on stopping the drug along with supportive steroid therapy. Re-challenging with the offending drug even in small doses is contraindicated if purpura occurs¹⁴. There were 3 patients from our centre who developed acute renal failure on re-treatment with intermittent rifampicin therapy and recovered completely on withholding the drug.

We have treated and followed up more than 8000 pulmonary and extra-pulmonary tuberculosis patients that included both adult and children who were treated with rifampicin-containing regimens. The regimens in which rifampicin was given daily or intermittent throughout or initial daily followed by intermittent proved to be extremely safe. But we encountered with one patient who developed rifampicin-induced thrombocytopenia which enforces the fact that the clinician must be aware of these rare

complications which are life threatening, but if detected early are completely reversible.

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