Case Report

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Rifampicin-Induced Concomitant Renal Injury and Hepatitis

Internal Medicine Section

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ABSTRACT

Adverse drug reactions are not unusual during Anti-Tubercular Therapy (ATT). One of the common complications of anti-tubercular treatment is drug induced hepatitis and renal insufficiency has also been reported. Renal failure and/or hepatitis encountered during treatment of tuberculosis can have varied aetiologies: drug induced, concomitant viral infection, pre-existing co-morbidities or a combination of these. Since, hepatitis and/or renal insufficiency can be life threatening a prompt diagnosis is warranted, where drugs should be kept as one of the important cause. Identifying the drug helps in treating hepatitis and/or renal insufficiency along with helping the physician to change the combination of ATT regimen. Rifampicin is one of the most important first line drugs in the treatment of tuberculosis. Hepatitis, epigastric distress, anaemia, thrombocytopenia, and interstitial nephritis are reported adverse drug reactions to rifampicin. As per literature rifampicin induced renal toxicity is usually seen on rifampicin re-exposure, or rifampicin administration on alternate days, both being present in this case. Here we are reporting a case of ATT induced renal failure with concomitant hepatitis where rifampicin was suspected to be the cause.

Keywords: Anti tubercular drugs, Liver function tests, Serum creatinine, Serum urea

CASE REPORT

A 28-year-old male, shop keeper, non-alcoholic, non-smoker presented to pulmonary medicine outpatient department with complaints of recent onset of vomiting, abdominal pain, fever and decreased urine output, which he developed after 7 days of starting ATT. He had been diagnosed to have smear-positive pulmonary tuberculosis relapse and was started on category 2 Directly Observed Treatment Short course (DOTS) which includes isoniazid, rifampicin, pyrazinamide, ethambutol and injection streptomycin given on intermittent basis. He was referred to our hospital for further management in view of above mentioned symptoms. At the time of presentation, general physical examination revealed icterus, pulse rate was 103/min regular, good volume and all peripheral pulses were felt, blood pressure was 104/76mmHg in supine position, temperature was 100°F, oxygen saturation 99% on room air at rest. Systemic examination revealed enlarged liver which was smooth, firm and tender on palpation. Rest of the examination did not reveal any positive finding. The chest roentogram postero-anterior view showed bilateral upper lobe fibrosis with right upper lobe cavitation and bilateral mid-zone infiltration. Haemogram showed leukocytosis (33200/μL) with neutrophilia (77%). Kidney function tests revealed elevated urea (62 mg/dL) and creatinine (2.3 mg/dL). The levels of creatinine increased upto 10.2 mg/dL on serial testing. Liver function tests showed increase in total bilirubin (8.6 mg/dL), direct bilirubin (2.6 mg/dL), aspartate amino transferase (285 IU/L). Prothrombin time was 18.6 seconds (normal range 9.7-11.8) with an International Normalized Ratio (INR) of 1.29; activated partial thromboplastin time was 29.3 seconds (normal range 25.4-33.7). Other routine blood investigations (haemoglobin, platelets, erythrocyte sedimentation rate, random blood sugar and serum electrolytes) were within normal limits. Urine routine examination showed presence of protein (3+). Urine protein was 490 mg/24 hours. Ultrasonography of abdomen revealed grade 1 parenchymal changes in right kidney associated with splenomegaly. Viral markers (hepatitis B, hepatitis C, Human immunodeficiency virus) were non-reactive. Bacterial blood culture did not grow any organism. Direct Coomb's test was positive. Serological test revealed drug specific antibody to rifampicin (test was performed according to American Association of Blood Banks Protocol). Sputum culture grew *Mycobacterium tuberculosis* and drug sensitivity testing showed sensitivity to all first line drugs except pyrazinamide.

ATT was stopped, in view of drug-induced acute kidney injury and hepatitis. Intravenous fluids were started, and the patient underwent haemodialysis. The cause for these biochemical abnormalities was thought to be sepsis at this point in time or perhaps drugs (streptomycin and rifampicin). After the renal functions and liver functions normalized, anti-tubercular drugs were reintroduced in a step wise manner, —isoniazid, ethambutol, levofloxacin, injection streptomycin and rifampicin. However, on re-introduction of rifampicin, he again developed renal function test and liver function test derangement. Hence, rifampicin was withdrawn once more and other four drugs were continued on a daily basis for two months, followed by isoniazid, ethambutol, levofloxacin for ten months.

Patient had a past history of smear-positive tuberculosis and had completed ATT for 6 months, which included isoniazid, rifampicin, pyrazinamide, and ethambutol (DOTS category 1) and was declared cured. The clinical course at that time had been uneventful.

Patient continued the modified regimen of ATT and was under regular follow-up. His renal functions normalized. He completed the modified ATT and was declared cured at the end of 12 months.

DISCUSSION

Adverse drug reactions are common during ATT [1]. Drug Induced hepatitis is one of the common adverse events with an occurrence of 4.28% to 11.5% [2]. ATT induced renal insufficiency is also well documented [3]. This compels the treating physicians to switch to alternative weaker regimens, thereby, possibly, compromising the efficacy of treatment. Rifampicin-induced nephritis usually occurs during re-exposure to the drug or with alternate day drug regimens [3]. The renal injury recovers on drug withdrawal within 30 days in 40% and 90 days in 96% of the patients [3]. The mean time required for developing disease from the day of re-exposure or initial exposure is 16.4 ± 10 days [3]. Renal biopsy is indicated, but no specific feature is suggestive of rifampicin-induced nephritis. Acute interstitial nephritis, crescentic glomerulonephritis or

mesangial proliferation pattern may be seen [4]. Renal injury may be associated with hepatitis in 10% of the patients [5], which does not adversely affect prognosis [6]. In contrast, streptomycin-induced renal injury is unlikely to be accompanied by drug induced hepatitis [7]. Increase in bilirubin along with direct Coomb's test positive indicate drug induced haemolytic anaemia. However, in our case no fall in haemoglobin was observed on serial monitoring. Reticulocyte count was <1%, peripheral smear was normal; and total bilirubin was more than 4 mg/dl. In view of these drugs induced haemolytic anaemia was less likely [8].

In the present case, the patient had a history of prior exposure to rifampicin (alternate day regimen) during management of pulmonary tuberculosis which was uneventful. The retreatment regimen was also given as intermittent therapy. The patient was, thus, re-exposed to rifampicin and that too with intermittent dosing. Re-exposure or intermittent therapy can lead to rifampicin-induced interstitial nephritis–as was the case in our patient. Later he again developed renal insufficiency and hepatitis when rifampicin was reintroduced, however there were no adverse events when treatment was, eventually, restarted with streptomycin, levofloxacin, isoniazid and ethambutol. As per Naranjo's algorithm, the causality assessment was done and the reaction was categorised as a probable adverse drug reaction [9]. The features in this case which suggested rifampicin-induced and not streptomycin-induced renal injury were presence of rifampicin specific antibodies, concomitant hepatitis which recovered on stopping rifampicin and non-recurrence of renal injury on restarting streptomycin.

CONCLUSION

Renal impairment and hepatitis, in a case of tuberculosis under treatment, should prompt an immediate search for drug as one of the possible causes. It is imperative for the treating physician to find out the incriminating drug, so that a modified regimen, comprising most effective drugs, can be designed. Rifampicin can be suspected if there is history of prior exposure to it, patient is on intermittent therapy, concomitant hepatitis is present or if rechallenge leads to recurrence of renal impairment.

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