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Acute reversible fulminant hepatitis associated with rifampicin

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Abstract

Tuberculosis in India contributes to significant endemicity, morbidity and mortality. Rifampicin is the most potent bactericidal drug used as a first line agent in the Anti-Tubercular Treatment (ATT) in rifampicin sensitive cases. Adverse effects of the ATT add to morbidity and decreased treatment compliance. Common side effects of rifampicin are pruritis, nausea, vomiting, diarrhoea, flu like syndrome and less commonly hypersensitivity reactions such as anaphylactic reactions, acute renal failure, haemolytic anaemia. Hepatitis is infrequently associated with rifampicin and usually occurs due to concomitant use of isoniazid, pre-existing liver disease, HIV seropositivity and regular alcohol consumption. Herein we present, the first case reported of fulminant, rapidly reversing hepatitis due to rifampicin, in a 38-year-old immunocompetent woman with mediastinal tuberculosis, who previously tolerated rifampicin without any major adverse effects. On second time exposure, she developed diarrhoea, hypotension, fulminant hepatitis and atrial fibrillation requiring hospitalisation within a week of starting first line weight-based ATT. Liver function tests rapidly normalised after cessation of ATT. Once the patient stabilised and all laboratory parameters were normal, sequential introduction of ATT was started with levofloxacin and ethambutol. When Rifampicin was restarted, similar symptoms of vomiting, diarrhoea with fulminant hepatitis occurred after just 1 dose, requiring hospitalisation. With the strong temporal relationship between drug intake and occurrence of symptoms, she was diagnosed to have a hypersensitivity reaction in the form of a fulminant, rapidly reversing hepatitis due to rifampicin. This case emphasizes the varied complexity of ATT adverse effects and the need for its timely diagnosis.

Keywords: Rifampicin; ATT; Fulminant hepatitis; Hypersensitivity reactions.

Case presentation

A 38-year-old woman with no known comorbidities presented with complaints of chest pain, low grade fever, loss of appetite and weight loss of 10 kg in the previous two months. Her general and systemic examination was unremarkable. Routine laboratory tests, including RFTs, LFTs, and blood sugars were normal except for low haemoglobin (9.4 gm/dl).

Three years ago, she had been treated for pansensitive cervical lymph node TB with Anti-Tubercular Treatment (ATT) which was adequately treated with isoniazid, rifampicin, pyrazinamide, ethambutol (HRZE) in the initiation phase followed by isoniazid and rifampicin (HR) in the continuation phase. The cervical adenopathy resolved and she had no adverse effects with ATT other than mild pruritus which was managed symptomatically.

Serology for Human Immunodeficiency Virus (HIV) was negative at presentation. X-ray of the chest showed mediastinal widening. Computed tomography of the chest and abdomen showed necrotic mediastinal adenopathy and mild splenomegaly. She underwent an EBUS-guided TBNA of a sub carinal node. TB GeneXpert revealed the presence of rifampicin sensitive mycobacteria . Histopathology of a core biopsy of the lymph node showed necrotising granulomatous inflammation suggesting mycobacterial etiology.

The patient was started on weight-based ATT- HRZE (300 mg /600 mg/ 1500 mg/1000 mg). After 7 days of ATT intake, she acutely developed several episodes of loose stool, high grade fever, dizziness, oral ulcers and icterus. She was hospitalised in the intensive care unit due to hypotension and tachycardia. Other vital parameters and physical examination findings were unremarkable, including a soft abdomen. Laboratory investigations (Tables 1 & 2) showed anemia (hemoglobin 7.1 g/l), 1.3% reticulocytes , thrombocytopenia (112 G/l), normal eosinophils and white cell counts, elevated bilirubin (15.9 mg/dl- direct bilirubin 8.8 mg/dl and indirect bilirubin 7. 1 mg/dl), SGOT (161 U/l) (normal range: 5-40 U/l) and SGPT (54 U/l) (normal range 7-56 U/l) and an alkaline phosphatase within normal limits. Acute phase response proteins were also elevated (procalcitonin {19.65 ng/ml}, ferritin 324 ng/ml}). Serum creatinine was 1.1 mg/dl (normal range: 0.59 to 1.04 mg/dl), serum electrolytes were within the normal range. Lactate dehydrogenase was 1457 U/L (normal range: 140-280 U/L) and vitamin B12 was more than 6000 pg/ml (normal range: 200-1100 pg/ml), serum iron was 55 mcg/dl and reticulocyte count were 1.35. Serology for hepatitis B and C, Leptospira, dengue and malaria tested negative. USG abdomen was normal. Blood cultures sent on day 1 was sterile.

A diagnosis of acute gastroenteritis with hypotension and fulminant hepatitis was made. HRZE was withheld due to hepatic dysfunction and the patient was started on supportive fluid therapy and intravenous antibiotics. Despite this, and although the loose motions had stopped, she remained hypotensive and required inotropic support with intravenous noradrenaline. On the second day of admission she developed atrial fibrillation, which could be controlled by amiodarone. Twenty-four hours later she had dramatically improved, she no longer required inotropic support and bilirubin had normalized. In view of a further fall in haemoglobin (6.9 g/l) and platelets (110 g/l), a blood transfusion was given. Further tests were done for a thorough evaluation of the cause of acute gastroenteritis with hypotension and fulminant rapidly reversing hepatitis. Viral markers for hepatitis A, E, Antineutrophil Cytoplasmic Antibody C and P , ANA by IFA and Anti Histone antibody were all negative. She could be discharged home on the fourth day.

At follow up four days later, all of her laboratory tests had normalized so sequential re-introduction of Antituberculosis Treatment (ATT) was commenced. Levofloxacin and ethambutol were both well tolerated, LFT then was normal (Total bilirubin- 0.73, SGOT-21, SGPT-23). Rifampicin 600 mg was initiated 3 days later. However, after just a single dose of rifampicin she developed watery stools and protracted vomiting requiring hospitalization. Supportive treatment with fluids and metronidazole was given and ATT again withheld. Laboratory investigation confirmed an elevated bilirubin (10.8 mg/dl, direct 4.4 mg/dl and indirect 6.5 mg/dl), elevated liver function tests (SGOT 174 U/l, SGPT 34 U/l) and mildly reduced haemoglobin (9.6 g/l) with normal platelet and white cell counts. Her symptoms resolved and her lab values returned to normal during the following three days. A diagnosis of acute fulminant, rapidly reversing hepatitis due to rifampicin was made and rifampicin permanently discontinued. Isoniazid could be safely added to levofloxacin and ethambutol and our patient continues to do well .

Discussion

Hypersensitivity Drug Induced Liver Injury (DILI) reactions are not dose related and often accompanied with skin reactions, eosinophilia, fever, lymphadenopathy occurring from 1-6 weeks after drug exposure [1]. Hypersensitivity to Rifampicin has been documented in the literature as acute renal failure, interstitial nephropathy, haemolytic anemia, disseminated intravascular coagulation and most commonly as DRESS syndrome (Drug related eosinophilia and systemic syndrome) [2,3].

Table 1: Sequential day wise investigations during 1st hospitalization.

Investigations	Day 1 of admission	Day 3	Day 8
HB	7.1 gm/dl	6.9 gm/dl	10.4 gm/dl
TLC	5.6 / c.mm	7.4 /c.mm	6.7/c.mm
Platelets	112 10^3/c.mm	110 10^3/c.mm	282 10^3/c.mm
Eosinophils	0 %		
Prothrombin time	11.4 sec		
INR	1		
Bilirubin	15.9 mg/dl	0.8 mg/dl	1 mg/dl
Indirect	7.1 mg/dl	0.5 mg/dl	0.5 mg/dl
Direct	8.8 mg/dl	0.3 mg/dl	0.5 mg/dl
SGOT	161 U/L	52 U/L	25 U/L
SGPT	54 U/L	39 U/L	16 U/L
ALP	75 U/L		
Creatinine	1.1 mg/dl		0.5 mg/dl

Table 2: Sequential day wise investigations during 2nd hospitalization.

Investigations	Day 1	Day 2	Day 3
HB	9.8 gm/dl		
TLC	7.38 /c.mm		
Platelet	196 10^3/c.mm		
Total bilirubin	10.8 mg/dl	3.3 mg/dl	1.1 mg/dl
Direct/Indirect	4.4/6.4 mg/dl	2.2/1.1 mg/dl	0.7/0.4 mg/dl
SGOT	174 U/L	108 U/L	43 U/L
SGPT	34 U/L	32 U/L	22 U/L
Creatinine	1.1 mg/dl		0.8 mg/dl
Anti-Mitochondrial Antibody	Negative		

Brockhaus et al has described a single case of hypersensitivity reaction occurring after re-exposure to rifampicin presenting as a diverse constellation of symptoms and multiorgan involvement including acute systemic inflammatory reaction, hemolytic anemia, hypersensitivity pneumonitis, nephritis and hepatitis [3]. In this case too, there was rapid normalization of the liver function, hypothesized due to an additional ischemic pathogenesis [3]. Our patient had developed severe hepatitis, hypotension and thrombocytopenia, a rare presentation for rifampicin hypersensitivity reaction [4].

The only well-established risk factor for hypersensitivity with anti-tubercular drugs is HIV seropositivity, including non-immediate hypersensitivity reactions [5]. In a systemic study of Type 1 hypersensitivity reaction to antitubercular drugs by Buhari et al, female gender was also identified as a risk factor [5]. In 1996, Canova et al reported a fulminant rapidly reversing hepatitis and anaphylaxis in a 28-year female HIV positive patient on re exposure to rifampicin [6]. This is the only case report in the literature which was very similar to the current case, but that was reported in an HIV positive patient.

Scattered dosing of rifampicin on either intermittent or discontinuous schedules can result in sensitization with a rapid increase in antibody titre after repeat drug exposure. Even a single dose of rifampicin can induce sensitization and result in immunoallergic reactions on a repeat exposure [7]. Many mechanisms have been proposed for rifampicin hypersensitivity causing multiorgan involvement and shock, such as Type 1-4 hypersensitivity reactions, combined hypersensitivity pathways, IgG- and IgM-mediated cytotoxic immune response [3,8]. Urticaria and anaphylaxis may occur through IgE mediated mechanism [9].

Rifampicin, in vitro also showed vasodilatory effects caused by histaminergic upregulation and increased synthesis of nitric oxide [8]. Other mechanisms known to play a role in rifampicin induced hepatitis are oxidative metabolism, genotypes of cytochrome p450, 2E1, glutathione S-transferase M1, and N-acetyl transferase [9].

In case of an adverse drug reaction in a multidrug regimen, as in the treatment of tuberculosis, a drug specific Lymphocyte Transformation Test (LTT) can be done after the adverse reaction has resolved to supplement the diagnosis [3,10]. The LTT is an in vitro test which quantifies the proliferation of circulating drug-specific memory T cells, on stimulation with the specific drug (i.e. antigen) indicating a type IV hypersensitivity reaction [3]. Although, rifampicin is a very important first line drug for tuberculosis, and there are limited replaceable first line agents, we did not attempt desensitization due to two life threatening episodes. In the literature there are very few case reports of rifampicin desensitization in hypersensitivity presenting with DIC, nephritis, hepatitis, ocular toxicity, haemolytic anemia [11,14].

In the current case presented, temporal association between recurrent reactions with repeat drug exposure, the quick resolution of liver function tests after discontinuation of rifampicin, with absence of any other identifiable cause for hepatitis, confirm the causal role of rifampicin in this patient's recurrent fulminating rapidly reversing hepatitis. To the best of our knowledge, this is the first case report of rifampicin hypersensitivity on re-exposure in a non-HIV patient . The current case suggests clinicians should be aware of the possible presentations of severe immuno-allergic reactions to rifampicin, particularly if prior exposure to the drug has occurred. A detailed drug history is vital to making this diagnosis. In patients experiencing life threatening hypersensitivity reactions to rifampicin, this medication must be permanently discontinued. Furthermore, it is vital to inform the patient, issue them with an "allergy pass" and document the allergy clearly in the patient`s medical records. Severe adverse drug reactions should also be reported to the national drug authorities for pharmacovigilance purposes.

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