Rifampicin Induced Immune Hemolytic Anemia: A Case Report

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Abstract

Tuberculosis is usually treated with multiple drugs and these drugs are known to cause various side effects like hepatic abnormality, skin rashes, peripheral neuropathy, and vision disturbances. Autoimmune hemolytic anemia is very rare with anti-tuberculosis drugs with only fifteen cases reported till date worldwide. Hence, we report a case of Rifampicin induced autoimmune hemolytic anemia in a patient, a known case of Gilbert's syndrome from a tertiary care hospital in Southern India.

Keywords: Tuberculosis, Rifampicin, Hemolytic anemia, Naranjo's scaling

Introduction

Rifampicin is bactericidal in action and belongs to rifamycin family. It is derived from Amycolatopsis rifamycinica and is a semisynthetic compound [1]. Rifampicin in 1967 was first used in treatment of tuberculosis along with isoniazid, ethambutol, pyrazinamide, and streptomycin [2]. It remains the anchor of first line Anti-Tuberculosis Therapy (ATT). Hepatitis, cutaneous syndrome, flu syndrome, abdominal syndrome, respiratory syndrome, orange colored urine are some known side effects of rifampicin. As per literature search there are only fifteen case reports of rifampicin induced immune hemolytic anemia [2]. We report a case of presumptive tuberculosis patient started on first line ATT who developed immune hemolytic anemia due to rifampicin.

Case Report

A 40-year-old male had presented elsewhere with complaints of fever with chills and rigors, cough with yellow sputum for ten days and of increased intensity since for 2 days. Patient was a known case of Gilbert's syndrome diagnosed at the age of 16 years and had past medical history of bronchial asthma, allergic rhinitis and was on intermittent medications for his allergy. His routine hematology tests, liver function tests, and chest X-ray were normal. With presumptive diagnosis of pulmonary tuberculosis patient was started on four drug Anti-Tuberculosis Therapy (ATT) by his family physician. After two days of starting ATT patient developed increase in yellowish discoloration of eyes, at which point he was referred to our center for further management. His vitals were stable, general, and systemic examination were unremarkable except for moderate icterus. On evaluation, liver functions were deranged with elevation of bilirubin and almost normal transaminases suggesting the diagnosis of unconjugated hyperbilirubinemia probably due to hemolytic anemia (Table 1). Lactate DeHydrogenase (LDH) was elevated with elevated reticulocyte count. Peripheral smear revealed normochromic normocytic anemia with anisocytosis, polychromasia, and spherocytosis. Sputum Acid Fast Bacilli (AFB) was negative and other diseases causing fever were ruled out which included dengue, typhoid, hepatitis.
B and C. Glucose 6 Phosphate Dehydrogenase (G6PD) level was normal. Direct and indirect Coombs’ antibody test was positive. Cold antibody test was negative. Patient had no complaints or symptoms and signs suggestive of autoimmune disorder. Hence, diagnosis of rifampicin induced immune hemolytic anemia was made. ATT was stopped immediately, and patient was prescribed oral prednisolone 10 mg/day. Patient also received one packed red cell transfusion. There was marked improvement in bilirubin levels by day 8 (Table 1). Patient was then discharged with prednisolone 10 mg/day for two weeks. Three months after discharge, patient remained asymptomatic and direct and indirect Coombs’ test was negative, and it confirmed the diagnosis of drug induced hemolytic anemia induced by rifampicin.

**Discussion**

Drug induced immune hemolytic anemia is very rare with incidence of one in million as compared to autoimmune hemolytic anemia which has an incidence of 1 in 80000 [3]. 125 drugs are known to cause DIIHA [4]. Three groups of drugs predominate namely 42% being antimicrobials, 15% being anti-inflammatory, and 11% being anti-neoplastic group contributing to DIIHA [4]. Some drugs that cause DIIHA frequently includes alpha methylldopa, penicillin, cefotetan, ceftriaxone, piperacillin, diclofenac, phenacetin [4]. Mechanisms suggested for DIIHA includes drug dependent autoantibody formation, drug independent autoantibody formation, and by non-immunologic adsorption of proteins [4].

In our case, in view of presumptive tuberculosis, patient was started on ATT and after two days of receiving ATT he developed jaundice and anemia. Investigations confirmed the diagnosis of immune hemolytic anemia. Jaundice in the present case could potentially be due to various conditions. Gilberts syndrome is associated with altered hepatic conjugation leading to elevated unconjugated bilirubin level. Notably, rifampicin is used as a provocative test drug to diagnose Gilberts syndrome in pediatric age group [5]. Jaundice in our case was unlikely to be due to Gilberts alone as bilirubin levels seldom raise beyond 6 mg/dl in such individuals. Drug induced hepatitis was unlikely in this case as it was predominantly indirect hyperbilirubinemia and the hepatic transaminases were normal. Indirect hyperbilirubinemia due to hemolysis was the most probable cause as there was clear evidence of immune hemolysis. A report in the literature implicates isoniazid to be the causative drug of immune hemolytic anemia after one year of treatment initiation [6]. Also, only one case of ethambutol induced hemolytic anemia is reported so far in literature [7]. As per literature pyrazinamide is not known to cause hemolytic anemias [6]. Since the treatment with ATT was only for a few days, possibility of isoniazid was ruled out as long-term administration of isoniazid causes hemolytic anemia as evidenced by a case report published [6]. Ethambutol as a causative agent was ruled out by the fact that ethambutol causing liver damage is very rare in acute setting with only one case report implicating the development of cholestatic jaundice due to ethambutol after 2 months of administration so far in literature [8]. In our case cholestatic jaundice was not seen. This supports the rifampicin to be the causative agent in our patient. Rifampicin usually causes conjugated hyperbilirubinemia due to cholestasis with or without elevation of transaminases but in our case, rifampicin caused elevated levels of indirect bilirubin with almost normal transaminases along with hemolytic anemia.

Rifampicin antibodies are found to have I antigen specificity [9]. Prompt resolution of symptoms and laboratory parameters after stopping rifampicin and treatment with small dose of prednisolone with supportive evidence of Coombs’ antibody positivity on drug exposure and persistent negative Coombs’ antibody test after 3 months confirmed the cause for immune hemolytic anemia to be rifampicin. Causality

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Day 1</th>
<th>Day4</th>
<th>Day 8</th>
<th>Day 14</th>
<th>Day 21</th>
<th>After 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin(g/dL)</td>
<td>10.9</td>
<td>6</td>
<td>5.8</td>
<td>10.5</td>
<td>12.3</td>
<td>14.8</td>
</tr>
<tr>
<td>Total white blood cell count (103/µL)</td>
<td>16.7</td>
<td>20.5</td>
<td>18.7</td>
<td>6.6</td>
<td>9.5</td>
<td>9.7</td>
</tr>
<tr>
<td>Platelets count (103/µL)</td>
<td>620</td>
<td>850</td>
<td>809</td>
<td>452</td>
<td>362</td>
<td>169</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>10.7</td>
<td>5.1</td>
<td>1.7</td>
<td>1.1</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Direct bilirubin (mg/dL)</td>
<td>2.6</td>
<td>1.4</td>
<td>0.8</td>
<td>0.5</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Aspartate aminotransferase (IU/L)</td>
<td>37</td>
<td>41</td>
<td>34</td>
<td>35</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Alanine aminotransferase (IU/L)</td>
<td>79</td>
<td>45</td>
<td>62</td>
<td>93</td>
<td>55</td>
<td>36</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>146</td>
<td>100</td>
<td>113</td>
<td>90</td>
<td>72</td>
<td>68</td>
</tr>
</tbody>
</table>

Table 1: Laboratory parameters.
assessment was done as per Naranjo's scale and it was found to be probable [10]. Furthermore, it was found to be moderately severe and not preventable as per Hartwig's severity and Thornton's preventability scale respectively [10]. Re-challenge with the offending drug is contra-indicated both in drug induced thrombocytopenia and hemolysis as minute quantity of the drug can trigger a very severe reaction.

**Conclusion**

Rifampicin is rarely associated with immune hemolytic anemia. This probability should be kept in mind and investigated systematically to confirm the diagnosis if a patient presents with symptoms and signs of hemolysis and or jaundice after being initiated with rifampicin. Repeat serological examination should be done 3 months after stopping the drug to confirm drug induced immune hemolytic anemia.

**References**


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