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ACUTE HEMOLYTIC ANEMIA CAUSED BY IRREGULAR RIFAMPICIN THERAPY*

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Acute hemolysis as an adverse reaction to rifampicin is a rarely encountered complication[1-6]. The number of cases that have been reported in the literature to date is about fifteen[7]. The adverse reaction has been seen only in patients taking the drug intermittently or irregularly.

Acute hemolysis is sometimes observed in association with acute renal failure. All patients with acute hemolysis and most with acute renal failure have rifampicin-dependent antibodies in their sera[8-19]. In this article, a patient with acute hemolysis due to irregular and high-dose rifampicin administration for pulmonary tuberculosis is presented.

Case Report

A thirteen-year-old girl was admitted to Cumhuriyet University Hospital in December, 1986 with complaints of fever, chills, nausea, vomiting, bilateral flank pain, diarrhea, pallor, and fainting. Two months prior to admission, the patient was diagnosed in another hospital as having tuberculosis and given rifampicin in a dose of 600 mg/daily and isoniazid in a dose of 400 mg/daily on an irregular basis. The patient discontinued the rifampicin treatment after 50 days. Following a six-day rifampicin-free interval, another doctor was consulted and recommended drug therapy. Twenty minutes after receiving a dose of rifampicin, the patient suffered nausea, vomiting, vertigo, bilateral flank pain and pallor. On the same day, the patient presented with these symptoms at Cumhuriyet University Hospital.

Physical examination revealed a temperature of 38°C, pulse rate of 132 per minute and a blood pressure reading of 90/40 mmHg. Her height was 142 cm and weight 30 kg. Her general condition was poor, and she had pallor. Diffuse rhonchal rales were auscultated. The liver was palpable three cm below the right costal margin and the spleen palpable two cm below the left costal margin. Both costavertebral regions displayed tenderness. Other findings were not contributory.

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Laboratory findings revealed the hemoglobin concentration to be 4.8 g/dl and white blood cell count 13,400/mm^3. Blood film showed evidence of hemolysis. Platelets were normal. The erythrocyte sedimentation rate was 45 mm/hour, urine color was dark and hemoglobinuria was observed. Other laboratory data revealed the BUN to be 18 mg/dl, serum creatinine 0.7 mg/dl, serum sodium 138 mEq/lt, chloride 98 mEq/lt, total serum bilirubin 7.2 mg/dl, direct bilirubin 0.4 mg/dl, SGOT 77 U, SGPT 35 U, and the PPD test 20 mm positive. The patient's blood group was A, Rh positive. The Paul-Bunnel test, HBsAg, sickling and direct Coombs tests were all negative. A bone marrow examination showed myeloid hyperplasia. Chest roentgenogram revealed mild bilateral infiltration.

During the tests carried out to determine the presence of anemia due to rifampicin-dependent antibodies in the patient, Cromatest Antiglobulin (Coombs) serum, Gama Biological Inc., anti C_3 and Gödecke anti C_4 sera and Biotest serum institute panel cells, a stock solution of rifampicin (100 mg in 100 ml saline), the patient's serum, compatible serum from a normal donor, fresh serum from a

TABLE I: Results of Antiglobulin Tests

	Anti IgG	Anti C_3	Anti C_4
1. Patient's serum Rifampicin solution Normal red cells Complement	–	+++	+++
2. Patient's serum Normal red cells Complement	–	–	–
3. Patient's serum (inactivated) Rifampicin solution Normal red cells	–	–	–
4. Normal serum Rifampicin solution Normal red cells Complement	–	–	–
5. Inhibition test (after incubation) Patient's serum Rifampicin solution Normal red cells Complement	–	–	–

group AB donor as a source of complement and group 0 human red cells in 5% suspension in saline were used in equal volumes. All the mixtures for the different reactions were incubated at 37°C for two hours and, after washing the red cells, the necessary antiglobin and anticomplement tests were carried out. Cold agglutinin tests performed by cord erythrocytes, and enzyme (Ficin) treated or normal adult erythrocytes were also negative. The same test was repeated after the patient's serum had been inactivated at 56°C for 30 minutes, and found to be negative due to a history of discontinuation of the drug after a short period of time. Acute hemolysis was not noted during the tests. The positive results in the third mixture carried out without adding complement revealed that the complement level had increased. When complement was added to the patient's inactivated serum, the test was found to be (++). In order to determine the inhibitory effect of rifampicin, tests were repeated after equal volumes of the patient's serum and rifampicin solution were incubated for two hours at 37°C and again found to be negative. The results are shown in Table I.

The patient was transfused and her hemoglobin levels increased to 10 g/dl. She was then discharged. The patient was followed for one year after the withdrawal of rifampicin. During this period her general condition was satisfactory and no hemolytical crisis was encountered.

Discussion

Since its introduction in the early 1960s, rifampicin has been widely used in the treatment of tuberculosis, nasopharyngeal carriage of *Neisseria meningitidis* and *Hemophilus influenzae,* and to a lesser degree, in various antibiotic combinations for bacterial and fungal infections[20].

When rifampicin is used regularly, adverse reactions are minimal and consist of hepatotoxic reactions and gastrointestinal symptoms[21]. These generally appear at the onset of treatment and immunological studies in these cases have shown no abnormality[22]. Adverse reactions occurring in the regimens of intermittent and high-dose rifampicin, flu-like syndrome characterized by fever, vomiting, diarrhea, muscle pain, thrombocytopenia, acute renal failure and hemolytic anemia have been reported[1,22-25]. Rifampicin-dependent antibodies have been found in patients with such reactions. An intermittent and irregular usage of drugs leads to an increase in rifampicin-dependent antibodies in the patient's serum.

Poole et al[22] have found rifampicin-dependent antibodies in 33 percent of 49 patients on bi-weekly and weekly doses of rifampicin. On the other hand, Girling[26] has encountered rifampicin-dependent antibodies in only one percent of 218 patients, and Rees[27] in one of 44 patients when rifampicin was administered three or more times per week.

It has been observed that the presence of rifampicin-dependent antibodies has no consistent correlation with clinically evident toxicity. While some patients on an intermittent regimen have had both symptoms and antibodies, others have not presented with the same picture[1,22,25].

Acute hemolysis due to rifampicin has been observed very rarely, and only in patients on intermittent or discontinuous therapy. In most reports, systemic symptoms developed two to three hours following a single discontinuous dose, and recovery was complete when rifampicin was withdawn[7]. Criel and Verwilghen[14] have reported a case with acute intravascular hemolysis and acute renal failure after a single dose of rifampicin following a six-month rifampicin-free interval. A strong relationship between reactions to rifampicin and the concentration of the drug in the blood has been considered to be possible[22]. This may likely be brought about by either dosage or rate of metabolism of the drug. Complications have been encountered more frequently in those receiving high doses of the drug[22,23].

The mechanism of rifampicin-induced hemolysis was noted to be similar to that described by Shulman and Rall[28] for quinidine. Both are relatively small molecules tightly bound to protein in the plasma, as haptens. These drugs can lead to the production of drug-specific antibodies in a given patient. In the presence of the drug in the serum, these antibodies fix and activate complement on the surfaces of the red cells which are eventually destroyed. The patient's serum fixes the complement to the surfaces of normal red cells only in the presence of this drug[9,27].

Diamond and Tahan[19] and Tahan et al[7] have reported intravascular hemolysis and non-oliguric renal failure after a single dose of rifampicin in a patient on an irregular regimen. They reported that their patients had rifampicin-dependent IgG antibodies with complement-fixing capability and concluded that the presence of rifampicin-dependent antibodies should be suspected in a patient with hemolysis and/or renal failure taking rifampicin.

In the case presented, acute hemolysis developed twenty minutes after the administration of a single dose of rifampicin following a six-day rifampicin-free interval. The presence of rifampicin-dependent antibodies was observed following special tests carried out on the patient's serum. Antibodies in the serum fixed the complement on the surface of normal red cells in the presence of the drug but failed to do so in its absence.

Although rifampicin-dependent acute hemolytic anemia is very rare and complete recovery may occur with its withdrawal, it causes very serious hemolytic anemia, displaying a reduced hemoglobin concentration of up to 4.8 g/dl, as observed in this case. In conclusion, we strongly recommend that this drug be not used irregularly and/or in high doses. Physicians should be advised to warn their patients regarding treatment with this drug.

Summary

Acute hemolytic anemia characterized by vomiting, diarrhea, vertigo, lumbar pain pallor and high fever due to an irregular and high dose of rifampicin is described in a 13-year-old girl during her treatment for tuberculosis. The presence of rifampicin-dependent antibodies was identified by special tests.

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