

Case Report: Recurrent Disseminated Intravascular Coagulation Caused by Intermittent Dosing of Rifampin

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Abstract. Daily rifampin therapy is associated with minimal adverse effects, but administration on an intermittent or interrupted basis has been associated with severe immunoallergic reactions such as hemolytic anemia, acute renal failure, and disseminated intravascular coagulation. We describe a patient with *Mycobacterium leprae* infection who experienced recurrent episodes of disseminated intravascular coagulation after intermittent exposures to rifampin, and review eight previously reported cases of rifampin-associated disseminated intravascular coagulation. In six (75%) cases, previous exposure to rifampin was reported and seven (87.5%) patients were receiving the medication on an intermittent or interrupted basis. Clinical features of rifampin-associated disseminated intravascular coagulation included fever, hypotension, abdominal pain, and vomiting within hours of ingestion. Average time to reaction was 3–6 doses if rifampin was being administered on a monthly schedule. Three (37.5%) of eight reported cases were fatal. A complete history of previous exposure to rifampin is recommended before intermittent therapy with this medication.

CASE REPORT

A 66-year-old woman was hospitalized in July 2009 after acute onset of fever, nausea, and vomiting. Her medical history was significant for lepromatous leprosy diagnosed at age 19, for which she had received multiple courses of therapy that included dapson, rifampin, clofazimine, and thalidomide. Her leprosy remained quiescent on monotherapy with dapson from 1986 until November 2008. At that time, she was started on the World Health Organization multidrug treatment regimen for leprosy that included ofloxacin, 300 mg orally/day; dapson, 100 mg orally/day; and rifampin, 600 mg orally/month to alleviate the need for lifetime monotherapy with dapson. Minocycline, 50 mg orally/day was substituted for ofloxacin after development of diarrhea. Other medical history included pulmonary tuberculosis diagnosed at age 37 that was treated with multidrug therapy including rifampin, cirrhosis secondary to hepatitis B virus infection for which she was receiving lamivudine, papillary thyroid cancer, bipolar affective disorder, and type II diabetes mellitus.

On July 21, 2009, she ingested her ninth monthly dose of rifampin as part of her intermittent dosing regimen. Within three hours, she experienced sudden onset of fever, nausea, and hematemesis and came to the Emergency Department. On examination, her blood pressure was 81/38 mm of Hg, her heart rate was 130/minute, and her temperature was 39.0°C. She was icteric. There was bleeding from the nares, oral cavity, urinary tract, and venipuncture sites. There was mild tenderness to palpation of the abdomen.

Laboratory investigations obtained within 12 hours of admission were compatible with disseminated intravascular coagulation (DIC): international normalized ratio = 3.33 (reference = 0.8–1.2); prothrombin time = 80 seconds (reference = 26–28 seconds); fibrinogen < 1.5 g/L (reference = 1.5–3.50 g/L), and D-dimers > 4,000 µg/L (reference = < 250 µg/L) and with intravascular hemolysis: hemoglobin = 89 g/L (reference = 120–160 g/L); bilirubin = 6.8 mg/dL (reference = < 1.3 mg/dL), and lactate

dehydrogenase = 1,317 U/L (reference = 125–243 U/L). The serum creatinine level was 2.9 mg/dL (reference = 0.6–1.1 µmol/L). Abdominal ultrasound showed trace free fluid adjacent to the gallbladder.

Her hypotension responded to two liters of intravenous normal saline. Pantoprazole was infused, and empiric antimicrobial therapy with piperacillin/tazobactam was initiated for a suspected intra-abdominal focus of infection. She required transfusion of two units of fresh-frozen plasma, 10 units of cryoprecipitate, and 2 units of packed erythrocytes to correct her hematologic abnormalities. Within 24 hours of presentation, she was afebrile, hemodynamically stable, and had laboratory evidence of resolving DIC. Blood cultures obtained on admission were negative. Gastroscopy showed antral gastritis and mild duodenitis without evidence of varices.

Because of the temporal relationship between the ingestion of rifampin and her acute illness, further history was obtained. Three months earlier on April 19, 2009 after her sixth monthly dose of rifampin, she had abrupt onset of nausea and oliguria. Outpatient laboratory investigations showed evidence of acute kidney injury and a decrease in hemoglobin concentration from baseline. Urinalysis showed heme-granular casts. Although a cause was not identified, the laboratory abnormalities resolved without need for therapeutic intervention. One month later on May 17, 2009, after her seventh monthly dose of rifampin, she was hospitalized with fever, abdominal pain, and anuria. Laboratory investigations showed acute and chronic kidney injury and laboratory abnormalities compatible with DIC with intravascular hemolysis. An infectious etiology was not identified. A renal biopsy showed acute tubular necrosis. She recovered after receiving blood product support and temporary hemodialysis. One month later on June 19, 2009, immediately after her eighth monthly dose of rifampin, she was hospitalized with a repeat diagnosis of DIC and anuric renal failure requiring re-initiation of hemodialysis. A precipitant was not identified, and she again recovered. Laboratory abnormalities associated with her four presentations are shown in Figure 1.

Serologic investigations performed within 48 hours of the ninth monthly intermittent dose of rifampin in July 2009 showed that she was blood group B+, erythrocyte antibody screen negative, and direct antiglobulin test negative. However,

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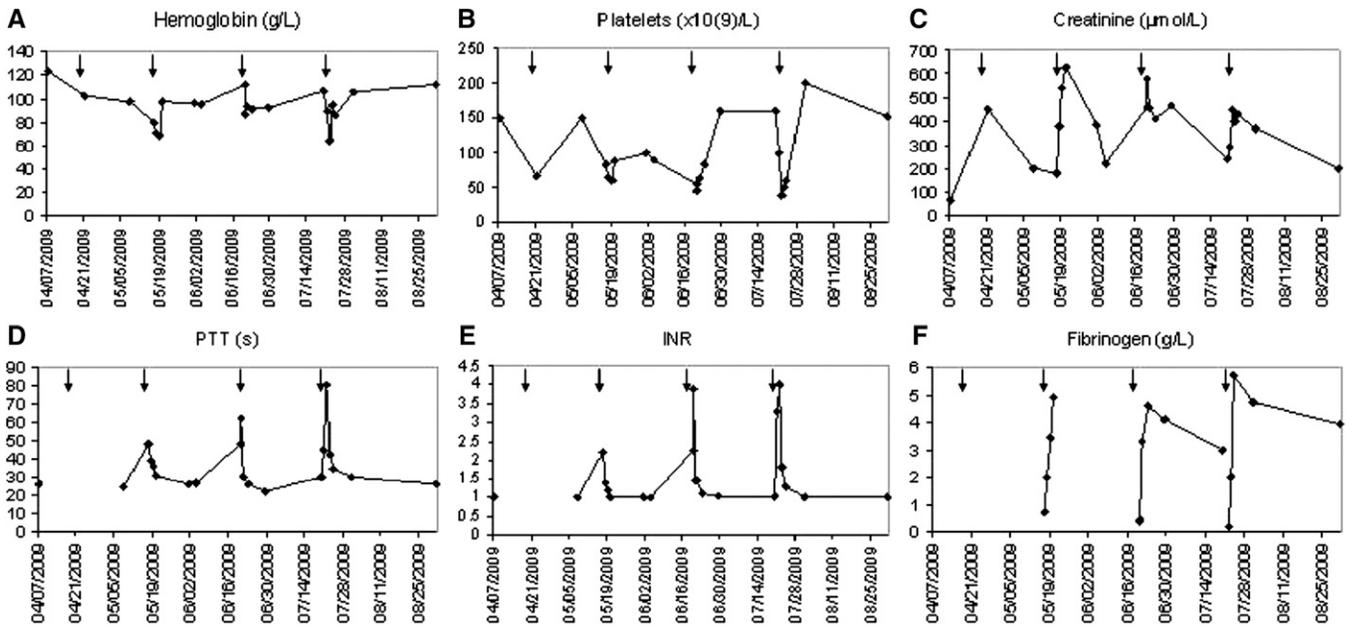


FIGURE 1. Time plots for trends in laboratory parameters over four episodes of immunoallergic reactions to rifampin in a 66-year-old woman for **A**, hemoglobin concentration; **B**, platelet count. **C**, creatinine; **D**, prothrombin time; **E**, international normalized ratio; and **F**, fibrinogen levels. Black arrows indicate times of ingestion of rifampin.

testing of her serum against rifampin-treated erythrocytes showed a rifampin-dependent antibody that was not reactive with rifampin metabolites or dapson. ¹

DISCUSSION

Rifampin is most commonly used in the treatment of mycobacterial infections in which it is given as part of multidrug therapy. It may be administered on a daily basis or on an intermittent dosing schedule. Adverse effects of rifampin, when administered on a daily basis, include IgE-mediated allergic reactions, rash, minor gastrointestinal upset, hepatotoxicity, and clinically important drug-drug interactions. ²

Rifampin is currently recommended as part of the World Health Organization multidrug treatment for *Mycobacterium leprae* infection, in which it is given on a once per month schedule in combination with dapson and clofazimine. ³ Rifampin administered on an intermittent or interrupted schedule can produce distinct and severe adverse effects known as immunoallergic reactions, which are mediated by IgG and IgM directed against erythrocytes, platelets, and other target cells that express the I blood antigen, including renal tubular epithelial cells. ⁴ These antibodies can be detected in the serum of up to 30% of patients after 3–4 doses of monthly intermittent therapy with rifampin, ⁵ and may also fix complement to rifampin-treated target cells. ^{4,6} Infrequent dosing of rifampin on either intermittent or interrupted schedules can result in sensitization with a rapid increase in antibody titer after repeat drug exposure. ⁷ Treatment with even a single dose of rifampin may induce sensitization and result in immunoallergic reactions upon repeat exposure. ⁷ In contrast, daily administration of rifampin is believed to confer immunologic tolerance against these reactions. ⁸

Immunoallergic reactions to rifampin occur in a dose- and schedule-dependent manner: 4–8% when 600 mg is given twice

a week, 22–31% when 900 mg is given once a week, and > 35% when 1,200 mg is given once a week. ^{6,8,9} A surveillance program of more than 20,000 patients receiving intermittent monthly dosing of rifampin for treatment of leprosy demonstrated that these reactions are rare when rifampin is administered on a monthly basis, and include fever and chills (0.26%), hemolytic anemia (0.03%), immune-mediated thrombocytopenia (0.01%), acute renal failure (0.1%) and DIC with hemodynamic compromise (0.005%). ¹⁰ In that program, 78% of patients who showed development of immunoallergic reactions had known prior exposure to rifampin, and 75% of reactions were observed after five or fewer doses. ¹⁰ Clinical manifestations may occur abruptly after re-exposure, and some reactions occur within 30 minutes of ingestion. ^{4,6}

A review of the English language literature identified eight previously reported cases of DIC associated with rifampin therapy, which are shown in Table 1. Five patients had received rifampin for treatment of pulmonary tuberculosis, ^{11–15} and three patients received rifampin on an intermittent monthly schedule for treatment of leprosy. ^{10,16,17} In six (75%) cases, prior exposure to rifampin was documented. ^{10,13–17} In the remaining two cases, there was no comment about prior exposure. ^{11,12} Seven (87.5%) patients received rifampin on an intermittent or interrupted schedule, ^{10,11,13–17} and when administered on a monthly basis, the development of DIC occurred after 3–6 doses. ^{10,16,17} Clinical features of rifampin-associated DIC included fever, hypotension, abdominal pain, and vomiting within hours of ingestion. Laboratory evidence of concomitant intravascular hemolysis was present in six (75%) cases. ^{11,13–17}

It is believed that rifampin-associated DIC results from antibody-mediated complement activation, which is triggered by circulating rifampin-erythrocyte complexes, resulting in erythrocyte destruction. Exposure of the circulation to erythrocyte constituents results in activation of the coagulation

TABLE 1
Nine cases of disseminated intravascular coagulation associated with rifampin therapy

Case no./reference	Age, y/ sex	Indication for rifampin	Rifampin dosage	Prior exposure to rifampin	Concurrent antimicrobial medications	Time to development of DIC	Symptoms/signs	Outcome
1/Brasil et al ¹⁰	NA/M	Leprosy	600 mg/month	Yes	Clofazimine, dapsone	Third dose	NA	Death
2/Denis and others ¹¹	48/F	Pulmonary tuberculosis	600 mg/day	NA	Streptomycin, ethambutol	5 months including many treatment interruptions	Fever, jaundice, vomiting, diarrhea	Recovery
3/Fujita and others ¹²	43/M	Pulmonary tuberculosis	450 mg/day	NA	Isoniazid, streptomycin	7 days	Bleeding	Recovery
4/Ip and others ¹³	29/F	Pulmonary tuberculosis	600 mg, three times a week	Yes	Isoniazid	6 months	Fever, hypotension, vomiting, oliguria, pruritis	Recovery
5/Luzzati and others ¹⁴	35/M	Pulmonary tuberculosis	600 mg/day	Yes	Isoniazid, pyrazinamide, ethambutol	First dose	Fever, rash, hypotension, abdominal pain, vomiting, myalgias	Recovery
6/Namimoto and Ogawa ¹⁶	64/M	Leprosy	600 mg/month	Yes	Clofazimine, dapsone	Third dose	Fever, hypotension, facial edema, vomiting, abdominal pain	Recovery
7/Nowicka and others ¹⁵	53/F	Pulmonary tuberculosis	450 mg; dosing schedule unclear	Yes	NA	Third dose	Lumbar and abdominal pain, anuria	Death
8/Souza and others ¹⁷	46/F	Leprosy	600 mg/month	Yes	Clofazimine, dapsone	Third dose	Fever, hematuria	Death
9/Present report	66/F	Leprosy	600 mg/month	Yes	Dapsone, minocycline	Sixth dose	Fever, hypotension, vomiting, abdominal pain, oliguria	Recovery

DIC = disseminated intravascular coagulation; NA = not available.

cascade. Three patients received empiric antimicrobial therapy for presumed sepsis-associated DIC.^{11,13,16} This misdiagnosis led to rifampin re-exposure in two instances,^{11,13} and rapid recurrence of DIC, which is similar to the case presented. Three (37.5%) patients died.^{10,15,17} In one of the surviving patients, rifampin-dependent antibodies were documented.¹⁴

We add to the literature the case of a patient with remote exposure to rifampin for the treatment of pulmonary tuberculosis and *M. leprae* infection in whom recurrent episodes of DIC and hemolytic anemia developed as a complication of intermittent rifampin therapy for treatment of leprosy. The patient's first immunoallergic reaction, resulting in acute renal failure, occurred immediately after ingestion of her sixth dose of rifampin. In the three subsequent presentations with DIC, broad-spectrum antibiotics were prescribed for suspected sepsis. Confirmation of rifampin as the trigger for DIC was made on the third presentation for DIC by identification of rifampin-dependent antibodies in her serum. This patient and others reported in the literature demonstrate that clinical and laboratory features cannot reliably distinguish between cases of rifampin-associated DIC and cases of DIC secondary to other causes.

In the case presented, temporal association of episodes of DIC with rifampin administration, recurrent reactions with repeat drug exposure, the absence of further episodes of DIC after discontinuation of rifampin, and presence of rifampin-dependent antibodies confirm the causal role of rifampin in this patient's recurrent episodes of DIC. Clinicians must be aware of the presentations of severe immunoallergic reactions to rifampin, which can appear during intermittent therapy, particularly if prior exposure to rifampin has occurred. A detailed drug history is paramount to making this diagnosis. In patients experiencing immunoallergic reactions to rifampin, this medication must be permanently discontinued because these reactions may be fatal.^{10,15,17} Daily administration of rifampin, as currently recommended in the United States for the multidrug therapy of leprosy, appears to be safer from an immunologic standpoint.^{8,18}

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