

# Rifampicin-induced disseminated intravascular coagulation in pulmonary tuberculosis treatment

## A case report and literature review

Guo Chen, MM (Master of medicine)<sup>a,b</sup>, Jian-Qing He, MD (Doctor of medicine)<sup>a,\*</sup>

### Abstract

**Rationale:** Disseminated intravascular coagulation (DIC) induced by daily rifampicin therapy is rare, especially the patient is absent of malignancy, severe infection, and prior exposure to rifampicin.

**Patient concerns:** We report a case of DIC induced by daily rifampicin treatment for pulmonary tuberculosis. A 22-year-old, previously healthy man received an anti-tuberculosis therapy consisting of isoniazid, rifampicin, ethambutol, and pyrazinamide on the daily dose recommended by the World Health Organization tuberculosis guidelines after a diagnosis of pulmonary tuberculosis. Two weeks later, he was transferred to the West China Hospital with nasal hemorrhage for 1 week, hematochezia, hematuria, and petechiae for 5 days.

**Diagnoses:** Laboratory data and symptoms on admission indicated DIC.

**Interventions:** The anti-tuberculosis drugs were discontinued after admission and he was initiated with targeted treatment for DIC, omeprazole and polyene phosphatidylcholine infusion, as well as nutrition supportive treatment. Five days after admission, ethambutol, moxifloxacin, and amikacin were added to the patient without further active hemorrhage. Eight days after admission, the platelet count had risen gradually. Isoniazid was administered on 24 days after admission, while his liver function tests and platelet counts returned to normal. No recurrence of DIC occurred. The diagnosis of rifampicin-induced DIC was confirmed.

**Outcomes:** The patient recovered and left hospital with isoniazid, ethambutol, levofloxacin, and streptomycin after 4 weeks of hospitalization. There was no recurrence of DIC or hemorrhage during the 8 months of follow-up. The literature review revealed that there were 10 other cases of rifampicin-induced DIC. Only 4 cases received rifampicin on a daily basis for pulmonary tuberculosis treatment and the others were on intermittent dosing schedule for pulmonary tuberculosis or leprosy treatment.

**Lessons:** As a rare adverse effect, DIC induced by rifampicin occurs irregularly and unpredictably, which is reported to be more associated with the intermittent usage of rifampicin, but can occur with rifampicin daily administration. Identification of early symptoms, drug discontinuation, supportive management, and regular monitoring are the key points to correct this adverse effect, which may contribute to severe even fatal results in patients and deserves more attention.

**Abbreviations:** ALT = alanine aminotransferase, AST = aspartate aminotransferase, CT = computed tomography, DBIL = direct bilirubin, DIC = disseminated intravascular coagulation, EMB = ethambutol, FIB = fibrinogen, HB = hemoglobin, IgG = immunoglobulin G, IgM = immunoglobulin M, I.M. = intramuscular injection, INH = isoniazid, Ivgtt = intravenously guttae, PLT = platelet, PT = prothrombin time, PTB = pulmonary tuberculosis, PZA = pyrazinamide, RMP = rifampicin, TB = tuberculosis, TBIL = total bilirubin, WBC = white blood cell.

**Keywords:** disseminated intravascular coagulation, rifampicin, tuberculosis

## 1. Introduction

As one of the most effective chemotherapy medicines for tuberculosis (TB), rifampicin (RMP) is widely used in China as

Editor: Oliver Schildgen.

The authors have no conflicts of interest to disclose.

<sup>a</sup> Department of Respiratory and Critical Care Medicine, West China Hospital, Sichuan University, <sup>b</sup> Department of Geriatrics, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, Chengdu, Sichuan, China.

\* Correspondence: Jian-Qing He, Department of Respiratory and Critical Care Medicine, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China (e-mail: jianqhe@gmail.com).

Copyright © 2017 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2017) 96:7(e6135)

Received: 9 November 2016 / Received in final form: 21 January 2017 /

Accepted: 24 January 2017

<http://dx.doi.org/10.1097/MD.0000000000006135>

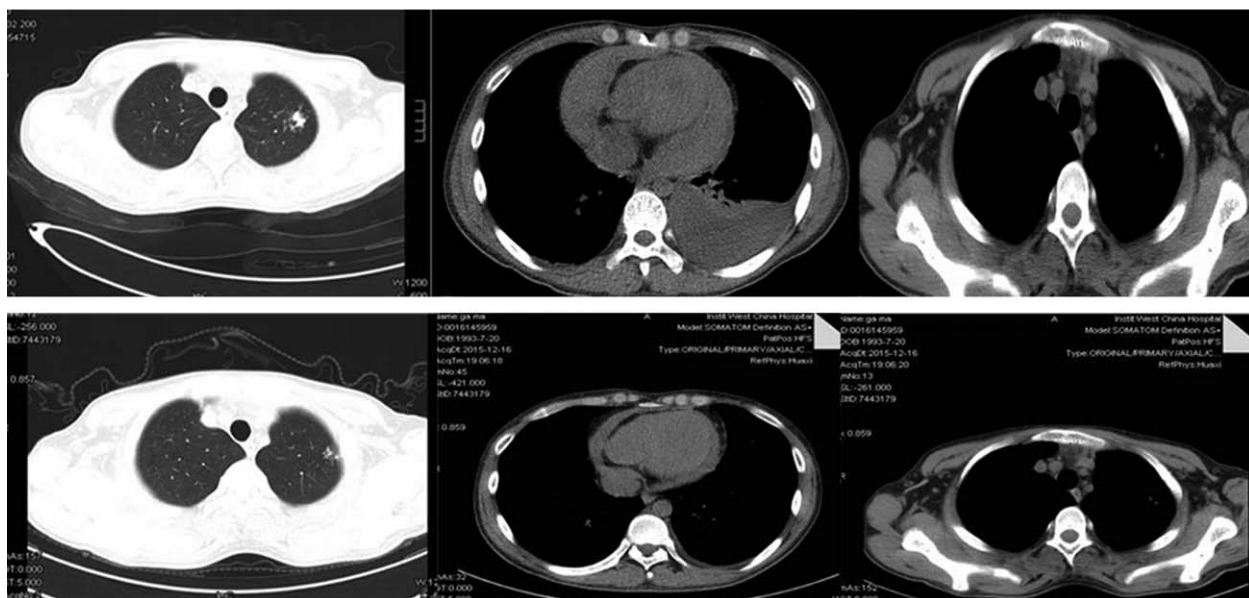
there is high incidence of this disease. Common adverse effects of RMP are liver toxicity and gastro-intestinal disorders.<sup>[1]</sup> Disseminated intravascular coagulation (DIC) induced by RMP is rarely reported. Here, we report a case of DIC as a severe complication associated with RMP treatment in China.

## 2. Method

This was a case report. The Institutional Review Board of the West China Hospital, Sichuan University, approved this study. Informed consent was obtained from the patient.

## 3. Case report

A 22-year-old Tibetan man without significant past medical history was diagnosed with pulmonary tuberculosis (PTB) in a routine medical examination and received anti-TB therapy that included isoniazid (INH, 300 mg/d), RMP (450 mg/d), ethambutol (EMB, 750 mg/d), and pyrazinamide (PZA, 1500 mg/d). After 1 week of continuous therapy, he was admitted to the Tibet People's Hospital with nasal hemorrhage and the platelet (PLT)



**Figure 1.** The chest computed tomography images of the patient. The figure shows the images of chest computed tomography (CT) of the patient on admission (November 18, 2015) and 1 month after admission (December 17, 2015). The upper images represent the CT examined on November 18, 2015 and show infiltrates on the upper lobe of the left lung, left pleural effusion, and pericardial effusion. The lower images represent the CT examined on December 17, 2015 and indicate the infiltration, hydrothorax, and pericardial effusion were absorbed well.

count was  $0.4 \times 10^9/L$  (normal range,  $100\text{--}300 \times 10^9/L$ ). Epistaxis was cured after symptomatic treatment. Two days later, he developed hematochezia, hematuria, and purpura, and required transfusion of fresh-frozen plasma and platelets in another local hospital. Four days later (November 18, 2015), he was transferred to the West China Hospital due to the ineffective treatment. On physical examination, he presented with pallor, mild jaundice on the sclera, purpura, tachycardia (heart rate 132/min) and weak breath sounds at the base of the left lung. Laboratory results on admission indicated DIC: prothrombin time (17.8 seconds; normal range, 9.6–12.8 seconds), international normalized ratio (1.53; normal range, 0.88–1.15), fibrinogen (1.13 g/L; normal range, 2.0–4.0 g/L), D-dimers (23.45 mg/L; normal range,  $<0.55$  mg/L), fibrin degradation product (60.4 mg/L; normal range,  $<5$  mg/L), and PLT ( $2 \times 10^9/L$ ; normal range,  $100\text{--}300 \times 10^9/L$ ). Other abnormal data were as follows: white blood cell (WBC,  $48.38 \times 10^9/L$ ; normal range, 3.5–9.5), hemoglobin (65 g/L; normal range, 130–175 g/L), total bilirubin (30.8  $\mu\text{mol/L}$ ; normal range, 5.0–28.0  $\mu\text{mol/L}$ ), direct bilirubin (16.6  $\mu\text{mol/L}$ ; normal range,  $<8.8$   $\mu\text{mol/L}$ ), aspartate aminotransferase (75 U/L; normal range,  $<40$  U/L), alanine aminotransferase (293 U/L; normal range,  $<50$  U/L), lactate dehydrogenase (380 U/L; normal range, 110–220 U/L), serum urea nitrogen (13.01 mmol/L; normal range, 3.2–7.79 mmol/L), C-reactive protein (16.70 mg/L; normal range,  $<5$  mg/L), complement 3 (0.41 g/L; normal range, 0.785–1.520 g/L), and complement 4 (0.0797 g/L; normal range, 0.145–0.360 g/L). Routine urine test showed blood cell  $>330$  Cell/uL, leukocyte 250 Cell/uL, protein 2 g/L, and urobilinogen 70  $\mu\text{mol/L}$ . Routine stool test showed red blood cell 4+/HP, white blood cell 1+/HP, occult blood test (+). T-SPOT result was positive. Real-time polymerase chain reaction analysis for mycobacterium TB on sputum was positive. Acid fast stain test of a sputum smear was negative. Chest computed tomography (CT) on admission (November 18, 2015) (Fig. 1) showed infiltrates on the upper

lobe of the left lung, left pleural effusion, and pericardial effusion, accompanied by enlargement of mediastinal lymph nodes. Abdominal ultrasound showed a small amount of fluid adjacent to the liver and spleen. Serologic markers were negative for acute or chronic viral hepatitis, HIV, direct Coomb test, and autoimmune hepatitis. Peripheral blood film and culture were negative. Bone marrow smear and medulloculture were also negative.

The antituberculosis drugs were discontinued immediately after admission. Besides fasting, he was initiated with infusion of fresh-frozen plasma, platelet, packed red blood cells, intravenous immune globulin, recombinant human thrombopoietin, omeprazole, and polyene phosphatidylcholine as well as nutrition supportive treatment. Five days after fasting (November 23, 2015), the patient started a therapy consisting of EMB, moxifloxacin, and amikacin, while he had no further active hemorrhage. Eight days after admission (November 26, 2015), the platelet counts had risen gradually. INH (200 mg/d, intravenously guttae) was administered on 24 days after admission (December 11, 2015), while his liver function tests and platelet counts returned to normal. The main laboratory features are summarized in Table 1. One month later (December 17, 2015), reviewed chest CT (Fig. 1) indicated the infiltration, hydrothorax, and pericardial effusion were absorbed well. Almost about 4 weeks after admission, the patient recovered and left hospital with INH (300 mg/d), EMB (750 mg/d), levofloxacin (500 mg/d), and streptomycin (750,000 U/d, intramuscular injection). There was no recurrence of DIC or hemorrhage during 8 months of follow-up. Unfortunately, the patient refused a follow-up chest CT after his discharge. Table 2 shows the timeline of this case.

#### 4. Discussion

Rifampicin is an important and effective drug in the treatment of TB and leprosy. It is recommended to be given either daily or 3

**Table 1**  
**Hematologic parameters after admission to the West China Hospital.**

Day (normal range)	PLT, $\times 10^9/L$ (100–300)	HB, g/L (130–175)	PT, s (9.6–12.8)	D-dimer, mg/L (< 0.55)	FIB, g/L (2.0–4.0)
November 18, 2015	2	65	17.8	23.45	1.13
November 19, 2015	3	49	16.6	–	0.77
November 21, 2015	3	66	–	–	–
November 24, 2015	6	78	20.5	13.65	1.51
November 26, 2015	35	85	17.9	–	1.55
November 27, 2015	86	82	20.5	12.1	1.37
November 28, 2015	113	97	18.5	14.61	1.38
December 1, 2015	42	98	15.7	–	1.92
December 3, 2015	92	105	15.3	12.33	2.11
December 5, 2015	167	116	14.5	13.14	2.75
December 10, 2015	146	95	14.6	8.47	3.63
December 15, 2015	192	94	14.6	–	4.81
December 17, 2015	228	106	–	–	–
December 24, 2015	153	148	–	–	–
January 8, 2016	130	140	–	–	–

FIB = fibrinogen, HB = hemoglobin, PLT = platelets, PT = prothrombin time.

times per week in the treatment of TB and on an intermittent dosing schedule (600 mg per month) for adult leprosy according to the World Health Organization multidrug treatment regimen for leprosy.<sup>[2]</sup>

The common adverse effects of rifampicin are gastrointestinal disorders, skin rash, hepatotoxicity, etc. DIC induced by RMP is rare, which may be caused by infection, malignancy, obstetric diseases, and severe toxic or immunological reactions. Bleeding, organ failure, massive bleeding, and nonsymptomatic types are the main types of DIC according to the effects of hypercoagulation and hyperfibrinolysis.<sup>[3]</sup> With the mortality ranging from 31% to 86%,<sup>[4,5]</sup> different types of DIC are associated with the underlying disorder or diseases. The bleeding type of DIC is mainly caused by leukemia, obstetric diseases, or aortic aneurysms.<sup>[6,7]</sup> The organ failure type is often observed in patients with infections, especially sepsis, and the major bleeding type occurs in patients with major bleeding after surgery or obstetric diseases. The last type presents abnormal laboratory results without clinical symptoms.<sup>[8]</sup> The above types may shift or change into each other.

We reviewed 10 English-language articles about RMP-associated DIC. There was no report on DIC induced by RMP in China through literature review. The clinical symptoms of DIC included bleeding, vomiting, fever, jaundice, abdominal pain, rash, hypotension, and renal failure, etc. Three cases (30%) died after active treatment. Six cases (60%) were diagnosed with PTB,<sup>[9–14]</sup> the others were leprosy.<sup>[15–18]</sup> Eight patients (80%) had a history of prior exposure to RMP.<sup>[10,11,13–18]</sup> Six cases (60%) were administered RMP on an intermittent way, in which 4 cases were 600 mg per month, 1 case was 600 mg 3 times a week, and 1 case was 450 mg with an unclear dosing schedule. The development of DIC occurred on 3 to 6 doses when the medication was administered once a month.

Four patients (40%) received RMP on daily doses<sup>[9,12,14]</sup> and in 1 case, a 48-year-old man, DIC occurred after 5 months of daily RFP treatment (600 mg/d) for PTB<sup>[9]</sup>. This patient was definitely without prior exposure to RFP, similar to our reported case. One case was a 43-year-old man with PTB who presented with DIC on 1 week of RMP application (450 mg/d), whose previous exposure to RMP was uncertain.<sup>[12]</sup> In the other 2 cases, DIC occurred on 2 hours following the first dose and 3 weeks of RMP administration for PTB, separately.<sup>[13,14]</sup>

To date, the main mechanism of DIC-induced by RMP is considered to be related to the RMP-induced immunoallergic reaction that may activate the coagulation process to initiate the DIC. RMP as an antigen binds to platelets and erythrocytes to form immune complexes. Then complement is activated and fixed to the RMP-target cells. The combination of antigen–antibody complexes with activated complement may cause platelet and erythrocyte injury, and vascular endothelium impairment mediated by immunoglobulin G (IgG) and immunoglobulin M (IgM),<sup>[19]</sup> subsequently resulting in the systemic intravascular activation of coagulation of DIC. Previous case reports considered that RMP administered on an intermittent or irregularly basis may repeatedly enhance patients' sensitivity and be easier to trigger the immunoallergic reaction than daily administration.<sup>[15]</sup> Literature reports indicated that after 3 to 4 doses of monthly intermittent therapy with RMP, about one-third of patients can be found to have positive RMP antibodies in the serum and DIC was reported as a severe adverse effect.<sup>[18,19]</sup> Thus, patients who use RMP on a daily basis may be more tolerant against the reaction.

However, in the present case, the young man, who was without prior exposure to RMP, presented with abnormal symptoms after the first week of daily therapy. The main symptom of this patient was bleeding from multiple organs without fever, acute renal failure, pain, and rash as described above. The high WBC counts on admission may be considered the leukemoid reaction due to DIC and hemorrhage, as there was no evidence of infection, malignancy, or autoimmune diseases in this patient. The abnormal liver function may be related to hepatitis induced by RMP. The patient had a good recovery with the discontinuation of RMP and supportive therapy for DIC. No recurrence of DIC, abnormal liver function, and high WBC counts occurred in the follow-up. Although testing for anti-RMP antibodies was not available to us, the clinical process of this case indicated to the diagnosis of DIC induced by RMP. However, the diagnosis of hemolysis induced by DIC was not appropriate in this patient, because of lack of evidence. Besides immunoallergic reaction, other underlying mechanisms of DIC caused by RMP, especially in patients with daily administration but without prior exposure history, were not clear. We propose that it may be related to the patient who was more sensitive to form immunoallergic complex than others during the short intermittent period of drug delivery.

**Table 2****The timeline between rifampin use and the appearance of DIC in the case.**

<b>Relevant past medical history and interventions</b>			
<b>November 5, 2015</b>			
<b>Diagnosed with pulmonary tuberculosis and received antituberculosis therapy consisting of INH (300 mg/d), RMP (450 mg/d), EMB (750 mg/d), and PZA (1500 mg/d)</b>			
<b>Date</b>	<b>Summaries from initial and follow-up visits</b>	<b>Diagnostic testing (including dates)</b>	<b>Interventions</b>
November 12, 2015	Nasal hemorrhage	Platelet: $0.4 \times 10^9/L$	Hemostatic therapy
November 14, 2015	Hematochezia hematuria purpura	Unknown	Fresh-frozen plasma and platelet transfusion
November 18, 2015	Hematochezia, hematuria purpura	Prothrombin time: 17.8 s	Discontinued antituberculosis drugs, fasting, fresh-frozen plasma, platelet, packed red blood cells infusion, supportive treatment
	Physical examination showed pallor, mild jaundice on the sclera, purpura, tachycardia, weak breath sounds at the base of the left lung	Fibrinogen 1.13 g/L D-dimers 23.45 mg/L Platelet: $2 \times 10^9/L$ Hemoglobin: 65 g/L TBIL: 30.8 umol/L DBIL: 16.6 umol/L AST: 75 U/L ALT: 293 U/L CT: infiltrates on the upper lobe of the left lung, left pleural effusion and massive pericardial effusion	
November 23, 2015	No active haemorrhage	Platelet $3 \times 10^9/L$ Hemoglobin: 66 g/L (November 21, 2015)	Added EMB, moxifloxacin, amikacin
November 26, 2015	No active haemorrhage	Platelet $35 \times 10^9/L$ Hemoglobin: 86 g/L	Antituberculosis therapy with EMB, moxifloxacin, amikacin
December 11, 2015	No active haemorrhage	Liver function tests: normal Platelet $146 \times 10^9/L$ Hemoglobin: 95 g/L	Added INH with 200 mg ivgtt per day
December 18, 2015	Recovery and left hospital	Platelet $228 \times 10^9/L$ Hemoglobin: 106 g/L CT: infiltration, hydrothorax, and pericardial effusion were absorbed well	INH (300 mg/d), EMB (750 mg/d), levofloxacin (500 mg/d), and streptomycin (750,000 U/d, I.M.)
December 24, 2015	No symptoms	Diagnose: DIC induced by RMP Platelet $153 \times 10^9/L$ Hemoglobin: 148 g/L	INH (300 mg/d), EMB (750 mg/d), levofloxacin (500 mg/d), and streptomycin (750,000 U/d, I.M.)
January 8, 2016	Follow-up in clinics, without any discomfort	Platelet $130 \times 10^9/L$ Hemoglobin: 140 g/L	INH (300 mg/d), EMB (750 mg/d), levofloxacin (500 mg/d), and streptomycin (750,000 U/d, I.M.)
August 2016	No symptoms	Laboratory results were normal and patient refused follow-up chest CT	Antituberculosis drugs were discontinued for 2 months

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CT = computed tomography, DBIL = direct bilirubin, DIC = disseminated intravascular coagulation, EMB = ethambutol, I.M. = intramuscular injection, INH = isoniazid, ivgtt = intravenously guttae, PZA = pyrazinamide, RMP = rifampicin, TBIL = total bilirubin.

The onset of RMP-induced DIC is not regular and unpredictable. It may occur between 2 hours and 6 months after continuous therapy or after 3 to 6 doses of intermittent therapy. Therefore, familiar with its presentation, early detection and treatment, and good monitoring are necessary to deal with this severe syndrome.

## 5. Conclusions

Clinicians should be aware of the manifestations of DIC, which occur irregularly during RMP administration. Identifi-

cation of early symptoms, drug discontinuation, and active supportive treatment are the key points to correct the rare adverse effects.

## References

- [1] Arbex MA, Varella Mde C, Siqueira HR, et al. Antituberculosis drugs: drug interactions, adverse effects, and use in special situations. Part 1: first-line drugs. *J Bras Pneumol* 2010;36:626–40.
- [2] WHOA guide to eliminating leprosy as a public health problem. Geneva (Switzerland) 1995;95:51–3.

- [3] Wada H, Matsumoto T, Yamashita Y. Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. *J Intensive Care* 2014;2:15.
- [4] Sakata Y. DIC associated with acute promyelocyte leukemia. *Ryoikibetsu shokogun shirizu* 1998;517-20.
- [5] Barbui T, Falanga A. Disseminated intravascular coagulation in acute leukemia. *Semin Thromb Hemost* 2001;27:593-604.
- [6] Wada H. Disseminated intravascular coagulation. *Clin Chim Acta* 2004;344:13-21.
- [7] Wada H, Matsumoto T, Hatada T. Diagnostic criteria and laboratory tests for disseminated intravascular coagulation. *Expert Rev Hematol* 2012;5:643-52.
- [8] Wada H, Minamikawa K, Wakita Y, et al. Hemostatic study before onset of disseminated intravascular coagulation. *Am J Hematol* 1993;43:190-4.
- [9] Denis J, Robert A, Johanet C, et al. Immunoallergic complication induced by rifampicin with disseminated intravascular coagulation. *Presse Med* 1983;12:1479-81.
- [10] Ip M, Cheng KP, Cheung WC. Disseminated intravascular coagulopathy associated with rifampicin. *Tubercle* 1991;72:291-3.
- [11] Nowicka J, Kotschy M, Chwistecki K, et al. Disseminated intravascular coagulation (DIC) during superacute haemolysis in a patient with ovarian dermatoid cyst treated with rifampicin. *Haematologia (Budap)* 1977;11:359-64.
- [12] Fujita M, Kunitake R, Nagano Y, et al. Disseminated intravascular coagulation associated with pulmonary tuberculosis. *Intern Med* 1997;36:218-20.
- [13] Luzzati R, Giacomazzi D, Franchi F, et al. Life-threatening, multiple hypersensitivity reactions induced by rifampicin in one patient with pulmonary tuberculosis. *South Med J* 2007;100:854-6.
- [14] Costiniuk CT, McCarthy AE, Talreja H, et al. Acute renal failure and disseminated intravascular coagulation associated with rifampin in tuberculosis treatment. *Int J Tuberc Lung Dis* 2011;15:421.
- [15] Havey TC, Cserti-Gazdewich C, Sholzberg M, et al. Recurrent disseminated intravascular coagulation caused by intermittent dosing of rifampin. *Am J Trop Med Hyg* 2012;86:264-7.
- [16] Brasil MT, Opromolla DV, Marzliak ML, et al. Results of a surveillance system for adverse effects in leprosy's WHO/MDT. *Int J Lepr Other Mycobact Dis* 1996;64:97-104.
- [17] Namisato M, Ogawa H. Serious side effects of rifampin on the course of WHO/MDT: a case report. *Int J Lepr Other Mycobact Dis* 2000;68:277-82.
- [18] Souza CS, Alberto FL, Foss NT. Disseminated intravascular coagulopathy as an adverse reaction to intermittent rifampin schedule in the treatment of leprosy. *Int J Lepr Other Mycobact Dis* 1997;65:366-71.
- [19] Martinez E, Muniz E, Domingo P. Evidence implicating rifampin-independent antiplatelet antibodies in the pathogenesis of rifampin-induced immune thrombocytopenia. *Clin Infect Dis* 1994;19:351-3.