Rifampicin-induced disseminated intravascular coagulation in pulmonary tuberculosis treatment
A case report and literature review

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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 polyethylene glycol to prevent gastrointestinal bleeding, and supportive treatment. Five 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, TBL = 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 there is high incidence of this disease. Common adverse effects of RMP are liver toxicity and gastrointestinal disorders.\textsuperscript{[1]} 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)
count was 0.4 × 10^9/L (normal range, 100–300 × 10^9/L). Epistaxis was cured after symptomatic treatment. Two days later, he developed hematoma, 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 × 10^9/L; normal range, 100–300 × 10^9/L). Other abnormal data were as follows: white blood cell (WBC, 48.38 × 10^9/L; normal range, 3.5–9.5), hemoglobin (65 g/L; normal range, 130–175 g/L), total bilirubin (30.8 umol/L; normal range, 5.0–28.0 umol/L), direct bilirubin (16.6 umol/L; normal range, <8.8 umol/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/μL, leukocyte 250 Cell/μL, protein 2 g/L, and urobilinogen 70 umol/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. The lower images represent the CT examined on December 17, 2015 and indicate the infiltration, hydrothorax, and pericardial effusion were absorbed well.

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
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.[2]

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.[3] WITH the mortality ranging from 31% to 86%,[4,5] 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.[6,7] 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.[8] 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,[9-14] the others were leprosy.[15-18] Eight patients (80%) had a history of prior exposure to RMP.[10,11,13-18] Six cases (60%) were administrated 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[9,12,14] and in 1 case, a 48-year-old man, DIC occurred after 3 months of daily RFP treatment (600 mg/d) for PTB.[9] 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.[12] In the other 2 cases, DIC occurred on 2 hours following the first dose and 3 weeks of RMP administration for PTB, separately.[13,14]

To date, the main mechanism of DIC-induced by RMP is considered to be related to the RMP-induced immunooallergic 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 plateletland, erythrocyte injury, and vascular endothelium impairment mediated by immunoglobulin G (IgG) and immunoglobulin M (IgM),[19] 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.[15] 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.[18,19] 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 1

| Hematologic parameters after admission to the West China Hospital. |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Day (normal range)          | PLT, \(\times10^9/L\) (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           | 97              | 97              | 16.5            | 14.6            | 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             | –               | –               | –               |

**Note:** FIB = fibrinogen, HB = hemoglobin, PLT = platelets, PT = prothrombin time.
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. Identification of early symptoms, drug discontinuation, and active supportive treatment are the key points to correct the rare adverse effects.

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