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Case report **Open Access**

Rifampin-induced vitamin K deficiency coagulopathy in a patient with brucellosis and rheumatoid arthritis: A clinical case report

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Coagulopathy as a reversible dose-dependent side effect of rifampin is rarely observed in patient on rifampin in associate to inducing vitamin K deficiency. We reported a middle-aged man on a brucellosis three-drug regimen (including rifampin) who was admitted to the hospital due to a rheumatoid arthritis flare-up with increased partial thrombin time and international normalized ratio. Abnormal coagulation tests were discovered as an unintentional finding in the absence of clinical signs of bleeding. However, the coagulation tests returned to normal in 48 hours by withdrawing rifampin and administering 2.5 mg of oral vitamin K. The patient was discharged with a new brucellosis regimen including doxycycline and trimethoprim/sulfamethoxazole.

Keywords: rifampin; coagulopathy; vitamin K; adverse drug reaction; case report

Introduction

Rifampin is a semisynthetic derivative of rifamycin, an antibiotic produced by *Amycolatopsisrifamycinica. It is* active against a wide range of infections caused by gram-positive and some gram-negative bacteria and shows bactericidal effects by binding to DNA-dependent RNA polymerase and inhibiting RNA synthesis. In addition to the aforementioned effects, rifampin is known as a potent liver cytochrome P450 enzyme inducer including CYP1A2, 2C9, 2C19, 2D6, and 3A4. Other medications, such as anticoagulants, anticonvulsants, integrase string transfer inhibitors, non-nucleoside reverse transcriptase inhibitors, and contraceptives, may be affected by this enzymatic induction [1].

Rifampin's side effects are categorized as dose-dependent and dose- independent. Dose-dependent ones are hepatotoxicity, nausea, loss of appetite, and yellow discoloration of body fluids (urine, tears, etc.). Dose-independent ones include acute renal failure, hemolysis, and thrombocytopenia. Coagulopathy induced by rifampin is a rare adverse effect, which ranges from mild thrombocytopenia to disseminated intravascular coagulation (DIC). The possible mechanisms are complex and multifactorial as follows: (I) Reducing the synthesis coagulation factor due to hepatotoxicity; (II) Reducing production of vitamin K by the intestinal flora; and (III) inhibiting vitamin K epoxide reductase

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which causes vitamin K degradation [2-5]. The mechanisms of II and III lead to reduced vitamin K-dependent coagulation factors (II, VII, IX, and X). There are only a few case reports in the literature that describe coagulopathy and bleeding in rifampin-treated patients with no known hematologic disorder. For the first time, in 1997, the study of Ishii et al. [5] reported a new dose and time-dependent adverse drug reaction (ADR) for rifampin in patients with small intestinal disease. To investigate the mechanism of observed ADR, they conducted an experiment in rat models. The authors declared that rifampin might inhibit vitamin K epoxide reductase, which leads to interference with vitamin K activation and coagulation factor synthesis. Also, the inhibition of vitamin K epoxide reductase induces the production of PIVKA-II (protein induced by vitamin K absence or antagonist-II). Furthermore, rifampin eradicates gut flora as the main source of vitamin K for humans. The observed ADR was reversible by discontinuing rifampin and starting vitamin K supplements [5]. In 2012, Sampaziotis et al. presented two cases with primary sclerosing cholangitis who had encountered an ADR of rifampin. In both cases, severe prolongation of prothrombin time (PT) was detected about 2–3 weeks after initiating rifampin 300 mg/day to approach pruritus. There was no change in liver function tests and bleeding. Both patients' PT returned to normal after discontinuing rifampin and replacing 10 mg of vitamin K [6].

Castillo Almeida et al. reported an 86-year-old man with severe bleeding in the surgery site after four weeks of total hip arthroplasty. Past medical history has included rheumatoid arthritis (RA) and chronic kidney disease. In laboratory assessment, he had a profound elevation in PT and more than a three-point drop in hemoglobin while he was only on oral rifampin and intravenous cefazolin combination therapy for prosthetic joint infection. In further evaluation, no liver failure or toxicity was detected. The combination of antibiotics was supposed to disturb the vitamin K reductase enzyme, which resulted in vitamin K deficiency. The antibiotics were discontinued, and 10 mg of oral vitamin K was administered two times; within 24 hours, PT was corrected, and the bleeding stopped [6].

The other case report explained an 8-month-old male infant who was treated with an anti-tuberculosis (TB) first-line treatment protocol including rifampin three months ago due to TB infection. The infant was admitted with multiple ecchymotic lesions in both lower limbs that appeared within 24 hours. According to laboratory data, prolonged partial thrombo-plastin time (PTT) (160 sec), PT (175 sec), and international normalized ratio (INR) (15.64) were detected, with mild microcytic anemia. Renal and liver function tests were normal. The anti-TB four-drug regimen was discontinued for three days, and a single dose of intravenous vitamin K 10 mg and fresh frozen plasma (FFP) were administered. Coagulation tests returned to the normal range within six hours. Then anti-TB medications were restarted to complete the treatment course. Supplemental oral vitamin K, 2 mg three times per day for a month and then every other day until three months (end of TB treatment) was given. In close follow-up, no complications were reported.

As previously stated, few cases of rifampin-induced abnormal coagulation tests in the absence of any known hematologic disorders or DIC have been reported in the literature. A patient with rifampin-induced prolonged INR and PTT was reported in this study, but no other serious adverse effects such as hepatotoxicity, thrombocytopenia, or DIC were reported.

Case report

A 51-year-old Caucasian man (173 cm in height and 70 kg in weight), a known case of RA from 7 years ago, was admitted to a general hospital in Urmia, West Azerbaijan, Iran, with complaints of weakness, fever and chills, severe sweating, and back pain since a week before admission. The patient had no other medical, surgical, or psychological history except for carpal tunnel release surgery about two years ago. His habitual history was positive for only cigarette smoking (37 packs/year). He did not use alcohol or illicit drugs. His family health history was unremarkable except for his sibling, who had RA too. His treatment regimen for RA

was hydroxychloroquine 200 mg BID, sulfasalazine 500 mg TDS, prednisolone 5 mg daily, calcium 400 mg, vitamin D 200 units daily, and folic acid 1 mg daily. A definitive diagnosis of brucellosis was made with two positive tests of Wright (1/320) and Coombs Wright (1/320) and related musculoskeletal symptoms in that center. No anti-brucella antibody was checked. Triple antibiotic therapy was started for the patient with oral rifampin 300 mg BID (for 6 weeks), oral doxycycline 100 mg BID (for 6 weeks), and intramuscular streptomycin 1000 mg daily (for two weeks).

Fifteen days after discharge, he was admitted to this hospital with arthralgia in his knees and shoulders. In physical examination, tenderness, reduced range of motion (ROM), and swelling were detected in both shoulders and knees. The remainder of the physical examinations, including skin and mucosa, were normal. With a diagnosis of RA flare up, methylprednisolone (500 mg) intravenous for three consecutive days was administered. All of his symptoms had improved, and he was discharged on all of his previous brucellosis and RA medications, with the exception of increasing the dose of prednisolone to 10 mg daily.

Two weeks later, he was re-hospitalized due to an RA flare-up (morning stiffness, tenderness, and reduced ROM of shoulders and knees). By the time of readmission, all 14 doses of streptomycin were administered, and the two other antibiotics were still in his regimen. On this admission, we incidentally found an abnormal coagulation profile (PTT: 141.4, PT: 54, and INR: 4.46). These results were rechecked,

Table1: Laboratory parameters of the patient at baseline and on each admission

Laboratory test	Baseline (October 3th)	1st admission (November 7th)	2nd admission (November 21st)	3rd admission (December 5th)	Reference Range
Leukocytes, /µL	12000	9690	7250	7210	4000-12000
Hemoglobin, g/dL	13.0	13.2	11.6	11.6	12-16
Platelet count, ×10^3/	310	228	381	318	150-400
µL AST, U/L	33	17	18	18	8-36
ALT, U/L	31	13	15	15	7-37
ALP, U/L	134	238	196	156	45-135
Total bilirubin, mg/dL	0.40	0.48	0.25	0.25	≤ 1.20
Total protein, g/dL	-	-	6.75	-	-
Albumin, g/dL	-	-	4.3	-	-
BUN, mg/dL	10	40	27	-	10-50
SCr, mg/dL	0.80	1.25	1.11	1.11	0.6-1.4
PTT, secs	15.3	44.2	41.2	135.1	26-38
PT, secs	11.3	17.2	13.0	53.5	11-15
INR	1.31	-	1.46	4.42	0.9-2
CRP, mg/dL	33.7	-	85.0	85.1	-
ESR, mm/h	56	91	73	75	-
Reticulocyte count, (%)	-	-	-	1.2	0.5-1.5
Ferritin, µg/dL	-	-	-	49	-
Serum iron, ng/ml	-	-	-	226	-
TIBC, µg/dL	-	-	-	175	-
Fibrinogen, mg/dL	-	-	-	273	-

AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; Bili, bilirubin; BUN, blood urea nitrogen; SCr, serum creatinine; PTT, Partial thromboplastin time; PT, Prothrombin time; INR, international normalized ratio; C-reactive protein; ESR, erythrocyte sedimentation rate; TIBC, total iron-binding capacity

and abnormal values were confirmed; meanwhile, he was notably not on any anticoagulation agent. No bleeding (hematuria, hemoptysis, hematemesis, etc.) and ecchymosis on skin and mucosa were detected. In addition, no signs and symptoms of thrombosis (including extremity swelling, warmth, and pain, shortness of breath, and chest pain) were found. He was not febrile or in a septic state. Following hematology consultation, total abdominal and pelvic ultrasound were performed, and no abnormality was detected. The laboratory data are shown in Table 1. Liver and thyroid function tests, fibrinogen, retic count, serum ferritin, serum iron, and total iron-binding capacity were normal (Table 1). D-Dimer was negative. The PTT mixing test in 0 and 120 min was 47 and 42 sec, respectively,while the PTT of the patient at the beginning of the test was 81.4 sec. Therefore, an acquired coagulation factor deficiency was confirmed. Except for drug-induced coagulopathy, all other causes of coagulopathy, including liver and hematologic disorders, were ruled out based on the above data and the fact that he was not on a special diet. Due to financial constraints and a lack of clear signs or symptoms of bleeding or clotting, coagulation factor levels were not measured. The Adverse Drug Probability Scale (NARANJO) for rifampin was categorized as probable according to pharmacotherapy consultation [7]. Therefore, it was recommended to stop rifampin as a culprit and substitute it with the trimethoprim/ sulfamethoxazole 480 mg double strength BID. Additionally, a 2.5 mg single dose of oral vitamin K was given. The applied treatment resulted in a coagulation profile correction after four days. Table 2 shows the coagulation test values changed during inpatient.

This case report was approved by the Ethics Committee of Urmia University of Medical Sciences (Ethics code: IR.UMSU.HIMAM.REC. 1401.019). Written informed consent was obtained from the patient for the publication of this case report.

Table 2: Time series of coagulation values on the third admission

Date (2021)	12-05	12-06	12-07 (rifampin Stopped)	12-08 (vitamin K administered)	12-09	12-10	12-11	12-12
PT, sec	53.5	50.2	51.0	48.0	44.4	32.0	16.6	14.5
INR, index	4.42	4.13	4.20	4.12	3.63	2.57	1.29	1.12
PTT, sec	135.1	105.4	103.0	100.1	81.4	65.7	27.9	25.9

PT, prothrombin time; INR, international normalized ratio; PTT, partial thromboplastin time; sec, second

Discussion

Coagulopathy is an abnormality in the coagulation cascade, which is detected by various tests, for instance, fibrinogen level, clotting times (INR and PTT), etc. The causes and risk factors of coagulopathy are malnutrition, vitamin K deficiency, liver disease, DIC, septic state, and adverse effects of some medications. [8] In this case, we reported a man receiving rifampin with abnormal coagulation tests; however, he did not have any known disease associated with coagulopathy. In this patient, rifampin did not induce hepatotoxicity, thrombocytopenia, or DIC, but caused an elevation in INR. Normal liver function was confirmed with a proper level of albumin, aspartate transaminase and alanine transaminase.

Three mechanisms can explain this ADR: (1) It is widely accepted that antibiotics can disrupt gut flora and cause coagulopathy due to a lack of vitamin K. The prevalence of this type of coagulopathy is higher in critically ill patients and/or those on anticoagulants [10]. Vitamin K, mainly produced by the normal flora of the intestine [11], plays a central role in synthesizing clotting factors II, VII, IX, and X [12]. In this case, our patient had received a variety of antibiotics, which could have

disrupted the intestinal flora, resulting in diarrhea, abdominal cramps, and vitamin K deficiency; however, he did not have diarrhea. (2) Rifampin is a semisynthetic bactericidal agent [9] that is known as a potent liver enzyme inducer (CYP450), which results in interactions with metabolism, activation, and degradation of other medications and vitamins [10,11]. Therefore, rifampin-associated coagulopathy through liver enzyme induction may have occurred in this case. This mechanism significantly increases vitamin K degradation and the risk of deficiency. This idea stems from some studies and case reports on vitamin K deficiency in neonates and adults taking liver enzyme inducer anticonvulsants like phenobarbital and phenytoin [16-18]. (3) According to the literature, rifampin can interfere with vitamin K reactivation through inhibiting vitamin K epoxide reductase, which leads to a rise in demand for active vitamin K supplements for coagulation factors synthesis; therefore, decreased coagulation factors synthesis and abnormal coagulation tests can be detected [5].

Conclusion

To the best of our knowledge, there is little evidence in the literature supporting rifampin's ADR. Rifampin may disturb coagulation factor synthesis by causing vitamin K deficiency through eradicating intestinal flora and inhibiting vitamin K epoxide reductase. According to a theoretical concept, rifampin may increase the rate of vitamin K degradation by inducing hepatic cytochrome P450 enzymes.
We presented a middle-aged man with RA and brucellosis who had rifampin-induced vitamin K deficiency and abnormal INR and PTT tests, which were reversed by discontinuing rifampin and administering vitamin K.As a result, close monitoring of coagulation tests is advised in rifampin patients, particularly those with co-risk factors for inducing coagulopathy.

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Conflict of interests

There are no competing interests and no any personal or financial relationship.

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References

1- Katzung BG, Masters SB, Trevor AJ. Basic & clinical pharmacology. 2004.
2- Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. ***Chest*** 1991; 99(2):465-71. doi: 10.1378/chest.99.2.465.
3- Westphal JF, Vetter D, Brogard JM. Hepatic side-effects of antibiotics. ***J Antimicrob Chemother*** 1994; 33(3):387-401. doi: 10.1093/jac/33.3.387.
4- Shevchuk YM, Conly JM. Antibiotic-associated hypoprothrombinemia: a review of prospective studies, 1966-1988. ***Rev Infect Dis*** 1990; 12(6):1109-26.
5- Ishii F, Iizuka B, Nakanishi T, Nagasako K, Hayashi N. [Vitamin K deficiency syndrome caused by antituberculous agents]. ***Nihon Shokakibyo Gakkai Zasshi*** 1997; 94(6):389-97.
6- Castillo Almeida NE, Stevens RW, Gurram P, Rivera CG, Suh GA. Cefazolin and rifampin: A coagulopathy-inducing combination. ***Am J Health Syst Pharm*** 2021; 78(24):2204-08. doi: 10.1093/ajhp/zxab210.
7- Naranjo C, Busto U, Sellers E, Sandor P, Ruiz I, Roberts E. Naranjo ADR probability scale. ***Clin Pharmacol Ther*** 1981; 30:239-45.
8- Lavrentieva A, Depetris N, Kaimakamis E, Berardino M, Stella M. Monitoring and treatment of coagulation abnormalities in burn patients. an international survey on current practices. ***Ann Burns Fire Disasters*** 2016; 29(3):172-77.
9- Beloor Suresh A, Rosani A, Wadhwa R. Rifampin. In: *StatPearls.* StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC., Treasure Island (FL); 2022.
10- Anderson MS, Cote J, Liu Y, Stypinski D, Auger P, Hohnstein A, *et al*. Effects of Rifampin, a potent inducer of drug-metabolizing enzymes and an inhibitor of OATP1B1/3 transport, on the single dose

pharmacokinetics of anacetrapib. ***J Clin Pharmacol*** 2013; 53(7):746-52. doi: 10.1002/ jcph.97.

11- Baciewicz AM, Self TH. Rifampin drug interactions. ***Arch Intern Med*** 1984;144 (8):1667-71. doi: 10.1001/archinte.144.8. 1667.