

# Unusual Cause of Coagulopathy in a Child

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A 13-year-old girl diagnosed with progressive familial intrahepatic cholestasis type 2 during infancy and underwent internal biliary diversion at the age of seven, developed worsening pruritus in the last few weeks. At that time, she was on ursodeoxycholic acid 500 mg twice daily. Cholestyramine was added which showed no effect. Therefore, she was started on rifampicin 150 mg twice daily. Her baseline coagulation profile was normal with mildly elevated transaminases. Physical examination revealed an active, well-grown girl with generalized icterus. She had scratch marks over both forearms. She has no other peripheral stigmata of chronic liver disease. Abdominal examination revealed a surgical scar from the previous internal biliary diversion surgery. There was no palpable hepatosplenomegaly. Two weeks into treatment

with rifampicin, her pruritus improved dramatically. However, her coagulation profile was significantly deranged [Table 1]. Prothrombin time was 66 s (normal range: 10.5–12.7 s), activated partial thromboplastin time was 116 s (normal range: 25–37.7 s), and the international normalized ratio was 6.7 (normal range: 0.90–1.10). The detailed coagulation factor assay revealed a low level of vitamin K-dependent factors: factor II at 0.073 IU/mL (normal range: 0.61–1.04), factor VII at 0.085 IU/mL (normal range: 0.6–1.15), factor IX at 0.12 IU/mL; (normal range: 0.6–1.2), and factor X at 0.06 IU/mL (normal range: 0.5–1.17). Consent for publication was taken from the patient's guardians.

## Questions

1. What is your diagnosis?
2. How to rule out other possible differential diagnosis?
3. How would you manage this patient?

## Answers

1. Rifampicin-induced vitamin K deficiency coagulopathy.
2. Through thorough history and physical examinations and doing the necessary investigations to look for other possible causes. From history, our patient was not on anticoagulation medications, and she reported no traumatic injury to the liver. Other liver parameters were similar to the results of her previous investigations.
3. Ceasing rifampicin, giving parenteral vitamin K supplementation and fresh frozen plasma (FFP) when indicated is the way to manage such complications.

**Table 1:** The patient's liver chemistry and coagulation profile at the baseline and two weeks after starting her on rifampicin therapy.

Liver tests	Baseline	Two weeks after starting rifampicin
ALT (0–33U/L)	111	63
AST (0–32U/L)	199	66
ALP (59–254 U/L)	311	225
GGT (< 29 U/L)	62	67
Total protein (60–80 g/L)	70	76
Albumin (38–54 g/L)	40	40
Bilirubin (0–17 umol/L)	219	85
PT (10.5–12.7 s)	12.1	66
INR (0.92–1.08)	1.06	6.7
APTT (25–37.7 s)	35.4	116.6

ALT: Alanine transaminase; AST: Aspartate transferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; PT: prothrombin time; INR: international normalized ratio; and APTT: activated partial thromboplastin time.

## DISCUSSION

The patient's deranged coagulation was thought to be an adverse reaction to rifampicin, as it occurred after starting the drug. Rifampicin was ceased, and she received 10 mg of intravenous vitamin K and 300 mL of FFP, which was not necessarily indicated as she was not actively bleeding. The patient's coagulation profile normalized within 12 hours and remained normal on two weeks follow-up. The patient's pruritus improved and remains asymptomatic. She was continued on ursodeoxycholic acid 500 mg twice daily. Her coagulation profile has remained normal since then.

Rifampicin has been used to treat pruritus which does not respond to bile acid sequestrants.<sup>1,2</sup> The mechanism by which rifampicin alleviates pruritus is unknown but thought to be either as a result of induction of microsomal enzymes, which subsequently speeds the metabolism of endogenous pruritogenic compounds or secondary to inhibition of bile salt uptake by hepatocytes which can lead to reduction in bile salt mediated disruption of hepatocyte membranes.<sup>2</sup> Rifampicin-induced vitamin K-dependent coagulopathy is a rare adverse effect.<sup>3</sup>

Rifampicin has many adverse effects, including hepatotoxicity and disseminated intravascular coagulation.<sup>3</sup> Rifampicin-induced vitamin K-dependent coagulopathy, although rare, has been reported in the literature previously.<sup>3</sup> Two infants reported to develop rifampicin-induced vitamin K coagulopathy while on anti-tuberculous medications which improved with vitamin K supplementation.<sup>3</sup> The pathogenesis of rifampicin-induced vitamin K deficiency is due to multiple factors including alteration of gut flora which subsequently results in a reduction in vitamin K and induction of hepatic microsomal enzyme activity by rifampicin, which leads to degradation of vitamin K.<sup>1</sup> In our patient, one might argue that this coagulopathy might be

attributed to an interaction between rifampicin and ursodeoxycholic acid; however, there is no reported drug-drug interaction between the two drugs.

Vitamin K deficiency is common in cholestasis as it is a fat-soluble vitamin and requires bile for absorption.<sup>1</sup> Three adult patients with cholestatic liver disease developed vitamin K deficiency after receiving rifampicin for pruritus.<sup>1,4</sup> Their coagulopathy improved with parenteral vitamin K and ceasing rifampicin. One possible cause of deranged coagulation in our patient is the worsening of her underlying disease; however, other parameters of synthetic liver function tests like albumin and bilirubin improved or remained the same after initiating rifampicin.

This case highlights the importance of routine monitoring of coagulation profile in children getting rifampicin if they have risk factors predisposing them to vitamin K deficiency including liver disease, malabsorption syndromes, anticoagulation use, and prolonged courses of antimicrobials. Ceasing rifampicin, parenteral vitamin K supplementation, and FFP, when indicated, is the way to manage such a complication.

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### Disclosure

The authors declared no conflicts of interest.

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