

Unusual Cause of Coagulopathy in a Child

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A 13-year-old girl diagnosed with progressive familial intrahepatic cholestasis type 2 (PFIC2) during infancy and underwent internal biliary diversion at 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 150mg twice daily. 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 of 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 (PT) was 66 seconds (normal range: 10.5 - 12.7 s), Activated Partial Thromboplastin Time (APTT) was 116 seconds (normal range: 25 - 37.7 s) and the International Normalized Ratio (INR) was 6.7 (normal range: 0.90 - 1.10). The detailed coagulation factor assay revealed 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-1; (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.

Table 1: Liver chemistry and coagulation profile of the patient at the baseline after 2 weeks of starting her on rifampicin therapy.

| Liver test | 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 (< 29U/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 aminotransferase; ALP: Alkaline phosphatase; APTT: Activated Partial Thromboplastin Time; AST: aspartate aminotransferase; GGT: Gamma-glutamyl transferase; INR: International Normalized Ratio; PT: prothrombin time.

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 examination 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. From the investigations done, other liver parameters were similar to her previous results.
3. Ceasing rifampicin, giving parenteral vitamin K supplementation and FFP when indicated is the way to manage such complication.

Discussion

The patient's deranged coagulation was thought to be an adverse reaction to rifampicin, as it happened after starting the drug. Rifampicin was ceased, and she received 10 mg of intravenous vitamin K and 300 ml of fresh frozen plasma (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 2 weeks follow-up. The patient pruritus improved and she is still asymptomatic since then. She was continued on ursodeoxycholic acid 500 mg twice daily. Her coagulation profile remains normal since then.

Rifampicin has been used to treat pruritus that is not responding to bile acid sequestrants.^{1,2} 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 membranes². Rifampicin induced vitamin K-dependent coagulopathy is a rare adverse effect³

Rifampicin has many adverse effects including hepatotoxicity and disseminated intravascular coagulation³. Rifampicin induced vitamin K-dependent coagulopathy, although rare, has been reported in the literature previously.³ Two infants reported to develop rifampicin induced vitamin K coagulopathy while on anti-tuberculous medications which improved with vitamin K supplementation.³ The pathogenesis of rifampicin-induced vitamin K deficiency is due multiple factors including alteration of gut flora which subsequently results in reduction in vitamin K and induction of hepatic microsomal enzyme activity by rifampicin which leads to degradation of vitamin K.¹ 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.¹ Three adult patients with cholestatic liver disease developed vitamin k deficiency after receiving rifampicin for pruritus.^{1,4} 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 complication.

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