

A Rare Adverse Effect of a Commonly Used Drug – Rifampicin-induced Disseminated Intravascular Coagulation and Acute Kidney Injury**Dr Kandan Balamurugesan¹, Dr Abdul Hamide², Dr Vadivelan M²***1 - Additional professor, Department of Medicine, JIPMER, Puducherry**2- Professor Department of Medicine, JIPMER, Puducherry***SUMMARY**

A 65-year-old male was brought with a three-day history of pain abdomen, vomiting, and oliguria. On examination, he had hypotension icterus and hepatomegaly. Routine investigations revealed elevated creatinine, bilirubin, and thrombocytopenia with coagulopathy.

He was treated with intravenous fluids and antibiotics considering the possibility of infection-related disseminated intravascular coagulation (DIC) and required haemodialysis for renal failure. Blood investigations and imaging ruled out infective causes for DIC.

The patient revealed an intake of rifampicin for furunculosis three days back and a similar intake of rifampicin two years previously. Hence the possibility of rifampicin-induced DIC was considered. The patient improved clinically, lab parameters normalized, and he was discharged after 2 weeks without the requirement for further dialysis.

Rifampicin-induced DIC is a rare phenomenon, that has been attributed to an immuno-allergic reaction. This case highlights the need to consider all the possible causes of DIC, including a detailed drug history.

BACKGROUND

Disseminated intravascular coagulation (DIC) is an acquired syndrome characterized by widespread activation of the coagulation cascade. It can be caused by several infectious and non-infectious insults.[1] The treatment of DIC is largely supportive with great emphasis being given to treat the underlying cause. Identification of a cause of DIC, therefore, becomes vital in the management of patients.

Rifampicin is a commonly prescribed antibiotic and is used in the management of conditions such as tuberculosis, leprosy and furunculosis. DIC secondary to rifampicin administration is a rare phenomenon and had previously been reported only in a handful of case reports.[2,3] This report describes, DIC which occurred in a patient who was prescribed rifampicin for furunculosis. It emphasizes the need to carefully examine a patients' medication history and to consider alternative causes while managing a patient with DIC. Future avoidance of drugs and toxins triggering DIC may prevent this potentially fatal complication.

CASE PRESENTATION

A 65-year-old poet was brought with complaints of abdominal pain, multiple episodes of non-bilious vomiting and decreased urine output for 3 days. He was previously healthy apart from a history of furunculosis for which he was on topical therapy, and he had no history of recent travel.

At presentation, he was found to be hypotensive with a blood pressure of 80/60mmHg. He was icteric and abdominal examination revealed mild right hypochondrial tenderness. His sensorium was normal and he had no bleeding manifestations.

Routine blood investigations at presentation revealed acute kidney injury with a creatinine of 3.8mg/dl, elevated total bilirubin of 7.9mg/dl with a direct fraction of 4.03mg/dl, and elevated AST (289IU/L) and ALT (69IU/L). His complete blood count revealed mild leucocytosis of 12350/mm³ with a neutrophilic predominance and thrombocytopenia of 100,000/mm³. Coagulation

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studies showed an elevated prothrombin time with an INR of 3, increased fibrinogen degradation products and D Dimer. International Society on Thrombosis and Haemostasis (ISTH) score for DIC was calculated as 6 which was suggestive of overt DIC.[4]

Given the presentation and investigations, he was provisionally diagnosed as sepsis with multi organ dysfunction syndrome and DIC. As workup for sepsis, 2 sets of blood cultures were sent which were sterile. Serology for scrub typhus, leptospirosis, dengue and hepatitis A, B and E viruses were negative. Abdominal ultrasound and contrast CT were normal, and serum procalcitonin was less than 0.05ng/dl which ruled out bacterial sepsis.

DIFFERENTIAL DIAGNOSIS

Common infectious causes of DIC like scrub typhus and leptospirosis were considered, however serology for both were negative. An abdominal focus of sepsis was also considered and imaging including abdominal ultrasound and contrast CT were normal. Furthermore, sterile blood cultures and normal serum procalcitonin levels ruled out bacterial sepsis.

Having ruled out infectious causes of DIC, we considered other causes including possible drug reactions. Careful retaking of his history revealed that he had taken 600mg of rifampicin on the day of onset of symptoms. He had been treated with rifampicin for the same indication 2 years previously.

TREATMENT

He was initially resuscitated with IV fluids and empirically treated with intravenous ceftriaxone and azithromycin. Antibiotics were discontinued after ruling out sepsis as the cause of DIC.

He had progressive decline in renal function with anuria for which he was initiated on haemodialysis, five days after hospitalisation, and he received 4 sessions of haemodialysis during hospital stay. By the 11th day of hospitalization, his urine output improved, and creatinine values showed a declining trend (Figure 1). He did not give consent for a renal biopsy.

His platelet counts, coagulation profile and liver function tests were monitored during hospital stay (Figure 2,3,4). During the initial five days of hospitalization, his platelet count dropped (Figure 2). However, he did not require any transfusion of blood products and platelet counts recovered spontaneously. His INR and liver function tests

normalised by day 5 of hospitalisation (Figure 3,4).

OUTCOME AND FOLLOW-UP

The patient was discharged asymptomatic after 2 weeks of hospitalisation. At the time of discharge, platelet count, liver function tests and coagulation profile had been normalised. His serum creatinine showed an improving trend and dialysis was discontinued prior to discharge. At follow up 2 weeks after discharge, his serum creatinine value normalised.

He was advised to avoid taking rifampicin in future and had no further similar episodes at follow up 6 months later.

DISCUSSION

Rifampicin is a synthetic analogue of rifamycin, which was first developed in the 1950s and entered clinical application in 1968. It has since become a widely used antibiotic and a mainstay in the management of tuberculosis and leprosy.[5] In addition, it is also found useful in the management of brucellosis, and the eradication of *Staphylococcus aureus*.[6,7]

The common adverse reactions associated with rifampicin include gastrointestinal effects such as nausea, vomiting and diarrhoea, central nervous system effects such as headache and fever, and dermatologic effects such as rash, itching and flushing. The other commonly described adverse effect of rifampicin is hepatotoxicity, which is commonly seen in patients with pre-existing liver disease or those taking other hepatotoxic drugs.[8] In contrast, hematologic adverse effects of rifampicin such as red cell aplasia, leukopenia and agranulocytosis, thrombocytopenia, and disseminated intravascular coagulation are much rarer.

The Scientific and Standardization Committee (SSC) on DIC of the International Society on Thrombosis and Haemostasis (ISTH) defined DIC as an acquired syndrome characterized by the intravascular activation of coagulation with a loss of localization arising from different causes.[4] DIC is a frequent complication of a systemic inflammatory response syndrome SIRS and can be caused by infectious insults such as sepsis, and non-infectious insults such as trauma, severe pancreatitis and malignancy. Other important underlying DIC-associated disorders include obstetric complications such as amniotic fluid embolism, placental abruption, pre-eclampsia, and postpartum haemorrhage.

[9]Epidemiologic studies have demonstrated that sepsis or infection is the underlying condition in 30–51% of patients with DIC and trauma or major surgery is the cause in up to 45% of patients.[10] In all these conditions, there is increased expression of tissue factor secondary to inflammation or malignant cells.[9] This in turn leads to activation of platelets and causing disseminated thrombosis and consumptive coagulopathy.

Drug induced DIC has been described in several commonly used drugs including heparin, methotrexate, paracetamol and vincristine.[11] While the exact mechanism is unknown, such drug related DIC have been attributed to hypersensitivity reactions to the drugs. Similarly, rifampicin induced DIC has been previously described in the context of an immuno-allergic reaction.[12]

These reactions manifest with abdominal pain and vomiting within few hours of ingestion of the drug followed by fever and hypotension. Renal dysfunction, intravascular haemolysis and DIC seen in laboratory investigations often lead to a misdiagnosis of sepsis.

These reactions have been attributed to IgG and IgM antibodies which act against cells expressing blood group antigen I, causing damage to red blood cells, platelets, and renal tubular epithelial cells.[13] DIC due to rifampicin is a clinical diagnosis and it has been confirmed by antibodies in only two previously reported cases and post-mortem in another case report.[12,13,14] Exposure to even a single dose of rifampicin may induce sensitization and result in immuno-allergic reactions upon repeat exposure. In one interesting report by Havey et al. the patient had recurrent episodes of DIC with each dose of rifampicin as part of an intermittent dosing regimen.[12]

Some previous authors have postulated that daily administration of rifampicin confers immunologic tolerance, thus leading to lower incidence of adverse reactions. In line with this, the majority of immune-allergic reactions to rifampicin have been described in intermittent dosing schedules.[12,13,14] barring case reports by Chen et al. and Fujita et al. in who's patients were being given daily dosing of rifampicin for tuberculosis [2,15]. In both these cases, the patient presented with overt bleeding manifestations including epistaxis, haematuria, and purpura. In contrast the other reported cases had no clinical signs of DIC. The

reason for such difference requires further study.

While most of the patients with rifampicin induced DIC recovered with cessation of the drug, there have been 3 recorded fatalities.[14] Most of the described patients were managed conservatively, but a few required blood transfusions or dialysis. Another interesting point to be noted is that, in the majority of published literature, rifampicin was used for the treatment of tuberculosis, leprosy or brucellosis.[14] However, in our case rifampicin was used for the eradication of staphylococcus aureus in furunculosis. This case highlights an important though rare adverse effect of rifampicin. Education of physicians is essential to prevent this potentially fatal adverse effect.

LEARNING POINTS

- Rifampicin-induced DIC is a rare adverse effect which occurs unpredictably and irregularly.
- DIC can occur following regular as well as intermittent usage of rifampicin.
- A detailed drug history, early recognition of signs, discontinuation of the offending drug and supportive treatment are key to effective management of this condition.
- Educating physicians to consider this rare adverse effect can aid in the early recognition and appropriate management of this potentially fatal condition.

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Figure 1: Time plot showing the trend of creatinine during hospital stay

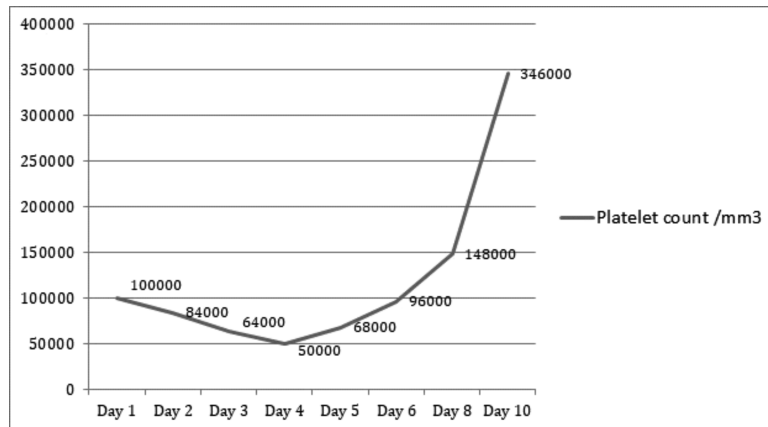


Figure 2: Time plot showing the trend of platelet count during hospital stay

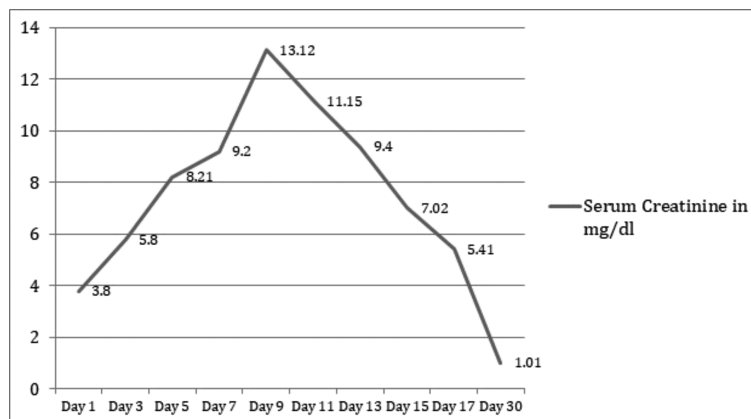


Figure 3: Time plot showing the trend of INR during hospital stay

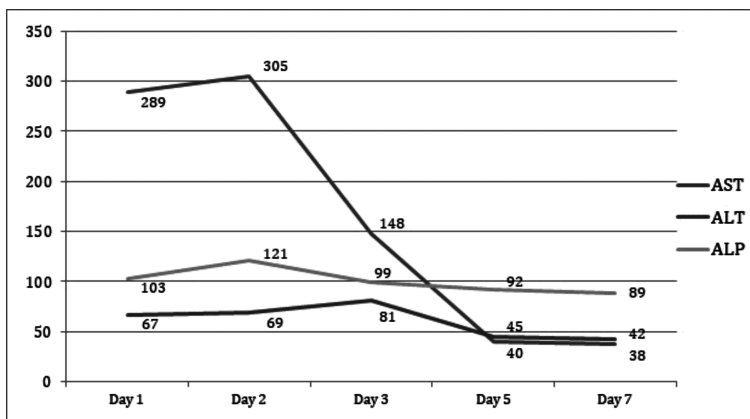
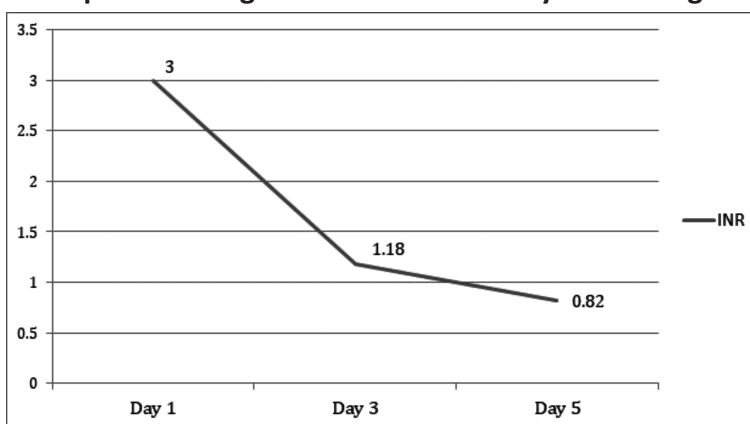


Figure 4: Time plot showing the trend of liver enzymes during hospital stay




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