

Case Report

# Acute Interstitial Nephritis, Hepatitis, Hemolysis Due to Rifampin: A Case Report

Parvin Soltani<sup>1</sup>, Nasser Saidi<sup>1</sup>, Farshid Haghverdy<sup>1</sup>, Mojtaba Ahmadlou<sup>2</sup>

<sup>1</sup>Department of Nephrology, Arak University of Medical Sciences, Arak, Iran; <sup>2</sup> Clinical Research Unit, Arak University of Medical Sciences, Arak, Iran

**Key words:** Rifampin, Interstitial Nephritis, Hepatitis, Hemolysis

## ABSTRACT

Here we report a patient suffered from nephrotoxicity, hepatotoxicity and hemolysis due to rifampin. In this case, nephrotoxicity, hemolysis and hepatitis presented simultaneously which was not reported previously. The patient was a 71 yr old woman treated with rifampin in 2014. One week after the treatment, the patient had fever and chills, weakness, nausea, vomiting, generalized abdominal pain, constipation, jaundice, altered urine color and anuria. Physical examination revealed lethargy, decreased lung sounds, bilateral fine crackles, abdominal distention, positive shifting dullness, 2+ lower extremities edema and generalize icterus. Liver and renal function tests were impaired.

The patient became severely ill. Immunological and virology tests were normal. Inflammatory indicators were increased and CBC was impaired. Jugular access was prepared for hemodialysis. The patient was hemodialyzed and had packed cell infusion. Laboratory tests returned to normal and her general condition improved. After discontinuation of rifampin, hemodialysis and blood transfusion, all the symptoms gradually were relieved and no other treatment was needed. In these patients in addition to hepatic damage, nephrotoxicity and hemolysis should also be considered and CBC and renal function tests must be evaluated. *JOURNAL OF IRANIAN CLINICAL RESEARCH 2015;1(2):54-57*

## INTRODUCTION

Rifampicin has been associated with adverse reaction such as nephrotoxicity, sometimes resulting in acute renal failure, hemolysis and hepatotoxicity. Hemolysis and febrile episodes were associated with rifampicin dependent antibodies in the serum [1].

## MATERIALS AND METHODS

In 2014, a 71 yr old woman referred to Vali-Asr hospital of Arak University of medical sciences was diagnosed as having brucellosis and was being treated with doxycycline 100 BD and rifampin 600 mg daily. One week after the commencement of treatment she developed fever, weakness, headache, decreased appetite, nausea and vomiting, generalized abdominal

pain (more severe in right upper quadrant), constipation, yellowish skin and sclera, orange urine color, decreased urine output, oliguria and then anuria. In physical examination, Bp=100/80 mmgh and T=37.2 °C, the patient was ill, JVP was elevated, sclera, skin of face and extremities was icteric.

## RESULTS

The examination of heart was normal and lung auscultation revealed fine crackles at base of lungs. The abdomen was distended and with shifting -dullness and the extremities were edematous (Table1).

Correspondence: Soltani, PHD in Nephrology – Assistance professor, Amir-Almomenin Hospital, Arak University of Medical Sciences, Arak, Iran. Email: p.soltani@arakmu.ac.ir.

**Table 1.** Changes of BUN, Cr, Hb, AST, ALT, Bil.(Total and Direct)

| Date            | 3/27 | 4/1  | 4/2  | 4/4 | 4/6 | 4/10 | 4/18 | 5/8  | 7/23 |
|-----------------|------|------|------|-----|-----|------|------|------|------|
| <b>BUN</b>      | 107  | 78   | 75   | 43  | 26  | 52   | 54   | -    | -    |
| <b>Crea</b>     | 7.1  | 7    | 7    | 5.5 | 4.7 | 4.2  | 2.8  | 1.47 | 1.1  |
| <b>Hb</b>       | 6.9  | 10.4 | 10   | 9   | 7.9 | 10.2 | 10.3 | 10   | 14.5 |
| <b>AST</b>      | 132  | 72   | 29   | -   | -   | -    | -    | 26   | 25   |
| <b>ALT</b>      | 328  | 100  | 40   | -   | -   | -    | -    | 36   | 27   |
| <b>B.Total</b>  | 41.9 | 39.4 | 31.8 | 8.5 | -   | 4.6  | 3.5  | 1.29 | 0.44 |
| <b>B.Direct</b> | 22.3 | 22.1 | 21.4 | 4.6 | -   | 2.4  | 1.99 | 0.72 | 0.15 |

LDH= 3945

CBC: WBC=36200

RBC=2.3\*10<sup>6</sup>

Hb=6.9 mg/dl

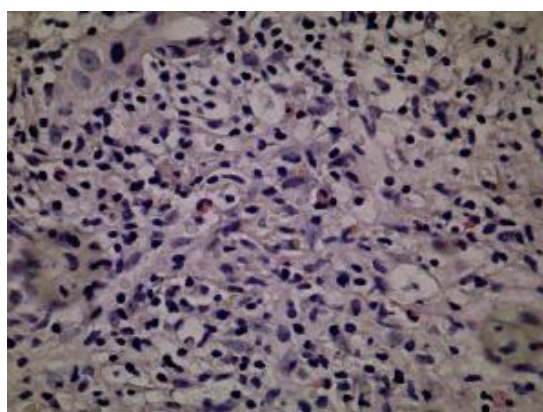
U/A was abnormal and RBC, WBC and epithelial cells were seen. Immunological and virology evaluation were normal and urine culture was negative. ESR = 101 and anti GBM Ab, wright, coombs wright and 2ME were negative. In abdominal ultrasonography, there was no organomegally but mild prehepatic ascities, enlargement of kidneys with increase cortical echogenicity and decreased corticomedullary differentiation (CMD) were reported.

During hospitalization the blood pressure was between 120/80-138/90 mmHg. In the second and third weeks of hospitalization, the patient

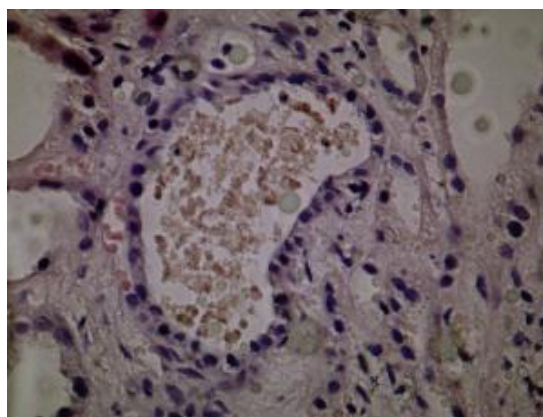
had two episode of fever that ameliorated with ceftriaxone.

The patient was dialyzed eight times, and 5 units of packed cells were infused in the course of hospitalization. Kidney biopsy was performed after patient became stable. Light microscopic examination revealed allergic interstitial nephritis with tubular necrosis and immunofluorescence microscopic examination reported local mesangial deposition of IgM but no IgG, IgA and IgE (Figure 1-2).

The patient was hospitalized for 3 weeks and was discharged in good condition. She had no more problems in follow-up visits.



**Figure 1.** Acute interstitial nephritis. Intense infiltration of lymphocytes plus scattered eosinophils, associated with destruction of tubular units



**Figure 2.** Acute tubular necrosis. The lumen contains a bilirubin cast. Adjacent tubules also disclose degenerative and regenerative changes. Lab data examination was performed in one and three months after discharge; BUN and creatinine were decreased, ALT /AST, total and direct bilirubin, ESR and WBC, Hb and RBC were in normal range and the patient was in good condition.

## DISCUSSION

In this study, we described a patient who after consuming rifampin suffered from nephrotoxicity, hepatotoxicity and hemolysis. In typical presentation, within minutes to hours after rifampin ingestion, dizziness, chills, fever, myalgia, nausea, vomiting, lumbar pain, and a protracted course of oligoanuric renal failure that usually requires dialysis therapy develops [2-3].

Several isolated cases of acute renal failure (ARF) following rifampin therapy have been reported [3-8]. Some pathogenic mechanisms for the renal failure have been proposed, including intravascular hemolysis with hemoglobinuria and its consequent nephrotoxicity. Although intravascular hemolysis with hemoglobinuria may play a role, it is not uniformly present [3, 9-10]. Being mostly tubular in nature, a variety of renal lesions including acute tubular necrosis, tubulointerstitial nephritis, light chain proteinuria, and nonspecific glomerulonephritis have been reported [10].

In the nineteen-seventies, the first case report of AIN was published. In patients receiving rifampin for 21 to 71 days, renal biopsies revealed interstitial infiltrates. After discontinuation of drug, renal function usually recovered. Due to this temporal relationship, an immune-mediated or direct nephrotoxicity of rifampin was postulated [11-12].

The management of drug-induced AIN includes immediate discontinuation of the offending agent and the use of corticosteroids [13-14]. However, in our case we refrained from corticosteroids administration.

Various mechanisms of rifampicin-associated ARF have been postulated [15] and it is difficult to determine the incidence of ARF among all patients treated with it. The mechanism of renal damage is thought to be due to allergic reactions to rifampicin or one of its metabolites that cause allergic interstitial nephritis. Immunogenicity of rifampicin has been demonstrated by the presence of rifampicin-dependent antibodies in serum, especially IgM [15-16], but the relationship between anti-rifampicin antibodies and the development of renal failure is not clear [17].

Rothwell and Richmond described one case of renal failure and jaundice occurring in a patient taking rifampicin intermittently (three doses of 450 mg over five weeks) for tuberculosis [18]. A Medline literature search identified only two previous cases of hepatitis occurring in patients treated with rifampicin in the absence of other hepatotoxic agents. Bachs et al. described two cases of rifampicin hepatitis in women treated for PBC [19].

Rifampin may cause hemolysis and hemolytic anemia in less than 1% of people [20]. Hematological side effects include: thrombocytopenia, leukopenia, hemolytic anemia in less than 1% of patients and hemolysis has been described as part of an immune-mediated reaction which generally occurs after interruptions in therapy [8].

In this patient, one week after the commencing rifampin, BUN and Cr increased and LFT became abnormal. In addition, RBC mass and Hb reduced. After stopping rifampin and hemodialysis and blood transfusion, all the symptoms relieved and the patient became stable. Kidney biopsy revealed allergic interstitial nephritis with tubular necrosis, and

in immunofluorescence study, local mesangial IgM deposit was reported. In this case, all symptoms of nephrotoxicity, hemolysis and hepatitis occurred simultaneously that have not been previously reported.

#### ACKNOWLEDGEMENTS

We are thankfully for Arak University of Medical Sciences Research Department

#### REFERENCES

- Lakshminarayan S, Sahn SA, Hudson LD. Massive haemolysis caused by rifampicin. *BMJ*. 1973;2(5861):282-3.
- Diamond J, Tahan S. IgG-mediated intravascular hemolysis and nonoliguric acute renal failure complicating discontinuous rifampicin administration. *Nephron*. 1984;38(1):62-4.
- Covic A, Goldsmith D, Segall L, Stoicescu C, Lungu S, Volovat C, et al. Rifampicin-induced acute renal failure: a series of 60 patients. *Nephrology Dialysis Transplantation*. 1998;13(4):924-9.
- Criel A, Verwilghen R. Intravascular haemolysis and renal failure caused by intermittent Rifampicin treatment. *Blut*. 1980;40(2):147-50.
- Gupta A, Sakhuja V, Gupta KL, Chugh KS. Intravascular hemolysis and acute renal failure following intermittent rifampin therapy. *Int J Lepr*. 1992;60:185-8.
- Sefer S, Ivanusa M, Kes P, Ratković-Gusić I, Vasilj D. [Acute renal failure, intravascular hemolysis and toxic hepatitis caused by repeated use of rifampicin (case report)]. *Lijecnicki Vjesnik*. 1998;121(4-5):126-8.
- Levine M, Collin K, Kassen BO. Acute hemolysis and renal failure following discontinuous use of rifampin. *Ann Pharmacother*. 1991;25(7-8):743-4.
- Tahan SR, Diamond JR, Blank JM, Horan RF. Acute hemolysis and renal failure with rifampicin-dependent antibodies after discontinuous administration. *Transfusion*. 1985;25(2):124-7.
- Conen D, Blumberg A, Weber S, Schubothe H. [Hemolytic crisis and acute kidney failure from rifampicin]. *Schweizerische Medizinische Wochenschrift*. 1979;109(15):558-62.
- De Vriese AS, Robbrecht DL, Vanholder RC, Vogelaers DP, Lameire NH. Rifampicin-associated acute renal failure: pathophysiologic, immunologic, and clinical features. *Am J Kidney Dis*. 1998;31(1):108-15.
- Power D, Russell G, Smith F, Simpson J, MacLeod A, Friend J, et al. Acute renal failure due to continuous rifampicin. *Clinical Nephrol*. 1983;20(3):155-9.
- Gabow PA, Lacher JW, Neff TA. Tubulointerstitial and glomerular nephritis associated with rifampin: Report of a case. *JAMA*. 1976;235(23):2517-8.
- Rossert J. Drug-induced acute interstitial nephritis. *Kidney Int*. 2001;60(2):804-17.
- Muthukumar T, Jayakumar M, Fernando EM, Muthusethupathi MA. Acute renal failure due to rifampicin: a study of 25 patients. *Am J Kidney Dis*. 2002;40(4):690-6.
- Carro MB, Rozas LP, Esteban MJ, Otero GA, editors. Acute kidney failure (AKF) and hemolysis secondary to accidental discontinuous treatment with rifampicin. *Anales de Medicina Interna (Madrid, Spain)*: 1984; 1991.
- Abu-Romeh S, Huraib S, Quadri M, Memish Z, Al-Mahmood S, Abdulla A, et al. Rifampicin-Induced Acute Renal Failure: A Case Report. *Saudi J Kidney Dis Transplant*. 1996;7(4):401.
- Gangadharam PR. Isoniazid, rifampin, and hepatotoxicity. *Am Rev Respiratory Dis*. 1986;133(6):963-5.
- Rothwell D, Richmond D. Hepatorenal failure with self-initiated intermittent rifampicin therapy. *BMJ*. 1974;2(5917):481-2.
- Bachs L, Parés A, Elena M, Piera C, Rodés J. Effects of long-term rifampicin administration in primary biliary cirrhosis. *Gastroenterology*. 1992;102(6):2077-80.
- Allen R, Almond S, Caiolsa S. Rifampin. *Drug Intell Clin Pharm*. 1971;5:364-5.