Rifampicin-induced nephrotoxicity in a tuberculosis patient

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1. Introduction

Rifampicin is a commonly used and effective drug to treat tuberculosis (TB). Although rare (occurring in 0.1% of patients with tuberculosis), rifampicin-induced acute renal failure may occur as a complication during treatment [1]. Many studies report that this complication is most common in cases where the drug is re-administered or used intermittently [2–4]. The outcome is usually favorable after discontinuation of the drug, with 96% of patients achieving full recovery within 90 days from onset of renal injury [2]. According to the American Thoracic Society guidelines, physicians are not currently required to monitor renal function during the course of TB treatment unless the patient is at high risk for hepatic or renal abnormalities [5]. In the following report, we describe a patient diagnosed with pulmonary tuberculosis who developed rifampicin-induced renal toxicity while on anti-tuberculosis therapy.

2. Case report

A 38 year old Hispanic male from Central America residing in the United States was seen with complaints of productive cough, fever, night sweats, weight loss of 50 pounds, anorexia and fatigue. These symptoms started three months prior to treatment and gradually progressed. The chest radiograph revealed airspace and interstitial opacities in bilateral upper lobes, more extensive on the left, with cavitation and left tracheal deviation (Fig. 1). The clinic physician, who was from a tuberculosis-endemic country, suspected tuberculosis and immediately referred him to the Arkansas Department of Health.

The T Spot TB (Oxford Immunotec Inc., Marlborough, MA) test was negative, sputum smears were 4+ and the GeneXpert MTB-Rif assay (Cepheid Inc., Sunnyvale, CA, USA) was positive and showed no rifampicin resistance. The patient was initiated on treatment with isoniazid, rifampicin, pyrazinamide and ethambutol daily with continued use of any other medications (including over the counter hepatotoxic medications like Tylenol® etc.) and a screen for hepatitis A, B, and C viruses was negative. The patient’s liver enzymes returned to baseline two weeks after stopping therapy. Pyrazinamide-related hepatotoxicity was suspected and hence he was re-challenged with isoniazid after 12 days, rifampin was introduced after 14 days and ethambutol after 16 days of stopping medications. The patient noted mild nausea without vomiting and a slight increase in enzymes was noted (AST 102 and ALT 53) eight days after re-introduction of rifampin. Medications were held for 3 days and then restarted. He tolerated this regimen without toxicity during the next 7 weeks. Culture was positive for Mycobacterium tuberculosis (MTB) complex, and sensitivities later showed pyrazinamide resistance, making us suspect infection with M. bovis. Our public health laboratory reports cultures as MTB complex (M. tuberculosis, M. bovis, M. microti, M. africanum) and if
Table 1
Patient’s renal function during course of treatment.

| Date       | Normal range | Renal function | Liver function |
|------------|--------------|----------------|----------------|
|            | Creatinine (0.57–1.0) | eGFR (>59) | BUN (6–20) | AST (0–40) | ALT (0–32) | T. bilirubin (0.0–1.2) |
| August 18  | 0.64         | 111           | 15            | 41          | 28          | 0.4               |
| 29         | 0.65         | 123           | 12            | 101         | 73          | 0.3               |
| September 3| 0.54         | 133           | 12            | 118         | 70          | 0.3               |
| 8          | 0.5          | 137           | 9             | 68          | 69          | 0.3               |
| 11         | 0.5          | 137           | 12            | 53          | 53          | 0.3               |
| 17         | 0.64         | 124           | 14            | 46          | 35          | 0.4               |
| 19         | 0.54         | 133           | 11            | 44          | 32          | 0.6               |
| October 2  | 0.51         | 136           | 9             | 56          | 38          | 0.3               |
| November 10| 2.45         | 32            | 22            | 26          | 10          | 0.2               |
| 12         | 2.92         | 26            | 24            | 23          | 10          | 0.2               |
| December 2 | 1.66         | 52            | 19            | 29          | 20          | 0.2               |
| 8          | 1.61         | 53            | 15            | 40          | 21          | 0.3               |
| March 20   | 1.10         | 85            | 15            | 30          | 23          | 0.3               |
| 27         | 1.09         | 86            | 13            | 31          | 19          | 0.3               |
| April 3    | 1.04         | 91            | 13            | 38          | 24          | 0.3               |
| 24         | 0.96         | 100           | 12            | 38          | 23          | 0.3               |
| June 25    | 0.91         | 107           | 7             | 31          | 24          | 0.4               |
| September 10| 0.86        | 109           | 13            | 27          | 27          | 0.2               |

Fig. 1. Chest radiograph at initial presentation.

As a public health clinic, we have limitations on tests and procedures that we can perform. A renal biopsy and/or kidney-specific tests could not be performed due to financial and contractual restrictions.

3. Discussion

Although uncommon, rifampin is the most frequent antituberculous medication associated with acute interstitial nephritis [6]. Adverse reactions associated with rifampin usually occur in patients who have either previously taken the drug or receive intermittent treatment [7–9]. In a retrospective study done between the years 1995 and 2007, 41 patients had a confirmed diagnosis of acute interstitial nephritis. All patients received an intermittent regimen of anti-tuberculous therapy containing rifampin [9]. This association of intermittent or previous exposure is hypothesized to be related to rifampicin’s ability to produce an immune response, which eventually leads to cell destruction [7]. It is suggested that rifampicin functions as a molecule that, when bound to proteins, elicits an immune response by creating anti-rifampicin antibodies [4]. Consequently, upon
re-exposure to rifampicin the patient’s body forms drug antibody complexes which lead to cell damage. In a study conducted on 25 patients, it was found that the immune complexes lead to glomerular endotheliosis and cellular destruction which results in tubular injury and a decrease in renal function [8].

Acute renal injury related to rifampin is usually a clinical diagnosis. Most reports or series do not include a pathological diagnosis. Beck and Salant note that when renal failure occurs in the setting of exposure to an offending agent, biopsy is generally not required for diagnosis [10]. When biopsy is performed the most common findings are acute interstitial nephritis or acute tubular necrosis [9,11]. Schubert’s series from South Africa included only patients with biopsy-proven acute interstitial nephritis who were on chemotherapy for tuberculosis. In this study of 41 patients, acute interstitial infiltrate was present in all cases but acute tubular necrosis was also noted in 90%. Other less common pathological associations noted with rifampin induced kidney disease include diffuse proliferative crescentic glomerulonephritis [8].

Acute interstitial nephritis is the immune-mediated cause of acute renal failure associated with rifampin. Although the prognosis of acute interstitial nephritis is good (1.6% mortality), it remains a serious complication that can progress to Fanconi syndrome, a proximal renal tubule defect leading to malabsorption of phosphorus, bicarbonate, sodium, potassium, glucose, and amino acids, which results in various symptoms including bone pain and fracture, fatigue, and muscular weakness [12]. Despite the predicted etiology of our patient’s acute renal failure, rifampin-associated acute interstitial nephritis was not proven. Acute kidney injury was noted incidentally which may be a common presentation [10]. He did not have the more commonly reported symptoms of fever, nausea, vomiting or elevated liver enzymes that some series note [8,9]. Interestingly, he initially presented with mild hepatitis and nausea, but these symptoms resolved prior to finding the elevated creatinine. He did not have eosinophilia and eosinophils were not found in the urine. No white or red blood cells were found in the urine sediment. A renal biopsy was not done.

Although controversial, there is some evidence suggesting that corticosteroid therapy accelerates renal recovery in patients diagnosed with drug-induced interstitial nephritis [13]. A retrospective study examined 61 patients with biopsy-proven drug-induced acute interstitial nephritis [13]. The patients were divided into two groups, with the first group (N = 52) receiving steroid treatment and the second group (N = 9) receiving no steroid treatment. Of the two groups, the outcome of the steroid group after treatment was significantly better, with the final serum creatinine representing a return to normal renal function. Without treatment, 44% of the non-steroid group progressed to chronic dialysis. The steroid group was further divided into two subgroups: one showed complete recovery to baseline renal function, while the other showed partial recovery.

The study concluded that there was a correlation between the delay in the onset of steroid treatment and final serum creatinine level [13]. Conversely, in another study of 42 patients with acute interstitial nephritis, 26 were given steroid therapy while 16 were not treated [6]. The study revealed no significant difference in serum creatinine levels between the two groups after one, six, and twelve months of follow up.

No randomized trial is available to determine the usefulness of corticosteroid therapy to guide clinicians. Further observational studies will assist providers making clinical decisions regarding these patients, but for now the approach is individualized and based on provider experience and preference.

The outcome of rifampicin-induced acute renal injury is favorable in a majority of cases; early detection of this condition should be considered a priority. One study suggests testing patients with previous exposure to rifampicin for hematuria during the early stages of treatment of tuberculosis in order to detect rifampicin toxicity [9]. If detected early, the drug can be discontinued, thereby preventing further damage to the patient’s renal system.

4. Conclusion
Rifampicin-induced renal toxicity is a rare but serious adverse effect amongst patients on anti-tuberculous therapy. Most patients recover their renal function upon discontinuation of the offending agent. The use of corticosteroids is controversial and more studies are needed to demonstrate the clinical benefit of using this therapy.

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