CASE REPORT

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Rifampicin-induced acute tubulointerstitial nephritis during pulmonary tuberculosis treatment: A case report

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Abstract

Drug-induced tubulointerstitial nephritis is an uncommon complication in patients on anti-tuberculosis therapy that can lead to permanent kidney damage. Rifampicin is the most offending drug. We report a case of a 41-years old man being treated for pulmonary tuberculosis and presenting with tubulointerstitial nephritis associated with rifampicin. We focus on diagnosis features and therapeutic challenges.

KEYWORDS
acute kidney injury, acute renal failure, acute tubulointerstitial nephritis, rifampicin, tuberculosis

INTRODUCTION

Tuberculosis (TB) is a global health problem that accounted for 1.5 million deaths in 2020.[1] Prompt treatment remains the most effective intervention to control the spread of the disease.

Adverse reactions to first-line anti-TB medications compromise drug adherence and worsen anti-TB treatment outcomes. Rifampicin (RIF) is the key drug in the treatment of TB. It has often been associated with hepatotoxic response and gastro enteropathy.[2] Only a few studies have investigated RIF-induced nephrotoxicity.

We present a case of RIF-induced acute renal failure due to acute tubulointerstitial nephritis (ATIN), successfully managed with second-line anti-TB treatment.

CASE REPORT

A 41-years old patient was admitted for acute renal failure. He has been diagnosed with a drug susceptible active pulmonary TB affecting both lungs. The initial diagnostic evaluation included a sputum smear examination for acid-fast bacilli (AFB) using Ziehl-Neelsen staining. The sputum smear results were positive for AFB, confirming the presence of active pulmonary tuberculosis. The patient was receiving first-line anti-TB drugs daily for 40 days according to the four-drug fixed-dose combination regimen: RIF (450 mg), isoniazid (INH) (225 mg), pyrazinamide (PZA) (1200 mg), and ethambutol (EMB) (825 mg). The patient reported taking the medication regularly at a dose of 4 tablets per day. No exposure to other medication was reported. The patient's renal function was normal before TB treatment.

On admission, the patient presented with asthenia and fatigue. A physical examination revealed a body weight of 43 kg, a body temperature of 36.7°C, a heart rate of 110 beats per minute, a blood pressure of 113/68 mmHg, and an oxygen saturation of 96% on room air. Crackles in the left lung were noted. The sputum smear results were still positive for AFB. Chest x-ray (Figure 1) screening showed bilateral pulmonary infiltrates and cavitary lesions on the upper lung and no significant improvement compared to the initial presentation. Creatinine levels rose from 60 μmol/L before

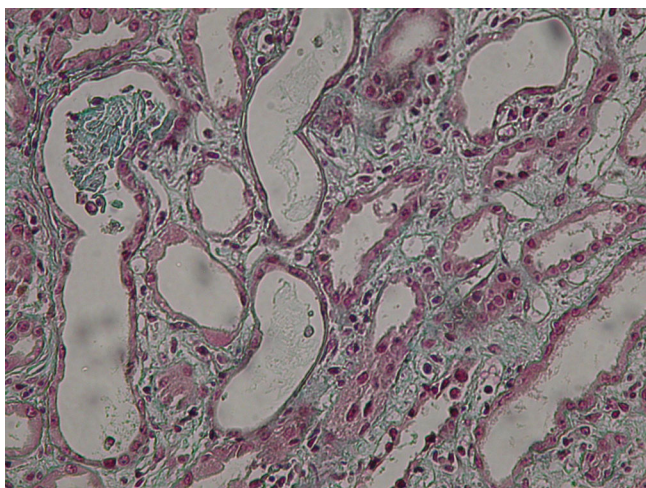**FIGURE 1** Chest x-ray, at 40 days of treatment: Bilateral pulmonary infiltrates and cavitary lesions on the upper lobes.

FIGURE 2 Histology of kidney biopsy: Tubular necrosis, Masson's Trichrome ×40.

treatment to 220 μmol/L, with a creatinine clearance of 23 mL/min. The urea level was 6 μmol/L. Other laboratory test analyses showed; elevated inflammatory biomarkers (white blood cell count: 20600 cells/μL, C-reactive protein: 70 mg/dL mg/dL). Liver function tests revealed no abnormalities, indicating that there were no signs of liver

dysfunction associated with the antituberculous treatment. HIV screening was negative. The etiological workup for renal insufficiency was initiated. Urine output was normal; eliminating obstructive causes of renal insufficiency. Autoimmune disorders such as systemic lupus erythematosus or granulomatosis with polyangiitis were ruled out based on negative immunological testing, and the absence of proteins and blood in the urine analysis. Renal sizes and cortical echogenicity were normal on kidney ultrasound.

Renal tuberculosis or a drug-induced non-oliguric acute kidney injury (AKI) were suspected. Medications were held. A kidney biopsy-performed 11 days later—confirmed ATIN. The appearance is consistent with acute tubulointerstitial nephritis (ATIN). This ATIN occurred on a background of non-proliferative IgA mesangial deposition nephritis, classified as E0 M0 S0 T0 C0 according to the Oxford classification. Neither tuberculous granuloma nor acid-fast bacilli were observed (Figure 2).

The patient remained hospitalized for 12 weeks with close supervision. The antituberculous treatment was withheld until the normalization of creatinine levels. Serum creatinine levels progressively decreased to near baseline within 11 weeks (Figure 3). The suspicion of rifampicin as the causative agent was based on a comprehensive review of the literature and consultation with pharmacovigilance experts.

The decision to initiate a treatment based on second-line anti-TB drugs was made following a multidisciplinary decision and considering that rifampicin is a key antitubercular agent. The new therapeutic regimen proposed consists of INH (225 mg), EMB (800 mg), PZA (1000 mg), levofloxacin (500 mg), ethionamide (500 mg) and cycloserine (500 mg) daily, along with pyridoxine supplementation. The culture-negative conversion was achieved at 12 months. He completed 18 months of treatment without a relapse of renal failure. The chest x-ray at the end of treatment showed radiological improvement with persistent left-sided retractive sequelae (Figure 4).

DISCUSSION

Tubulointerstitial nephritis is an uncommon complication in patients on anti-TB therapy. It can lead to permanent kidney damage.[1] Although RIF is the most frequently involved drug in this complication, other first-line anti-TB drugs, such as INH, ETB, and PYZ were also associated with AKI.[1–5] In a prospective study, the incidence of AKI during anti-TB treatment was 10.3%. This percentage is higher than reported in previous retrospective studies (0.05%–7.1%).[1]

RIF-induced AKI usually occurs in patients who have previously taken this drug or who are undergoing intermittent treatment.[2,3] It is assumed that previous or intermittent exposure to RIF triggers an immune response.[3] Upon re-exposure, anti-RIF antibodies form immune complexes that are deposited in the renal vessels, the interstitial area, and the glomerular endothelium, leading to acute tubular necrosis, and acute interstitial nephritis.[2,6]
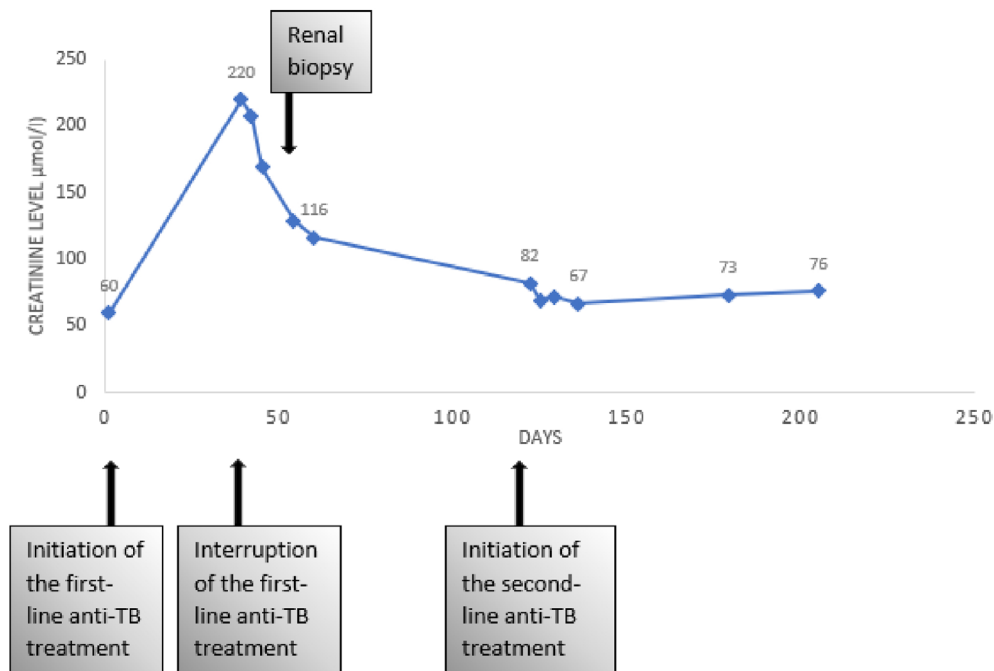
FIGURE 3 Clinical course of creatinine level.

FIGURE 4 The chest x-ray at the end of treatment showed radiological improvement with persistent left-sided retractive sequelae.

The diagnosis of RIF-induced AKI is based on the typical disease course and by excluding other potential etiologies.[6] It is important to identify the aetiology, as management may differ based on biopsy results.[4] When a biopsy is performed, ATIN and acute tubular necrosis are the most common histopathological findings during RIF-induced AKI.[1] The kidney biopsy is the gold standard for the diagnosis of ATIN.[5]

In cases where renal biopsy is contraindicated or not feasible, The diagnosis can be based on a compatible clinical course and laboratory findings. such as eosinophiluria and accumulation of ^{67}Ga in the bilateral kidneys.[4]

In the present case, acute renal failure occurred during anti-TB treatment and improved after the medications were discontinued. The pathological findings on the kidney biopsy specimen were consistent with drug-induced nephrotoxicity. Features of a non-proliferative IgA nephropathy (IgAN) were also found. Confirming the aetiology of the IgAN remains challenging. In our case, rifampicin was the most implicated drug. Although isoniazid and ethambutol can also potentially cause acute interstitial nephritis, the available evidence and clinical experience strongly implicated rifampicin in this particular case. The assessment of causality (imputability) in pharmacovigilance involves considering various factors, including temporal relationship, known drug-related adverse effects, alternative explanations, dechallenge/rechallenge, and published case reports. In this case, the temporal relationship between rifampicin administration and the onset of renal symptoms, along with the absence of other identifiable causes, led to a high probability of rifampicin's involvement in the development of acute interstitial nephritis.

According to Chang et al., more than 50% of AKI cases occurred within 2 months of starting TB treatment. The onset of AKI was more commonly seen in older patients with a higher baseline estimated glomerular filtration rate and blood eosinophil count (>350 (10^9/L)).[1]

Although chronic kidney disease has not been associated with AKI occurrence, it is, along with hypoalbuminemia, a possible risk factor for severe and permanent kidney damage.[4,6] Dehydration and hypoperfusion in patients with gastrointestinal disturbance can participate in renal function impairment. Therefore, fluid management and correct regimen modification are crucial to prevent further injuries.[6]

Renal recovery is better in acute interstitial nephritis than in acute tubular necrosis.[6] The prognosis in acute interstitial nephritis is good, with a 1.6% mortality and a recovery rate between 73% and 100%.[1,3] But it can lead to serious complications such as Fanconi syndrome, resulting in bone pain and fracture, fatigue, and muscular weakness.[3]

Tuberculosis treatment in the setting of ATIN is challenging. The offending medication should be discontinued as soon as possible.[5] In our case, the collegial decision was an alternative regimen based on second-line anti-TB treatment usually used for drug-resistant TB, without RIF. Given the importance of rifampicin in standard anti-tuberculous regimens, the exclusion of rifampicin necessitated an alternative treatment approach. Considering this situation, the management was approached as a possible case of drug-resistant tuberculosis. Hence, a longer duration of therapy, involving a combination of multiple drugs such as isoniazid, ethambutol, pyrazinamide, levofloxacin, ethionamide and cycloserine, was initiated to ensure effective treatment and minimize the risk of relapse. Kizilbash et al. also reported using a drug-resistant regimen based on linezolid, moxifloxacin, ethambutol and high doses of INH in such circumstances.[5]

There are no clear recommendations for the management of RIF-induced AKI. However, several therapeutic approaches have been reported in the literature. In some studies, authors have utilized steroid therapy in patients with a pathological or clinical diagnosis of acute interstitial nephritis (AIN) to expedite the recovery of renal function. However, it is important to note that the use of steroids for AIN remains a topic of controversy.[7,8] We debated the use of steroids however, given the potential for corticosteroids to exacerbate the underlying tuberculosis infection, it was decided to refrain from their use in order to avoid potential worsening of the initial disease.

Several studies support RIF desensitization in patients with RIF-induced AKI. Although the rifampicin desensitization protocol varies, success rates are high (80%–82%).[6] According to other studies, patients with RIF-induced ATIN may experience more severe kidney damage if they restart RIF, even at lower doses. Desensitization therapy should be avoided.[4]

Levofloxacin may be an alternative to rifampicin thanks to its safety and potency. A culture-negative conversion in drug-susceptible TB was observed using levofloxacin instead of RIF for at least 18 months with no major side effects and no AKI relapse.[4]

In our case, we saw that adding levofloxacin was not sufficient. According to the national tuberculosis guidelines in Tunisia, the rationale for selecting a second-line treatment was based on the risk of developing drug-resistant tuberculosis due to the interruption of an effective treatment for 11 weeks.[9] The patient did not receive an adequate duration of the intensive phase of treatment, as evidenced by the lack of radiological improvement and positive direct examination results. The decision was made by a panel of experts.

The selection of an unconventional treatment approach can be considered a limitation of this study. However, the favourable progression of the patient's condition and complete recovery serve as evidence that this therapeutic choice is a viable option in countries with a high tuberculosis endemicity.

The key learning points of this case are that rifampicin-induced AKI typically occurs during the discontinuation of rifampicin treatment. However, this case demonstrates that even with regular administration of the treatment, rifampicin can still lead to renal failure. A definitive diagnosis of ATIN requires renal biopsy as noninvasive laboratory tests and imaging studies lack sensitivity and specificity. The choice of treatment to replace rifampicin is challenging as it involves selecting a second-line antitubercular drug, and there are multiple treatment regimens available, with or without corticosteroids. The decision should be made within the context of a multidisciplinary approach, involving expert opinions and a collegial decision-making process.

In conclusion, drug-induced ATIN is a rare and serious adverse reaction of anti-TB treatment. Early diagnosis and discontinuation of the offending medication are important to prevent further kidney damage and to promote renal function recovery. Conducting large-scale studies to establish clear management protocols is necessary.

AUTHOR CONTRIBUTIONS

CONFLICT OF INTEREST STATEMENT

DATA AVAILABILITY STATEMENT

ETHICS STATEMENT

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