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BRIEF REPORT

Acute Tubular Necrosis and Thrombocytopenia Associated With Rifampin Use: Case Report and Review

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A case of rifampin-induced acute tubular necrosis requiring hemodialysis in a patient receiving thrice-weekly rifampin with daily dapsone for retreatment of relapsed Hansen's disease is reported. The patient had positive rifampin-dependent antiplatelet antibodies. Case reports of acute renal failure associated with the use of rifampin are summarized.

Keywords. rifampin; renal failure; antibodies.

A case of rifampin-induced acute renal failure requiring hemodialysis is reported. The patient received intermittent (thrice-weekly) rifampin dosing, having been previously exposed to the drug for retreatment of *Mycobacterium leprae* with positive rifampin-dependent antiplatelet antibodies. We review the literature of this rare but important phenomenon since 1998 and describe the clinical patterns observed as well as patient outcomes. The methodology for conducting the literature review is described in the Supplementary Data.

CASE REPORT

A 40-year-old man presented in September 2019 with a 6-month history of an erythematous patch on the cheek with raised borders and papular lesions on his ear lobes bilaterally. He had migrated to Australia from Sri Lanka 12 years prior, and his only medical history was hypertension that was stable on perindopril. A biopsy of these lesions revealed granulomatous inflammation with perineural foci, although acid-fast stain and *M. leprae*–specific polymerase chain reaction was negative. Based on the clinical symptoms and typical histopathological findings, a diagnosis of paucibacillary Hansen's disease was made. He was commenced on rifampin 600 mg 3 times per week and dapsone 100 mg daily. Baseline HIV serology was negative, and glucose-6-phosphate dehydrogenase activity was within the normal range. He completed 6 months of therapy with complete resolution of the skin lesions in March 2020.

Unfortunately, the papules on the left ear returned rapidly after ceasing treatment. Re-initiation of treatment was delayed due to difficulties with in-person consultation during the coronavirus disease 2019 pandemic, and the lesions were stable over a prolonged period. In March 2021, rifampin and dapsone were recommenced at the same dosing for presumed relapsed Hansen's disease. The patient took 5 doses of rifampin (3 times weekly) before missing the sixth dose due to feeling progressively unwell, with presentation to the hospital 2 days later. On presentation, he had 3 days of subjective fevers, generalized abdominal discomfort, diarrhea, vomiting, and nausea. He had been anuric for 24 hours. Investigations revealed creatinine of 824 μmol/L (reference range: 45–90 μmol/L), urea of 25.9 mmol/L (reference range: 2.8–7.2 mmol/L), and platelets of 81 $\times 10^9$/L (reference range: 150–450 $\times 10^9$/L). Baseline creatinine and platelets 2 months before commencing therapy were normal. His hemoglobin was normal, with no evidence of hemolysis. He had nephrotic-range proteinuria (urine protein/creatinine ratio, 1.10 g/mmol) with normal serum albumin of 32 g/L and mild hematuria; urine microscopy showed leucocytes of 17×10^6/L and erythrocytes of 43×10^6/L. A glomerulonephritis screen was negative including serum-free light chains. Renal tract imaging demonstrated normal cortical architecture without evidence of hydronephrosis. Histopathological examination of a renal biopsy showed acute tubular necrosis (ATN) with associated eosinophilic globular casts and no glomerular abnormality. There was mild chronic parenchymal damage, with ~25% of the cortex showing interstitial fibrosis and tubular atrophy.

Suspecting a drug-induced adverse event, rifampin and dapsone were ceased. He remained anuric despite volume correction with a rising creatinine (1212 μmol/L) and worsening acidosis (bicarbonate 15 mmol/L), and hemodialysis was initiated. He was febrile on days 4–6 of admission with recorded temperatures up to 39.7°C. Multiple peripheral and line blood cultures were negative, and no source of infection was identified. His platelet count normalized to 286 $\times 10^6$/L on day 8 after admission.

Blood samples were sent for rifampin-dependent antiplatelet antibody testing given the concurrent moderate thrombocytopenia. Using a platelet immunofluorescence test, strong immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies were detected in the presence of rifampin.

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On day 14, he showed some renal recovery, and hemodialysis was ceased on day 23. His renal function steadily improved and normalized by 10 months postpresentation. No new lesions developed during the period off antibiotics. After complete recovery, second-line therapy with daily moxifloxacin and minocycline was commenced, with a plan of 12 months of retreatment.

DISCUSSION

Rifampin-induced acute renal failure was first described in 1971 during a clinical trial investigating the use of high-dose twice-weekly rifampin [1]. Rifampin-dependent antibodies were detected in 16 out of 49 trial participants. The trial had to be terminated early due to significantly increased side effects observed in participants who developed rifampin-dependent antibodies (9/16 of those with antibodies vs 2/33 of those without antibodies; $P < .001$), and acute renal failure occurred in 1 patient. A 1998 review identified 4 patterns of renal failure in the context of rifampin therapy [2].

Acute tubular necrosis was reported most frequently, in 37 out of 48 cases (77%), followed by acute interstitial nephritis, occurring in 5 patients (10%). There were also 4 cases of light chain proteinuria (8% of cases) and 2 cases of rapidly progressive glomerulonephritis (4%). ATN was associated with the presence of rifampin-dependent antibodies and more commonly occurred with intermittent or interrupted dosing of rifampin, as we observed in our patient. The other 3 patterns tended to occur with continuous rifampin therapy.

Since that review was published, there have been 22 case reports of presumed rifampin-induced acute renal failure with renal biopsy findings (summarized in Table 1) [3–24]. Of these 22 cases, the majority were being treated for tuberculosis, and the majority occurred in males (17/21; 77%). In 3 patients, ATN was found on renal biopsy, all with a history of previous rifampin exposure, but none had rifampin-dependent antibodies tested. Acute tubulointerstitial nephritis (ATIN) was the most common biopsy finding, with glomerulonephritis, minimal change disease, and focal segmental glomerulosclerosis also described. Rifampin-dependent antibodies were reported in only 4 cases. Positive antibodies were seen in 1 patient with glomerulonephritis on a daily rifampin regimen who had never been exposed to the drug previously [24]. This differs from the patterns described by De Vriese and suggests that there may be multiple potential mechanisms for this phenomenon.

A number of case series have also reported acute renal failure in the context of rifampin therapy [25–30]. One series reported 41 cases of biopsy-proven ATIN [27]. Other case series report renal biopsies in a small number of patients, with similar histopathological findings to individual case reports. Testing for rifampin-dependent antibodies was low; however, a large case series of 170 patients in Romania found that 54% of patients had antibodies detected, and all had been previously exposed to rifampin [28]. Generally, it is challenging to conclude that renal failure is definitely due to rifampin in the absence of antibody testing; however, in the majority of reported cases in the literature, the other potential causative drugs (eg, other TB therapies) were reintroduced without recurrence of adverse events.

Renal failure has been reported with both daily and intermittent rifampin dosing in those with previous exposure and those taking the drug for the first time. In those previously exposed, the rifampin-free period was highly variable (4 days to 43 years). As seen with our patient, associated thrombocytopenia was common in other reported cases, occurring in 36.5% of the larger cohort of 170 patients [28]. The potential postulated mechanism is binding of rifampin-dependent antibodies to the "I" antigen that is present on the surface of erythrocytes, platelets, and tubular epithelial cells but not on glomerular cells [2]. Hemolysis and hepatitis were also frequently reported, with rare occurrences of intercurrent anaphylaxis [31], pancreatitis, and hyperthyroidism [13]. Flu-like symptoms and fevers commonly accompanied the renal failure and occurred in 94% of patients in a larger case series [28]. Given that no infective diagnosis was made in our case, it is likely that the fevers we described were part of this syndrome. Other commonly described symptoms were abdominal pain, nausea, and vomiting, also experienced by our patient. Although acute hemodialysis was commonly required (Table 1), the overall prognosis appears to be very good, with most reported cases making a full recovery with cessation of rifampin. Chronic kidney disease (CKD) appears to be uncommon. A previous series reported CKD in 7 out of 170 patients, and no patients required ongoing renal replacement therapy [28].

Several case reports described rifampin reintroduction after renal failure, and all resulted in worsening adverse events and even rapidly progressive renal failure and death. It is not clear if there is cross-reactivity with other rifamycin antibiotics such as rifabutin. One case report of marked thrombocytopenia with rifampin therapy reported no adverse events when rechallenged with rifabutin [32]. Currently there is a lack of evidence available to enable recommended use of rifabutin or an alternative rifamycin antibiotic in this scenario. In the event of rifampin resistance, current guidelines recommend combination therapy with at least 2 second-line agents: a quinolone (moxifloxacin, ofloxacin, or levofloxacin), minocycline or clarithromycin, plus clofazimine [33]. In this case, we opted to recommence treatment with 2 agents because of the minimal burden of paucibacillary disease.

This report highlights the importance of close monitoring of patients on rifampin therapy, with regular testing of renal function and full blood examination. Prompt recognition and cessation of rifampin in such cases are important as the prognosis for full recovery of renal function is excellent.

Table 1. Reports of Presumed Rifampicin-Induced Acute Renal Failure With Renal Biopsy Findings Since 1998

Reference (Year)	Case Demographics	Condition	Rifampicin Dosing	Previous Rifampicin Exposure	Biopsy Findings	Associated Adverse Events	Rifampicin-Dependent Antibodies	Dialysis Required	Renal Recovery
Sanwal (2020) [3]	49-y-old M	Latent TB	Interrupted	Yes	Acute tubular injury with hemoglobin casts	Hemolytic anemia	Not tested	Yes	Recovered
Nagata (2019) [4]	64-y-old M	Pleural TB	Daily	No	Tubulointerstitial nephritis	NS	Not tested	No	CKD
Kim (2018) [5]	51-y-old F	Latent TB	Daily	No	Minimal change disease	NS	Not tested	Yes	Recovered
Wortham (2017) [6]	32-y-old M	Latent TB	Daily	Yes	Acute tubular injury with heme-pigmented casts	Hemolytic anemia	Not tested	Yes	Recovered
Manika (2013) [7]	57-y-old M	Pulmonary TB	Daily	No	Acute tubulointerstitial nephritis	Hemolytic anemia	Not tested	Yes	Recovered
Chiba (2013) [8]	47-y-old M	Pulmonary TB	Daily	No	Tubulointerstitial nephritis	Hepatitis; anemia	Not tested	No	CKD
Rosati (2013) [9]	50-y-old M	Pulmonary TB	Daily	No	Focal segmental glomerulosclerosis	Anemia	Not tested	No	Recovered
Min (2013) [10]	42-y-old M	Pulmonary TB	Daily	No	Tubulointerstitial nephritis	Hypokalemic paralysis	Not tested	No	Recovered
Salih (2008) [11]	52-y-old F	Brucellosis	Intermittent	Yes	Tubulointerstitial nephritis	NS	Not tested	No	Recovered
Wiggins (2007) [12]	40-y-old F	Staphylococcal	Daily	No	Segmental necrotizing glomerulonephritis	NS	Not tested	No	Recovered
Wen (2006) [13]	73-y-old M	Pulmonary TB	Daily	No	Crescentic glomerulonephritis	NS	Not tested	Yes	Recovered
Paydas (2005) [14]	50-y-old M	Brucellosis	NS	Yes	Tubulointerstitial nephritis	Hemolytic anemia; pancreatitis; hyperthyroidism	Not tested	Yes	Recovered
Banu Rekha (2005) [15]	14-y-old M	Pulmonary TB	Intermittent	Yes	Tubulointerstitial nephritis	NS	Not tested	Yes	Recovered
Yoshioka (2002) [16]	60-y-old M	Pulmonary TB	Interrupted	Yes	Crescentic glomerulonephritis	NS	Negative	No	Recovered
Bassilios (2001) [17]	61-y-old M	Pulmonary TB	Daily	No	Acute interstitial nephritis	NS	Negative	No	Recovered
Mehendru (2001) [18]	63-y-old M	Pulmonary TB	Daily	No	Acute interstitial nephritis	NS	Not tested	Yes	Recovered
Kohno (2000) [19]	43-y-old F	Pleural TB	Daily	No	Minimal change disease	NS	Negative	No	Recovered
Gallieni (1999) [20]	67-y-old M	Pleural TB	Daily	Yes	Tubulointerstitial nephritis	Hemolytic anemia	Not tested	Yes	Recovered
Feinfield (1999) [21]	27-y-old M	Previous pulmonary TB	Intermittent	Yes	Acute interstitial nephritis	NS	Not tested	Yes	Recovered
Kistler (1999) [22]	69-y-old F	Pulmonary TB	Daily	No	Mesangiocapillary glomerulonephritis	NS	Not tested	No	Recovered
Basile (1998) [23]	38-y-old M	Pulmonary TB	Intermittent	Yes	Tubular necrosis with interstitial infiltrate	Anemia; hepatitis	Not tested	Yes	Recovered
Ogata (1998) [24]	64-y-old M	*Mycobacterium kansasii*	Daily	No	Tubulointerstitial nephritis	Anemia	Positive	No	Recovered

Intermittent = intentional prescribed nondaily dosing (eg, thrice weekly, bimonthly); Interrupted = unintentional doses missed from a daily dosing regimen.

Abbreviations: CKD, chronic kidney disease; NS, not specified; TB, tuberculosis.

Because this syndrome can develop rapidly after rifampin is commenced, educating patients on these potential side effects and early reporting of symptoms are likely to be of value. Although renal failure can occur with any dosing schedule, treating physicians should be particularly aware of this in those on intermittent therapy and those with previous exposure to the drug. In the absence of a state-wide or national system for reporting adverse events to routine antibiotics, it is difficult to ascertain the true incidence of this complication. Testing for rifampin-dependent antibodies, if available, is useful in confirming the likely causative role of rifampin.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. The patient's written consent was obtained for publication.

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