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 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 and his only medical history was hypertension that was stable. 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 × 10^9/L (reference range: 150–450 × 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 × 10^9/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. A biopsy of these lesions revealed granulomatous inflammation with perineural foci, although acid-fast stain was negative. 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 × 10^9/L (reference range: 150–450 × 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.

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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 described 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     |
| Basilloso (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     |
| Galleni (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 copypedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

We would like to thank the patient for providing consent for us to share the details of his presentation. We would also like to thank the Victorian Transplantation and Immunogenetics Services for rifampicin-dependent antiplatelet antibody testing.

Financial support. No funding sources.

Potential conflicts of interest. All authors: no reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Author contributions. E.L.S.: literature review, summarizing of previous cases, write-up of the case report. L.B.: write-up of the case report. RP: re-manuscript have been disclosed.

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

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

References

1. Poole G, Stradling P, Worlledge S. Potentially series side effects of high-dose twice-weekly rifampicin. Br Med J 1971; 3:343–7.
2. De Vriese AS, Robbrecht DL, Vanholder RC et al. Rifampicin-associated acute renal failure: pathophysiological, immunological, and clinical features. Am J Kidney Dis 1998; 31:108–15.
3. Sanwal C, Kalidas A, Surani S, Bailey M. Rifampicin-induced acute intravascular haemolysis leading to heme pigment-related kidney injury. Cureus 2020; 12: e9120.
4. Nagata M, Ohji G, Iwata K. Acute tubulointerstitial nephritis caused by rifampicin: an increasing and often overlooked side effect in elderly patients. Int J Clin Pharmacol Ther 2019; 57:264–69.
5. Kim J-S, Kim K-J, Choi E-Y et al. Minimal change disease related to rifampicin presenting with acute renal failure during treatment for latent tuberculosis infection: a case report. Medicine 2018; 97:e10556.
6. Wortham JM, Goggin M, Mora C, et al. Acute kidney injury during treatment for latent tuberculosis infection with rifampicin. Int J Tuberculosis Lung Dis 2017; 21: 596–7.
7. Manika K, Tadipentulou K, Vlogias I, et al. Rifampicin-associated acute renal failure and haemolysis: a rather uncommon but severe complication. Renal Failure 2013; 35:1179–81.
8. Chiba S, Tsuchiya K, Sakashita H, et al. Rifampicin-induced acute kidney injury during the initial treatment for pulmonary tuberculosis: a case report and literature review. Internal Med 2013; 52:2457–60.
9. Rosati S, Cherubini C, Iacomini F, et al. Acute rifampicin-associated interstitial tubulopathy in a patient with pulmonary tuberculosis: a case report. J Med Case Rep 2013; 7:106.
10. Min HK, Kim EO, Lee SJ, et al. Rifampicin-associated tubulointerstitial nephritis and Fanconi syndrome presenting as hypokalaemic paralysis. BMC Nephrol 2013; 14:13.
11. Salih SB, Khalar M, Qahtani M, Dahneem L, Nohair S. Acute interstitial nephritis induced by intermittent use of rifampicin in a patient with brucellosis. Saudi J Kidney Dis Transpl 2018; 19:450–2.
12. Wiggins KJ, Galanos JW, Hill PA, Scott KV, Langham RG. Rifampicin-associated segmental necrotizing glomerulonephritis in staphylococcal endocarditis. J Nephrol 2007; 20:489–94.
13. Wen YK, Chen ML. Crescentic glomerulonephritis associated with rifampicin in a patient co-infected with tuberculosis and human immunodeficiency virus. Clin Nephrol 2006; 65:284–9.
14. Paydas S, Balal M, Karayaylali I, Seryek N. Severe acute renal failure due to tubulointerstitial nephritis, pancreatitis and hyperthyroidism in a patient during rifampicin therapy. Adv Ther 2005; 22:241–3.
15. Banu Rekha VV, Santha T, Jawahar MS. Rifampicin-induced renal toxicity during re-treatment of patients with pulmonary tuberculosis. J Assoc Physicians India 2005; 53:811–3.
16. Yoshioha K, Satake N, Kasamatsu Y. Rapidly progressive glomerulonephritis due to rifampicin therapy. Nephron 2002; 90:116–8.
17. Bassilios N, Vantelon C, Baumelou A, et al. Continuous rifampicin administration inducing acute renal failure. Nephrol Dial Transplant 2001; 16:190–1.
18. Mehendru S, Goel A. A reversible cause of acute renal failure. Postgraduate Med J 2001; 77:478–80.
19. Kohno K, Mizuta Y, Yoshida T, et al. Minimal change nephrotic syndrome associated with rifampicin treatment. Nephrol Dial Transplant 2000; 15:1056–9.
20. Gallieni M, Braidotti P, Cozzolino M, et al. Acute tubule-interstitial nephritis requiring dialysis associated with intermittent rifampicin use: case report. Int J Artificial Organs 1999; 22:477–81.
21. Feinfield DA, Ansari N, Nuovo M, Hussain A, Mir R. Tubulointerstitial nephritis associated with minimal self reexposure to rifampin. Am J Kidney Dis 1999; 33:E3.
22. Kistler A, Lappin DWP, Coward RA. Therapeutic dilemma: crescentic mesangio-capillary glomerulonephritis type I in a patient on antituberculous therapy with rifampicin. Nephrol Dial Transplant 1999; 14:243–4.
23. Basile C, Maranghi AL, Montanaro A, et al. Rifampicin-associated acute renal failure. Am J Kidney Dis 1998; 32:533.
24. Ogata H, Kubo M, Tamaki K. Crescentic glomerulonephritis due to rifampicin treatment in a patient with pulmonary atypical mycobacteriosis. Nephron 1998; 78:319–22.
25. Sakashita K, Murata K, Takahashi Y, et al. A case series of acute kidney injury during anti-tuberculosis treatment. Internal Med 2019; 58:521–7.
26. Chang C-H, Chen Y-F, Wu V-C, et al. Acute kidney injury due to antituberculosis drugs: a five-year experience in an aging population. BMC Infect Dis 2014; 14:23.
27. Schubert C, Bates WD, Moosa MR. Acute tubulointerstitial nephritis related to antituberculosis treatment in a patient with pulmonary atypical mycobacteriosis. Nephron 2013; 123:413–9.
28. Covic A, Golea O, Segall L, et al. A clinical description of rifampicin-induced acute renal failure in 170 consecutive cases. J Indian Med Assoc 2004; 102:21–5.
29. Muthukumar T, Jayakumar M, Fernando EM, Mathulesshepathi MA. Acute renal failure due to rifampicin: a study of 25 patients. Am J Kidney Dis 2002; 40:690–9.
30. Prakash J, Kumar NS, Saxena RK, Verma U. Acute renal failure complicating rifampicin therapy. JAPI 2001; 49:877–80.
31. Luzzati R, Giacomazzi D, Franchi F, Barcobello M, Vento S. Life-threatening, multiple hypersensitivity reactions induced by rifampicin in one patient with pulmonary tuberculosis. Southern Med J 2007; 100:854–6.
32. Sarkar T, Riccardi N, Wagh H, Udwaadia ZF. Safety of rifabutin in patients with rifampicin-induced thrombocytopenia. Indian Chest Soc 2020; 455–6.
33. World Health Organisation. Guidelines for the diagnosis, treatment and prevention of leprosy. 2018. Available at: https://www.who.int/publications/i/item/ 9789290226383. Accessed 3 May 2022.