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Rifampin-Associated Renal Failure

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Abstract

Rifampin is an effective and widely used for the treatment of both active and latent tuberculosis. Although significant side effects are rare, severe side effects such as acute renal failure have been reported in the literature, usually secondary to acute interstitial nephritis. We report a case of rifampin-induced acute renal failure due to heme pigment–related injury in a patient who was receiving daily rifampin as therapy for latent tuberculosis. The patient case illustrates considering rifampin as a potential cause of acute renal failure when no other cause is identified.

Keywords

Acute renal failure; Tuberculosis; Renal failure; Nephritis; Hospital medicine; Hemoglobin; Case series; Bilirubin; Platelets; Medical dialysis; Pigment associated nephropathy; Rifampin; Hemolytic anemia

Background

Rifampin therapy is used frequently for the treatment of tuberculosis and is generally well tolerated, although it has many drug interactions. The most common side effects include nausea/vomiting, headache, rash, leukopenia, and hypersensitivity syndrome. Hepatitis can be seen but is associated more frequently with concomitant isoniazid use or baseline liver disease. In rare cases, acute renal failure can develop, as seen in our patient case.

Objective

We present this case to highlight the rare complication of acute renal failure due to heme pigment deposition injury in a patient on daily rifampin therapy and the importance of close monitoring of patients for adverse events while on therapy.

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Disclosures

Disclosure forms are available with the article online.

Case Report

A 29-year-old woman initially from the Dominican Republic who moved to the United States in 2014 presented in January 2016 to establish prenatal care. At that time, a purified protein derivative skin test was positive at 21 mm, and the chest radiograph did not show abnormalities. Treatment was deferred due to pregnancy. Five years later in January 2022, she presented to her primary care provider to discuss treatment of latent tuberculosis. She was started on rifampin, 300 mg daily, for a planned 4-month course. She was taking no other medications. Baseline liver function tests and blood counts were in the normal range, and baseline creatinine was 0.96 mg/dL. After 3 months of therapy, bilirubin was noted to be mildly elevated (total bilirubin 3.5 mg/dL; direct bilirubin 0.7 mg/dL) with normal aspartate aminotransferase and alanine aminotransferase and no symptoms related to liver injury. Creatinine and blood counts were not checked at this time, and she did not undergo further work-up. She was continued on rifampin and reported daily adherence.

However, several days later in late April 2022 she presented to our emergency department after 2 days of nausea, vomiting, and subjective fevers. Her laboratory results on arrival were notable for creatinine of 3.8 mg/dL, blood urea nitrogen of 41 mg/dL, and platelets of 84 K/μL. Her bilirubin levels had normalized, although her aspartate aminotransferase was elevated to 115 U/L. Her hemoglobin was initially in the normal range at 12.1 g/dL. Haptoglobin was less than 10 mg/dL, and lactate dehydrogenase was elevated to 1125 U/L, consistent with hemolysis. She also was noted to have proteinuria (urine protein 102.7 mg/dL) and mild hematuria. Initial renal ultrasound findings were notable for markedly echogenic renal cortices bilaterally, consistent with parenchymal disease, but no hydronephrosis. Given suspicion for possible drug-related adverse reaction, rifampin was stopped on arrival. We also considered a diagnosis of hemolytic uremic syndrome, given previous gastrointestinal symptoms, but there were no schistocytes observed on the peripheral blood smear. Renal biopsy demonstrated pigmented casts and signs of acute tubular injury, consistent with rifampin-associated hemoglobinuria with acute tubular injury and focal tubular necrosis (Figure 1, A and B). Her kidney function continued to worsen, with a creatinine nadir of 11.44 mg/dL and glomerular filtration rate of 4 mL/min, and she was started on dialysis on hospital day 2. Her hemoglobin dropped, with a nadir of 9.3 g/dL on day 5, and platelets also continued to drop, with a nadir of 49 K/μL on day 3. Her platelets returned to normal range by hospital day 7, and her hemoglobin began to improve steadily by hospital day 10. She continued to require dialysis until hospital day 10. Her renal function then improved, and she did not require any further dialysis. Her creatinine returned to normal range (0.87 mg/dL) 1 month after her initial presentation. She has done well since that time and has not received further therapy for latent tuberculosis.

Discussion

Although rare, development of acute renal failure while on rifampin has been reported in many case reports and case series in the literature (1, 2). The clinical presentation usually occurs as a flu-like illness with concomitant gastrointestinal distress and in some cases associated anuria (2, 3). Common laboratory abnormalities in addition to renal

dysfunction include thrombo-cytopenia, anemia with associated hemolysis, and elevation of liver enzymes (3–5).

There are several pathologic patterns notable on renal biopsy for patients who present with rifampin-associated acute renal failure. In most case series, acute interstitial nephritis is the most frequently associated pathologic finding on biopsy (4–7). However, other patterns, such as acute tubular necrosis, crescentic glomerulonephritis, mesangial proliferation, and minimal change disease, have been noted in case reports (5, 8, 9).

Although uncommon, there have been rare case reports similar to ours of rifampin leading to intravascular hemolysis and heme pigment–related kidney injury (10, 11). The pathophysiology of rifampin-induced acute kidney injury in cases of intravascular hemolysis is mainly immune-mediated and is related to the formation of rifampin-dependent antibodies. These rifampin-dependent antibodies can bind directly to I-antigens on renal tubular cells, causing destruction and an interstitial nephritis pattern on pathology (12). Rifampin antibodies can also bind to I-antigens on red blood cells, leading to hemolysis and heme pigment release. Heme pigment is nephrotoxic to the renal tubules and also can lead to direct heme pigment–related injury to the kidney, as seen in our patient.

In most cases, the rifampin-induced renal failure was associated with intermittent dosing or with those reintroducing the medication after a break in therapy (7). However, cases of renal failure also have been associated with daily dosing of rifampin without interruption as well, as was the case with our patient (13). Although many patients require hemodialysis for a time, the clinical course is overall favorable, with most patients regaining full renal function by 90 days from onset of disease (3, 5, 7). Mortality is rare but has been noted in cases when rifampin was reintroduced after the initial episode of renal failure (2). Given the high risk, rifampin should not be reintroduced in patients who develop rifampin-associated renal failure, and alternative agents should be sought if needed.

In summary, although rare, rifampin should be considered as a cause of acute renal failure in patients who present with severe acute kidney injury while on either daily or intermittent use of the medication. Given the rarity of this diagnosis, adjustment of baseline laboratory monitoring is not required, but it is important that clinicians be aware of this entity. Prompt cessation of rifampin is crucial, as prognosis for renal recovery is excellent assuming further rifampin is avoided.

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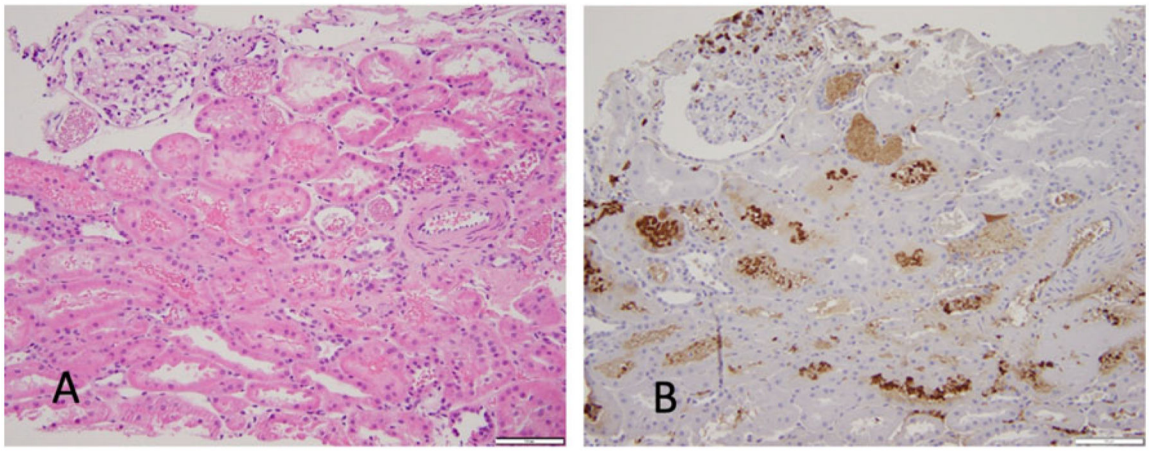

Figure 1.

(A) Many tubules in the cortex contain eosinophilic proteinaceous material and cell debris (hematoxylin–eosin stain 20× objective). (B) The content of these tubules shows strong reactivity for hemoglobin by immunohistochemistry (immunoperoxidase stain, 20× objective).