Minimal Change Disease Induced by Rifampicin: A Case Report

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ABSTRACT

Rifampicin, the medicine used for the treatment of tuberculosis (TB), has the potential to causekidney damage, most commonly manifested as acute interstitial nephritis. The potential of causing minimal change disease (MCD) of the kidney is very rare, and it is often relieved after the use of glucocorticoids. Although self-remission of MCD following rifampicin withdrawal has been reported internationally, such cases are undocumented in China. This paper presents a case of nephrotic syndrome induced by rifampicin used for TB treatment, that was diagnosed as MCD *via* renal biopsy. The symptoms improved after discontinuation of rifampicin. A literature review is also provided to summarise the clinical features, pathogenesis, and treatment of this condition.

Key Words: *Rifampicin, Tuberculosis, Minimal change disease, Nephrotic syndrome.*

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INTRODUCTION

Rifampicin can cause renal damage when used to treat tuberculosis (TB). The most common pathological type is acute interstitial nephritis, while minimal change disease (MCD) is rare.[1] MCD caused by rifampicin can be relieved by the use of glucocorticoids. Here, we report a case of complete remission of MCD by withdrawing the medicine. To our knowledge, this is the first case in China with renal biopsy confirmed MCD caused by rifampicin and complete remission achieved by simply stopping the medicine, which has certain implications for the clinical treatment.

CASE REPORT

A 34-year female was diagnosed with isoniazid-resistant infiltrative pulmonary TB in April 2023 and began regular anti-TB treatment (ATT) in August 2023. The regimen included oral administration of rifampicin (600 mg/day), pyrazinamide (1500 mg/day), ethambutol (750 mg/day), and levofloxacin (500 mg/day). On December 19, 2023, the patient presented with nausea and vomiting, testing positive for urinary protein (3+) and having a serum albumin level of 19.3 g/L. Symptomatic treatment was initiated, and levofloxacin was replaced with moxifloxacin (400 mg/day).

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On December 29, 2023, the patient developed oedema of both lower limbs and experienced dyspnoea on exertion. Given the worsening oedema, the patient sought treatment at our hospital and completed the relevant laboratory examinations (Table I). Immunoglobulins (Ig) A, M, and G were within normal ranges; complement C3 and C4 were normal. Serum electrophoresis showed no M protein bands, and the proteins in the serum showed no reaction with anti-IgG, anti-IgA, and anti-IgM antibodies, and the ratio of Ig light chains κ (kappa) and λ (lambda) was within the normal range. Anti-neutrophil cytoplasmic antibody (ANCA) and extractable nuclear antigen (ENA) antibodies were negative. There were no significant abnormalities in echocardiography, ultrasound, and chest CT.

Table I: Laboratory investigations.

Parameters	Results
24-hour urinary protein quantification	3.79 g
Leucocytes	2+
Haematuria	1+
Non-squamous epithelial cells	2.2 cells/μL
Platelet count	176 × 10^9/L
Total cholesterol	10.21 mmol/L
Triglycerides	3.67 mmol/L
High-density lipoprotein cholesterol	2.27 mmol/L
Low-density lipoprotein cholesterol	5.66 mmol/L
Calcium	1.86 mmol/L
Alanine transaminase	39 U/L
Aspartate transaminase	34 U/L
Total bilirubin	1.7 μmol/L
Direct bilirubin	2.8 μmol/L
Lactate dehydrogenase	275 IU/L
Uric acid	261 μmol/L
Total protein	44.73 g/L
Albumin	20.63 g/L
Thyroid-stimulating hormone	6.549 μIU/mL
Parathyroid hormone	321 pg/mL
Folic acid	2.72 ng/mL
Urine N-acetyl-β-D-glucosaminidase	67 U/L

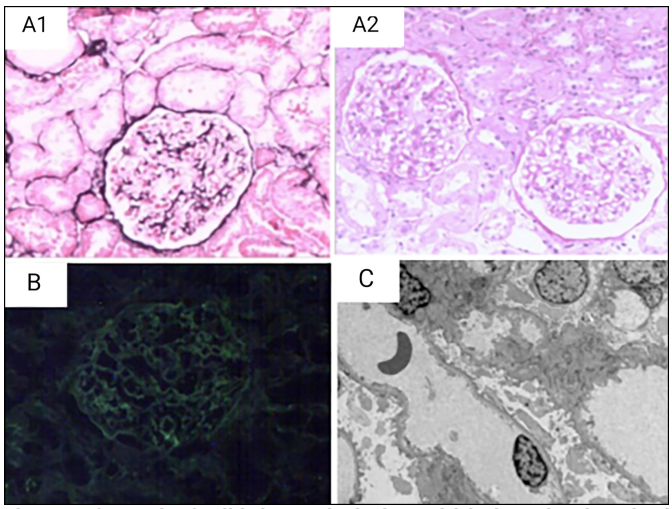

Figure 1: (A1 and A2) Mild glomerular lesions with ischaemic sclerosis of 1/32 glomeruli, slightly enlarged glomeruli, and no significant mesangial expansion (A1: PASM × 200, A2: PAS × 200), (B × 200, C × 1500). (B) The negative immunofluorescence for IgG. Similar results were seen for IgA and IgM. (C) The diffuse foot process effacement and vacuolar degeneration in some podocytes, segmental mild mesangial cells, and matrix proliferation without significant electron-dense deposits in the mesangial area. No endothelial cell proliferation or glomerular basement membrane changes were seen.

Based on the patient's medical history and renal biopsy results, MCD was diagnosed. Upon admission, anti-TB medicines were immediately discontinued, and a renal biopsy was performed. By January 5, 2024, the 24-hour urinary protein was reduced to 0.06 g/24h, and serum total protein and albumin levels improved to 55.8 g/L and 31.1 g/L, respectively, achieving complete remission. By January 24, 2024, the patient's 24-hour urinary protein remained low at 0.07 g/24h.

DISCUSSION

Rifampicin is a first-line bactericidal agent used in the initial and retreatment of pulmonary TB. Its adverse effects on the kidney range from mild proteinuria to acute renal failure. Renal biopsy findings in rifampicin-related nephropathy typically reveal acute interstitial nephritis, with MCD being rare.[1] While cases of MCD induced by rifampicin have been reported internationally, they are scarce in the literature.[1] Most reported cases involved intermittent dosing regimens, with few describing continuous administration.[2] This case uniquely presents MCD under continuous rifampicin therapy without steroid use, achieving remission solely by discontinuing the medicine.

TB itself can cause renal damage, usually presenting with bladder irritation, pyuria, and radiographic changes in renal papillae. In this patient, these were absent, excluding renal TB. This patient had no relevant medical history or medicine use, and proteinuria appeared after starting anti-TB medicines. Given the normalisation of proteinuria post-discontinuation, this case supports the diagnosis of medicine-induced MCD.

Both pyrazinamide and ethambutol are first-line anti-TB medicines, but there is no literature linking them to MCD. Pyrazinamide's main metabolite, pyrazinoic acid, inhibits renal uric acid excretion, primarily causing hepatotoxicity, rash, and arthralgia.[3] Ethambutol's adverse effects include ocular toxicity and rare cases of interstitial nephritis with anuric renal failure.[4] Given this patient's normal liver enzymes and uric acid levels, absence of rash, arthralgia, and normal eye examination, MCD is likely not caused by pyrazinamide or ethambutol. Therefore, this patient's MCD is attributable to rifampicin.

Tada *et al*. reported MCD in a patient on continuous rifampicin therapy for TB, noting endothelial damage as the primary renal injury mechanism.[5] Unlike their case, this patient had normal platelet counts and no signs of intravascular haemolysis, with only diffuse foot processes' effacement observed on electron microscopy. This suggests glomerular podocyte injury, possibly linked to direct medicine toxicity or the release of permeability factors.

Neugarten *et al*. first reported rifampicin-induced nephrotic syndrome, observing no significant glomerular changes but marked interstitial lesions and electron-dense deposits.[6] Rifampicin's mitogenic effect on lymphocytes suggests a cell-mediated immune response in acute interstitial nephritis. Other studies suggest that rifampicin-induced interstitial nephritis results from tubular antigen release and immune complex deposition. The hypothesis is that rifampicin can trigger both cell-mediated and humoral immune responses.[6] Rifampicin, a small molecule, binds to plasma proteins, forming immunogenic complexes that, if not promptly cleared, activate the immune system, leading to antibody production and subsequent immune injury upon re-exposure.[7] Rifampicin antibody production is linked to intermittent dosing, with titers declining post-therapy, detectable *via* anti-globulin tests. However, due to technical limitations, we could not measure antibody titers in this patient. In this patient, no significant interstitial lesions, inflammatory cell infiltration, or fibrosis were observed on light microscopy (Figure A1and A2), and the immunofluorescence of IgA, IgM, IgG was negative (Figure 1B). There was diffuse foot process effacement and vacuolar degeneration in some podocytes, segmental mild mesangial cell, and matrix proliferation without significant electron-dense deposits in the mesangial area, and no endothelial cell proliferation on electron microscopy (Figure 1C), excluding an immune-mediated glomerulonephritis. Similar cases have been reported by Park *et al*.[8]

Typically, MCD is treated with glucocorticoids, achieving complete remission in 80-95% of adult patients.[9] This patient did not receive glucocorticoid therapy; instead, symptoms improved, and proteinuria resolved following rifampicin discontinuation. This is the first report of such a case in China, though Park *et al*. have described a similar case internationally.[8] The similarity lies in considering the renal injury to be related to direct medicine toxicity, which may explain the complete remission achieved solely through medicine discontinuation. In previous cases, MCD was improved by stopping rifampicin and administering oral prednisolone.[5,6] Barman *et al*. reported a case of childhood nephrotic syndrome unresponsive to prednisolone at 2 mg/kg/day, requiring an increased dose of 3 mg/kg/day for four weeks, followed by 2 mg/kg every other day

for six weeks, with complete remission upon sudden withdrawal.[10] Rifampicin induces hepatic microsomal enzymes, reducing glucocorticoid blood levels, which may necessitate increased glucocorticoid dosages when co-administered. This interaction highlights the need for clinicians to monitor rifampicin and glucocorticoid co-administration closely.

ATT medicine-induced renal injury presents varied pathological types and complex mechanisms, requiring careful clinical evaluation. Patients on rifampicin should have their renal function and proteinuria closely monitored to detect renal injury early. Clinicians should suspend anti-TB medicines in such patients, observe changes in proteinuria and creatinine, and perform a renal biopsy if necessary to determine the pathological type of renal injury and select appropriate treatment strategies. Precise treatment improves clinical outcomes and reduces complications.

PATIENT'S CONSENT:
Explicit consent was obtained from the patient to publish this case report.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
KH: Literature, drafting, and revision of the manuscript.
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LY: Editing and proofreading.
All authors approved the final version of the manuscript to be published.

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