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Rifampicin-associated acute renal failure with light-chain proteinuria

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INTRODUCTION

Rifampicin is a commonly used anti-tuberculosis agent with reported adverse effects, one of which is nephrotoxicity[1-3]. The most frequent form of nephrotoxicity is tubular necrosis, with or without haemolysis and thrombocytopenia. Other patterns of rifampicin-induced renal failure include rapidly progressive glomerulonephritis, acute interstitial nephritis and light-chain proteinuria.

We describe a patient with light-chain proteinuria and reversible renal failure after discontinued rifampicin therapy for pulmonary tuberculosis.

Key-Words:
Acute renal failure; light-chain proteinuria; rifampicin.

CASE REPORT

A 48 year-old black male was admitted to the hospital in June 2006 presenting with a rash and fever.

He had been well until April 2006 when he developed a productive cough, fever, night sweats and weight loss. Chest radiography showed a dense infiltrate in the right lower lobe and mycobacterium tuberculosis was isolated in sputum culture.

He started isoniazid (INH) 300 mg/day, pyrazinamide (PZA) 1500 mg/day, rifampicin 600 mg/day and ethambutol 1200 mg/day for pulmonary tuberculosis on 5 May 2006.

Allopurinol 450 mg/day was introduced one month before admission as patient presented hyperuricemia.

Two weeks before admission he had noticed a sudden pruritic rash on the lower extremities which rapidly extended to his chest and back, and low fever (axilar temperature 37.5ºC).

There was no respiratory distress, vomiting, diarrhoea, polyarthralgias or decreased urine volume. There was no use of analgesic.

His pulmonologist first suspended allopurinol and some days later suspended all antituberculous drugs, suspecting drug toxicity. Despite the drug suspension patient maintained cutaneous lesions, fever, weakness and myalgias, and was referred to our emergency department on 26 June 2006.

He had never smoked or used illicit drugs and did not drink alcohol. He had no allergies. He had emigrated from Guinea-Bissau seven years earlier and was married. He worked as a stone mason.

The pertinent findings on physical examination included a chronically ill appearance, temperature of 38ºC, dehydration, sinus tachycardia, blood pressure 100/50 mmHg, right basilar rales, nontender hepatomegaly (liver edge was palpable 2 cm below the costovertebral margin) and maculopapular rash on both legs, chest and back, with palms and soles spared.

Admission laboratory findings

Haemoglobin level 14.6 g/L, with a leukocyte count of $10.5x10^9$/L and a normal differential blood cell count. The platelet count was $268x10^9$/L, blood urea 116 mg/dl, creatinine 2.3 mg/dl, serum potassium 5.4 mmol/L, serum sodium 130 mmol/L, lactic dehydrogenase 1505 UI/L, creatine phosphokinase 806 U/L, alkaline phosphatase 289 U/L, SGOT 202 UI/L SGPT 161 UI/L and total bilirubin 0.5 mg/dl. Prothrombin rate was 85% (control 70-100%). His sputum was negative on smear, but was positive on culture for acid-fast bacilli (AFB).

The urinalysis revealed 3+ protein, and demonstrated otherwise unremarkable findings.

Prednisone 30 mg day orally was started immediately due to the severity of cutaneous lesions, and rehydration was instituted.

Additional findings

Calcium 6.2 mg/dl, phosphate 3.2 mg/dl, total protein 7.2 g/dl, albumin 1.9 g/dl, with a diffuse increase in gamma globulins on electrophoresis, IgG 2264 mg/dl (normal 700-1600); IgA 398 mg/dl (normal 70-400); IgM 189 mg/dl (normal 40-230). CH 50, C3 and C4 levels were normal. Hepatitis B antigen, hepatitis C antibody and HIV 1 and 2 serology were negative. Three blood cultures were all negative.

On the 10^{th} day of hospital stay (eleven days after the discontinuation of rifampicin) 24-hour urine protein excretion was 17.7 g.

The Bence-Jones reaction for protein was negative and immunoelectrophoresis of the urine was not conducted. No tests were performed for the detection of antibodies to rifampicin.

Chest radiography revealed right lower lobe infiltrate and right pleural effusion.

Renal ultrasonography showed normal dimensioned kidneys with good parenchyma, without evidence of hydronephrosis. A bone marrow biopsy specimen showed no amyloid, plasmocytosis, or other evidence of multiple myeloma (performed on the 25^{th} day of hospital stay).

Percutaneous renal biopsy was performed on 15^{th} day of hospital stay.

Renal biopsy findings. Renal tissues samples were stained with haematoxylin and eosin, periodic acid-Schiff and Congo red. Immunofluorescence studies were performed using antiserum to IgG, IgA, IgM, C3,C4, kappa and lambda light-chains.

Up to 8 glomeruli were seen on light microscopy, which were normal (Fig. 1). Results of Congo red stain were negative. Immunofluorescence studies revealed a granular deposition of IgM in the mesangium and kappa and lambda light-chains in the casts. The blood vessels were unremarkable. The most extensive changes were in the interstitium and tubules. The tubules were widely separated by interstitial oedema and infiltrate consisting mainly of mature plasma cells. No eosinophils were present. There was degeneration of tubular epithelium, which was variably swollen or shrunken. Particularly prominent was the presence of a variety of tubular casts within the tubules. Strongly haematoxylin and eosin positive casts were frequently composed of homogeneous material with an irregular outline and cracked or granular appearance present in the lumens of distal convoluted and collecting tubules. The changes resembled those seen in multiple myeloma except for the lack of giant cells (Fig. 2).

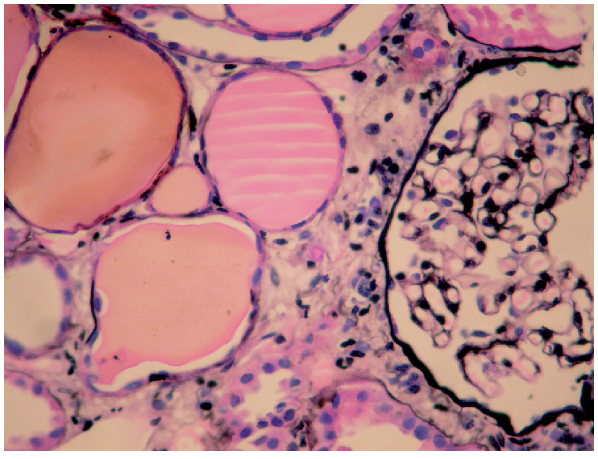

Figure 1

Renal biopsy specimen; many tubules are dilated and contain protein casts. Glomeruli tuft is normal (Silver Stain)

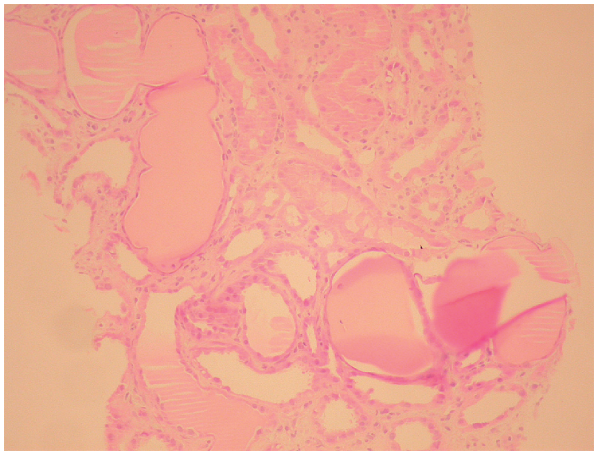

Figure 2

Tubular hyaline fractured casts without surrounding syncytial giant cell reaction (Hematoxilin-eosin stain)

Electron microscopy was not performed.

In summary, these findings were suggestive of cast nephropathy.

Twenty days after rifampicin discontinuation, non nephrotic proteinuria persisted (1.5 g per 24 hours). Serum creatinine and urea peaked at 2.8 mg/dl and 150 mg/dl respectively but patient did not require dialysis.

The patient's renal function returned to normal (serum creatinine level 1.2 mg/dl) within two weeks of stopping rifampicin. After 25 days, with resolution of cutaneous and hepatic toxicity, isoniazid, rifampicin and pyrazinamide were restarted while the patient was receiving prednisone 20 mg/day. There was no further recurrence of the renal problem.

In September 2006, three weeks after discharge, he was feeling well with normal renal function but non nephrotic proteinuria persisted (1.3 g per 24 hours) and patient continued to receive isoniazid, rifampicin and pyrazinamide.

DISCUSSION

In our case, abrupt renal failure developed in a patient who had suspended antituberculous treatment some days before due to cutaneous and hepatic toxicity. Treatment had been started one month earlier for pulmonary tuberculosis. Initially the clinical picture seemed acute renal failure compatible with an underlying acute interstitial nephritis, supported by the rash, myalgias, low-grade fever and concomitant hepatotoxicity. The nephrotic range proteinuria is well documented in acute interstitial nephritis, although in this case the proteinuria was very exuberant, and not simply justified by tubule-interstitial lesions. An interstitial nephritis induced by rifampicin hypersensitivity could not be completely excluded, because prednisone was administered some days before the renal biopsy.

The most striking histological feature, however, was the numerous tubular casts in the distal tubules and collecting ducts, resembling a "myeloma kidney". Despite this, the lack of a typical giant cell histological reaction and absence of the other clinical criteria made this diagnosis much less likely. Warrington *et al*[4] pointed out the similarity between the cast nephropathy in their case and that in cases of multiple myeloma. The lack of evidence of proliferative and reactive cellular responses to the tubular casts, so characteristic of myeloma kidney, distinguishes between these two conditions. Soffer *et al*[5] speculated that the explanation of this difference lies in the polyclonal origin of the light-chains in rifampicin cast nephropathy and in the monoclonal, usually lambda chain, origin of light-chains in multiple myeloma. The short duration of the disease and reversibility after stopping rifampicin could be an additional factor, making the more likely diagnosis a rifampicin-associated acute renal failure with polyclonal light-chain proteinuria, as immunofluorescence studies revealed light-chain λ and κ immunoglobulins in the casts. Deterioration in renal function was probably associated with a period of dehydration and toxic concentrations of free light-chains may have occurred in the urine, resulting in renal tubular cell damage. As described before by Warrington *et al*[4] and Winter *et al*[6] we suggest that renal failure was provoked by dehydration and that concentration of the light-chains with subsequent precipitation played a crucial role. We reintroduced rifampicin to our patient only following normalisation of renal function and rehydration, since volume depletion appears to have played a role in the induction of cast nephropathy. He did not develop further light chain proteinuria. In other reported cases, rifampicin was suspended definitely.

We cannot completely exclude concomitant glomerular involvement (we did not perform electron microscopy), despite normal glomerular appearance in light microscopy, although heavy glomerular proteinuria and effacement of epithelial foot process associated with rifampicin is described in literature[7,8].

While other drugs such as ethambutol, pyrazinamide, isoniazid and allopurinol were concomitantly administered, it is unlikely that these drugs played any part in the pathogenesis of this case. Renal damage due to these drugs usually produces tubule necrosis or interstitial nephritis rather than invasive tubular casts. Reviewing the literature, heterogeneous light proteinuria has not been found in those being treated with these drugs.

This is, to our knowledge, the fifth case of rifampicin-associated acute renal failure with light-chain proteinuria.

How light-chain proteinuria develops in tuberculous patients treated with rifampicin is unknown, but possible mechanisms were reviewed by Graber *et al* thirty years ago[9,10]. It was postulated that rifampicin interferes with heavy chain synthesis, making this portion of the immunoglobulin molecule unavailable for combination with light-chains, with subsequent urine excretion. They found light-chain proteinuria in 27 of 38 tuberculous patients treated with rifampicin and concluded that it was not of clinical significance in these patients. Some years later Kumar *et al* and Warrington *et al* described three tuberculous patients with acute renal failure associated with light-chain proteinuria that resolved with suspension of rifampicin[4,11].

As described previously practically all cases of acute renal failure reported in the literature were reversible[12,13], except for one case with permanent renal damage[8].

In conclusion avoidance of dehydration and contrast materials must be considered in tuberculous patients treated with rifampicin. Renal function parameters and proteinuria should be particularly monitored during the follow-up of a patient started on this drug.

Conflict of interest statement. None declared.

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