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ACUTE RENAL FAILURE AFTER RIFAMPICIN

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SUMMARY

A patient with miliary tuberculosis and a chronic urogenital focus is described, who had a borderline renal function at diagnosis and developed overt renal failure upon daily treatment with rifampin (RMP), isoniazid (INH) and ethambutol (EMB). This is the first Brazilian report of RMP induced renal damage. A renal biopsy taken on the third day of oliguria showed recent tubular necrosis with acute interstitial inflammation and granuloma formation. The aspect of the granulomatous lesion hightly suggested drug etiology because of the lack of palisading, high incidence of neutrophils and absence of facid-fast bacilli. This is the first presentation of an acute granulomatous interstitial nephritis probably due to RMP. Furthermore the pathogenesis of the renal damage caused by tuberculosis and RMP are discussed.

INTRODUCTION

Tuberculosis is a very common disease in Brazil and RMP has been widely used as an anti-TB drug during the last decade. Although many hundreds of patients received this antibiotic, there are no previous cases of Brazilian origin of renal impairment due to RMP, which is surprising when compared with the general medical literature where more than 60 cases have already been gathered. Herewith we are reporting such an occurrence to emphasize the possibility of this complication and its management.

CASE REPORT

A 55-year-old man was admitted to our service with a 25-day history of shaking chills and dysuria. Two years before he had noticed a scrotal abscess which was surgically drained at another medical center and evolved into a persistent scrotal fistula. He was complaining of back-pain, hematuria and urgency and there was also weakness, anorexia and weight loss. He specifically denied dyspnea, cough or hemoptysis. Three days before admission he had received a gentamicin 80 mg t.i.d. regimen.

On admission he looked wasted and moderately anemic. Temperature was 37.5°C, pulse 84 b.p.m., respiration 24/min, blood plessure 110/70 mm Hg, weight 40 kg. Physical examination was remarkable for an enlarged liver, a left scrotal fistula draining a white, thick material, and a nodular prostate with ill defined borders. Laboratory data were as follows: hemoglobin 10.7 g/100 ml, WBC 8,200 with 1 band cell, 52 neutrophils, 5 eosinophils, 42 lymphocytes and 1 monocyte; ESR 25 mm in one hour (control 17 mm); plasma urea 83 mg/100 ml; plasma creatinine 1.6 mg/100 ml; AST 60 IU/1, ALT 51 IU/1, AP 362 IU/1 LDH 305 IU/1; γGT 36 IU/1; Albumin 1,8 g and globulin 2.3 g in 100 ml. Ziehl-Neelsen staining of the scrotal discharge and of several urine samples disclosed acid-fast bacilli. Sputum smears were negative. Intradermal reaction to PPD 2 UT was absent. A chest radiography showed miliary infiltrate of the lungs. Excretory urogram revealed normal

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right kidney and exclusion of the left one without any other abnormality. Ultrasound examination of the left renal lounge was suggestive of hydronephrosis.

Considering these findings a diagnosis of miliary tuberculosis from a chronic urogenital focus was settled and a daily dosage of RMP 600 mg, INH 400 mg and EMB 800 mg was started.

Prostate biopsy taken soon after the admission revealed nodular hyperplasia and scattered chronic inflammatory infiltrate.

Fifteen days after the beginning of the therapeutics the patient developed high, spiking fever together with itching rash. He was put on a β1-histamine blocking agent, the rash disapeared in 24 h but fever and malaise persisted. On the 22nd day of treatment the urinary volume diminished. Investigation showed plasma urea, 61 mg/ 100 ml, plasma creatinine 2,0 mg/100 ml, normal hepatic and hematologic tests. Three days later a surgical biopsy of the right kidney was performed. Light microscopy displayed 19 normal glomeruli, recent tubular necrosis, acute interstitial inflammation and poorly developed granulomas (Fig. 1). The immunofluorescence fragment contained 15 glomeruli, 3 arteries and 5 arterioles and was negative for IgG, IgM, IgA, C3 and fibrinogen. A diagnosis of RMP nephrotoxicity was considered, this drug was discontinued and a daily dosage 40 mg prednisone was started. The course of the renal function is illustrated on Graph 1. Four peritoneal dialysis were performed. There was steady improvement after RMP withdrawal, so 3 weeks later prednisone was tapered and discontinued after another 2 weeks. Four months after the commencement of antituberculosis therapeutics the patient was submitted to left nephro-uretero-epididymo-orquiectomy that showed hydronephrotic kidney with chronic interstitial nephritis and acid-fast ba-

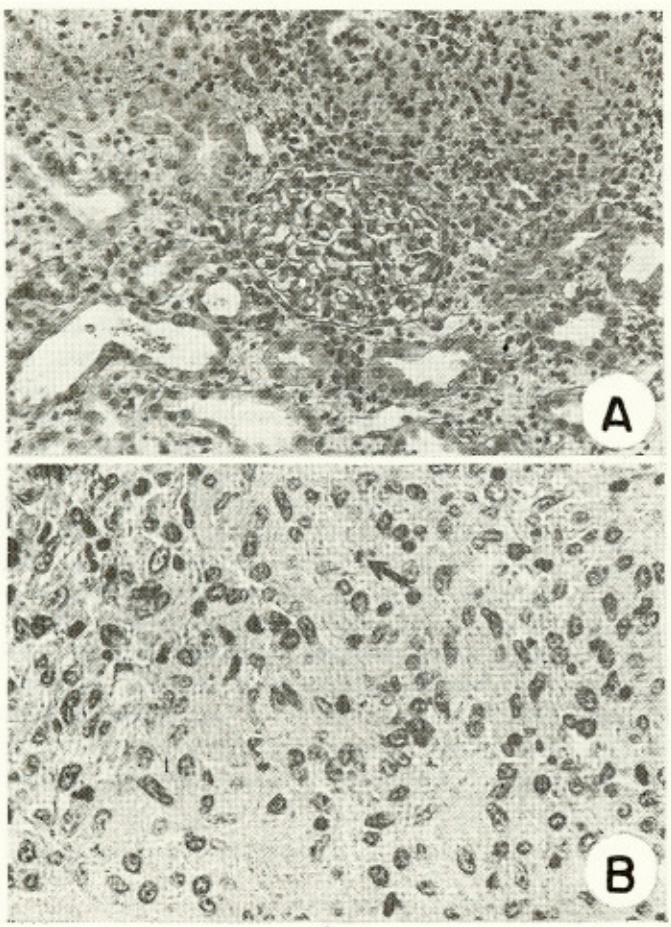
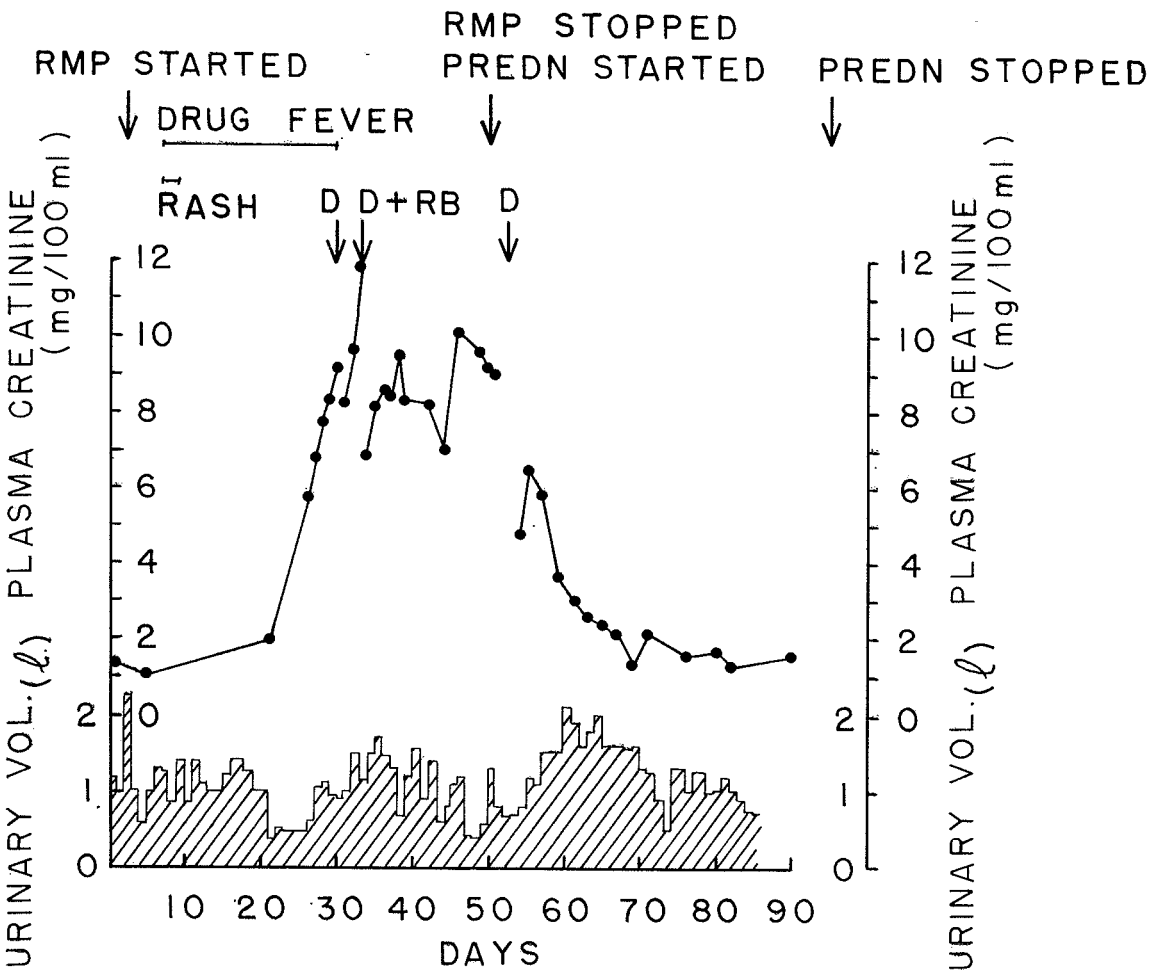


Fig. 1 — **Renal biopsy.** Fig. 1A — Well preserved glomerulus. Dilated tubules with necrotic epithelial cells. Acute interstitial inflammation. A loose granulomatous formation is seen in the right bottom of the plate. Fig. 1B — Higher magnification of the granuloma shown in Fig. 1A. Note the irregular displayment of the cells and presence of neutrophils (arrow). Ziehl-Neelsen staining of this fragment was negative (not shown). (H.E., × 160)



Graph 1 — Serum creatinine level, urinary volume and outstanding clinical events after start and discontinuation of therapy with RMP. P.D.: Peritoneal dialysis; Predn.: Prednisone; R.B.: Renal biopsy. See text for detailed discussion.

cilli ladden tubercles (Fig. 2); fibrotic ureteral structures; granulomatous epididymitis; chronic orquitis. He recovered from the surgical procedure uneventfully and was discharged from the hospital a week later.

DISCUSSION

Tuberculosis has been known for a long time to determine renal failure either by parenchimal loss upon cavitation or by mechanical obstruction of the urinary tract. More recently microscopical lesions were emphasized in the genesis of uremia. A series of 52 roentgenological observations of urogenital tuberculosis disclosed a 30% rate of poor renal function without obstruction of the upper urinary tract [13].

In fact, it is long known that renal injury associated with tuberculosis of any site is more frequent than clinically suspected [8]. Further studies of biopsy material described a high incidence of tuberculous glomerulonephritis [1] which might determine some loss of renal function and the granulomatous interstitial nephritis by itself was responsible for acute renal failure in another group of patients [7].

The case described in this report showed extensive tuberculous urinary injuries at admission, comprising hydronephrosis of one kidney and overall poor renal function. These evidences suggest that RMP toxicity settled on previously damaged kidneys.

Since the first communications ascribing renal impairment to RPM, in 1972, a clinical

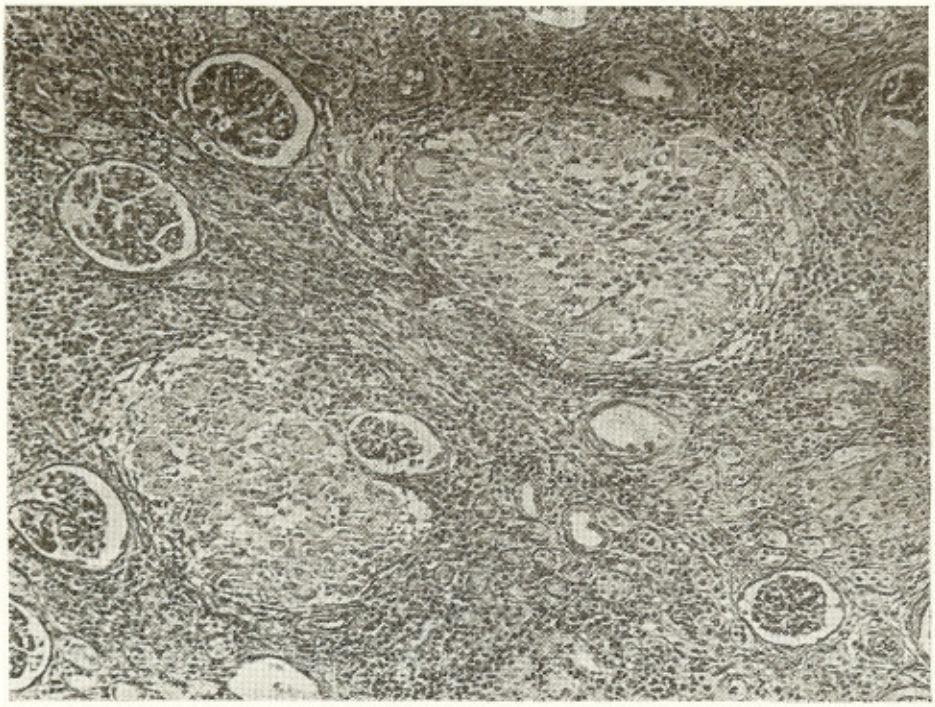


Fig. 2 — Section of nephrectomy specimen. Well preserved glomeruli. Normal and atrophic tubules. Chronic interstitial inflammation and fibrosis. Granulomas with surrounding epithelioid cells and lymphocytes and giant cells. Ziehl-Neelsen of this preparation revealed acid-fast bacilli (not shown). There are no granulomatous formations similar to those represented in Fig. 1 (H.E., × 32)

characterization of the entity has been accomplished. It rarely occurs during continuous therapy, being rather a complication of intermittent or discontinuous schedules, often preceded by a flu-like syndrome, diarrhoea, vomiting or rash[9] and sometimes accompanied by hepatic abnormalities[12]. It appears after a period of time which varies from some days[11] to some years from the beginning of therapeutics. The renal function is promptly recovered upon drug withdrawal with a single reported exception of permanent impairment[2]. There is a record of steroid administration favorably influencing the course of the disease[11].

The patient that we followed developed acute uremia on the 22nd day of continuous RMP regimen, preceded by other signs of drug toxicity like fever, malaise and rash. The renal failure persisted for 3 weeks after RMP discontinuation and prednisone commencement, evidencing an earlier recovery than the literature predicted. The use of steroids must have been beneficial in this case.

The previously reported histological pattern associated with RMP nephrotoxicity comprises interstitial nephritis and acute tubular necrosis. Further work-up was done trying to correlate these histologic findings with the well-known immuno-allergic disturbances caused by this antibiotic. Antibodies and-RMP are invariably detected and sometimes circulating immune complexes too[3]. The occurrence of renal failure consequent to drug induced immuno-hemolysis is verified in a few instances[14]. Some Authors favor renal ischemia secondary to a vascular primary site of action based either on the observation of high renin activity[5] or on histologic details[10]. Isolated reports of positive immunofluorescent staining of the tubular basement membrane suggest a type II reaction[4,15]. Conversely, type I reaction is sypported by high Ig E anti-RMP (12) and elevated histamine realeasing activity of the serum of some patients[9]. Finally, light-chain proteinuria was described in association with renal failure, but its pathogenetic implications are unknown[6].

The histological picture in our case was of recent tubular necrosis with granulomatous interstitial inflammation. The aspect of the granulomas highly suggested drug etiology because of lack of palisading, abundant neutrophilic infiltration and absence of acid-fast bacilli. The contralateral kidney examined two months after RMP withdrawal, displayed typical tubercles and chronic interstitial inflammation. Although we could not definitely exclude tuberculous etiology of the lesion viewed on biopsy, we believe that we probably registered the first granulomatous presentation of RMP nephrotoxicity. There was no additional pathogenetic work-up as RMP antibodies or other procedures are not yet avaliable at our medical center.

Finally we would like to emphasize that RMP renal failure was observed only with concurrent tuberculosis in spite of its use in other infections in many countries. The length of the treatment is not a convincing argument because renal impairment appeared within days of use in some reports. There must be some interaction between tuberculosis and RMP in the genesis of the renal damage.

RESUMO

Insuficiência renal aguda por rifampicina

Apresentamos um paciente com tuberculose miliar a partir de um foco crônico urogenital. Em sua entrada no hospital tinha uma função renal limítrofe e desenvolveu franca insuficiência renal na vigência da terapêutica específica constituída por RMP, INH e EMB. Biópsia renal realizada no 3.º dia de uremia revelou necrose tubular recente, com inflamação intersticial aguda, permeada por granulomas. As formações granulomatosas foram altamente sugestivas de reação alérgica à droga devido à ausência de paliçadas, alta incidência de neutrófilos e o não encontro de bacilos-álcool-ácido-resistentes. Esta é a primeira descrição de nefrite intersticial granulomatosa provavelmente causada pela RMP.

São discutidos os principais aspectos fisiopatogênicos da insuficiência renal causada pela tuberculose acrescida dos efeitos nefrotóxicos da RMP.

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