

ACUTE RENAL FAILURE AND NEPHROTIC SYNDROME AFTER MANEB EXPOSURE. A NEW CASE WITH LIGHT AND ELECTRON MICROSCOPIC STUDY*.

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SUMMARY

A new case of nephrotoxic effect of Maneb is related. The patient used this product as fungicide and developed a progressive illness with acute renal failure. The study by light and electron microscopy revealed severe tubular lesions that disappeared some months later with tubular cell regeneration. However, in spite of the renal function returning to normal, a steroid-dependent nephrotic syndrome persisted with glomerular minimal change like lesions.

RESUMO

Insuficiência renal aguda e síndrome nefrótica. Após exposição a Maneb. Um novo caso com estudo microscópico de luz e electrões

Os autores apresentam um novo caso de nefropatia após o uso de Maneb. O doente utilizou este produto como fungicida tendo sofrido posteriormente de doença progressiva com insuficiência renal aguda. O estudo das lesões renais, em microscopia de luz e electrónica, mostrou alterações profundas tubulares de que o doente recuperou alguns meses mais tarde. Todavia e a despeito da função renal ter voltado aos valores normais, mantiveram-se as lesões glomerulares do tipo de lesões mínimas, associadas a síndrome nefrótica esteróide dependente.

INTRODUCTION

Maneb (Manganous ethylenebis (dithiocarbamate) is a widely employed fungicide, considered to be of low toxicity to man and limited to inflammatory reactions of the skin and mucous membranes. However, Koizumi et al.¹ described a case of acute renal failure (ARF) associated to Maneb exposure and adverted against the probable renal toxicity of this product. In this paper we report a new case of renal toxicity, with light and electron microscopy of renal lesions, observed in a patient after unprotected use of Maneb, and in which a persistent nephrotic syndrome followed ARF.

CASE REPORT

A 54-year-old man was admitted to the hospital on July 2, 1984, with peripheral edema and oliguria. He was a previously healthy farm worker and had never used Maneb before.

Present illness—On the morning of June 27, 1984, the patient had been preparing a solution that consisted of 100 g of Maneb in 50 L of water. During the whole day, he spread this solution over potato plants using a mechanical sprayer. He did not take any protective measures, namely, he did not wash his hands or body after finishing the work and he used his lips to clean the holes of the sprayer.

On the following day, nausea, vomiting and diarrhea occurred and the patient felt very sick and weak. On the three consecutive days, those symptoms worsened and he developed peripheral edema and reduced diuresis.

Findings on Admission—Physical examination revealed peripheral edema, most evident on the face and ankles. There were no signs of cutaneous or conjunctival inflammation. Neurologic examination was negative. Lung and heart auscultation was normal. The pulse was 76, rhythmic, the blood pressure 120/80 mmHg, and the respirations 16. The temperature was 37°C and the body weight 89 kg (the patient's anterior weight was 80 kg).

On laboratory studies, the serum levels of the nitrogen was 93,5 mg/dl, the creatinine 2,3 mg/dl, and the uric acid 8 mg/dl. Arterial blood gas determinations showed that

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metabolic acidosis was present. Other blood tests, including hemogram, platelets, sodium, potassium, calcium, phosphorus, proteins complement IgM, IgG, IgA, pseudocholinesterases, CPK, and aldolase, had values within normal ranges. No antinuclear antibodies and cryoglobulins were found. On urine examinations, the sediment contained 10 red cells and 5 white cells per high power field; in a 24-hour specimen, the protein was 2.4 g; the culture yielded no growth.

Clinical course—During the hospital stay, the renal function decreased progressively, and the patient was submitted to a low salt diet and a balanced water intake. Twenty two days after Maneb exposure, the patient underwent a closed renal biopsy. On August 1, the average diuresis was 500 ml/24 hours, the peripheral edema was more marked than it was on admission; the body weight had increased to 91 Kg, the serum creatinine was 3.8 mg/dL and the creatinine clearance 25 mL/min. On August 19, the plasma protein was 4.1 g/dL (the albumin 1.9 g/dl and the globulin 2.9 g/dL), the 24-hour urinary protein was 12.7 g/1.73 m² and the presence of a nephrotic syndrome was confirmed. Two days later, the patient began the therapy with oral prednisolone (80 mg/day) and a low salt albumin infusion was administered for twelve days. Daily urine volume increased steadily then, and the weight and edema lessened. On September 21, still on prednisolone therapy with the same dosage, the patient felt well, the weight was stable around 80 Kg, and all the symptoms and signs disappeared; the serum creatinine was 0.8 mg/dL, the serum urea nitrogen was 28 mg/dl, the plasma protein was 5.3 g/dL (the albumin 2.8/ g/dL and the globulin 2.5 g/dL); in a 24-hour specimen of urine, the protein was 1.0 g and the sediment was normal.

In November 1984, the creatinine and urine sediment were normal, but the steroid-dependent nephrotic syndrome persisted. In March 1985, the patient underwent a second closed renal biopsy. In July 1986, the renal function was normal but there was still a vestigial steroid-dependent proteinuria.

First renal biopsy—In the specimen observed by light microscopy (Fig. 1), severe tubular lesions were observed, affecting mainly the proximal convoluted tubules. Cell swelling, vacuolization, disappearance of the brush border, reduced tubular lumina and necrosis were present. Some hyaline casts were observed in distal tubules and there were leukocyte accumulations in medullary vasa recta. No interstitial inflammation or any significant glomerular lesions were seen.

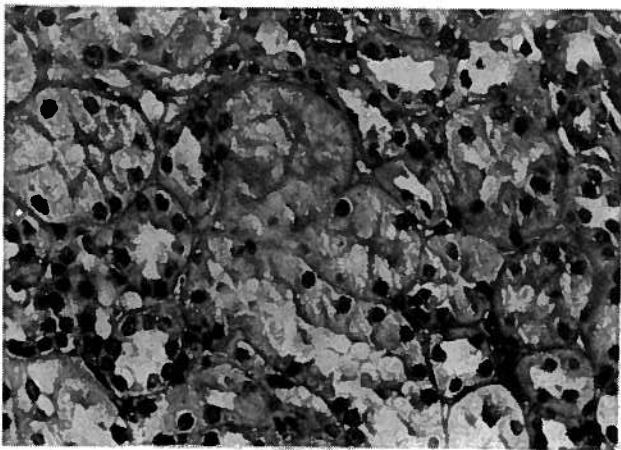


Fig. 1—Tubular lesions observed by light microscopy (375X). Cell swelling, vacuolization and disappearance of the brush border.

The electron-microscopy confirmed the previous findings at the proximal tubules and further demonstrated organelles destruction, total or partial disappearance of the brush border, formation of blebs in the tubular lumina and other signs of irreversible cell lesions. Noteworthy, the tubular basement membrane was not destroyed and some tubular regeneration cells with large nucleoli and cytoplasm rich in organelles, like ribosomes, were found. (Figs. 2,3). In the glomeruli, the

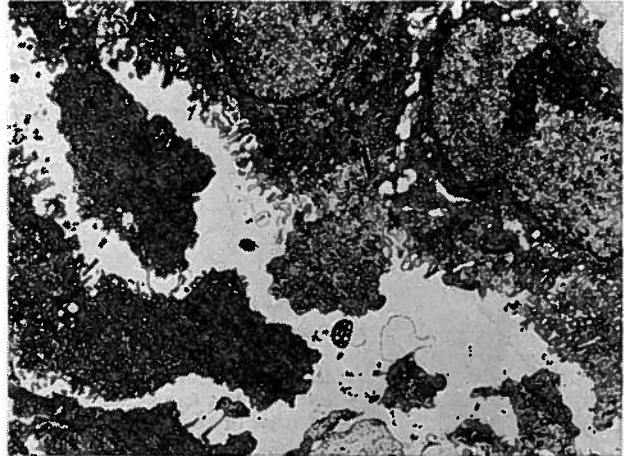


Fig. 2—Proximal tubule with disappearance of the brush border and formation of blebs in the tubular lumina (8.000X).

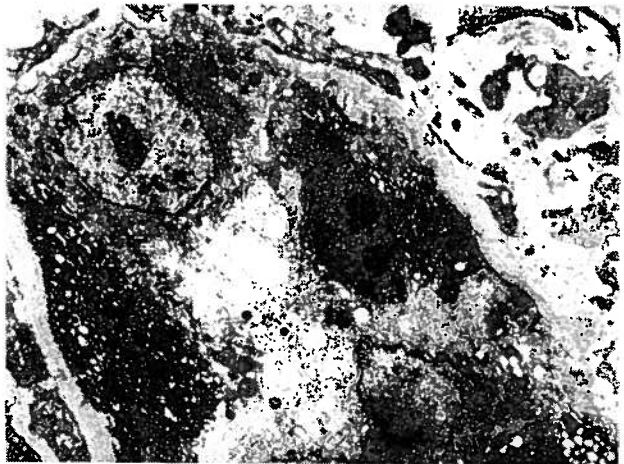


Fig. 3—Proximal tubule with signs of cell lesions, brush border disappearance and with some regeneration cells. (4.800X).

epithelial foot processes were fused along extensive areas of the capillary walls (Fig. 4) and there was only mild segmentary thickening of the mesangium.

Second renal biopsy—In the specimen observed by light microscopy the tubular structure was reconstituted without remarkable sequel. The ultrastructural study showed that the structure of the proximal tubules had completely recovered (Fig. 5); however, the glomerular lesions persisted with fusion of the epithelial foot processes and even greater mesangial reaction (Fig. 6).

COMMENTS

The relationship between Maneb exposure and ARF is strongly suggested by the present case, which provides sup-

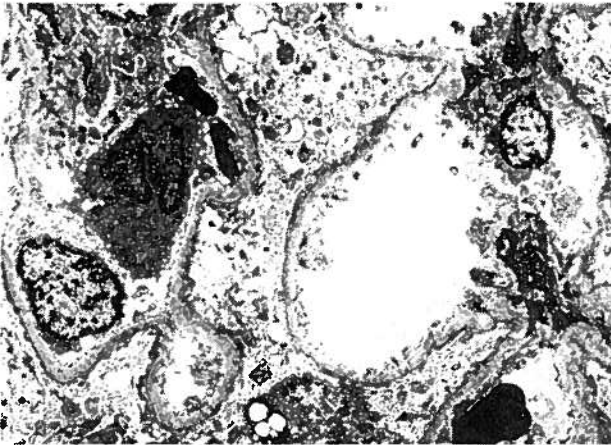


Fig. 4—Glomeruli with epithelial foot processes fused along extensive areas of the capillary walls (4,800X).

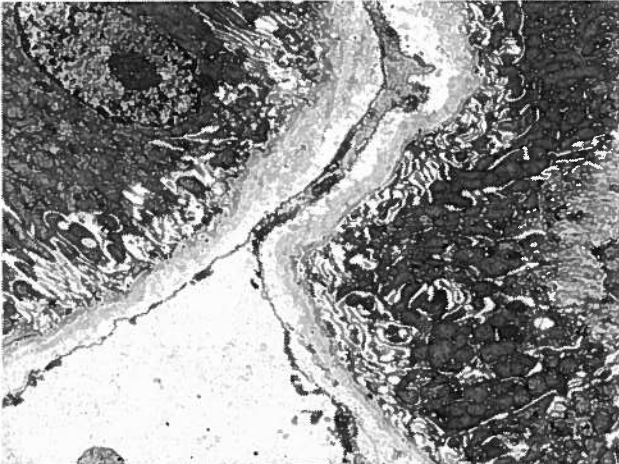


Fig. 5—Proximal tubule recovered ultrastructural characteristics namely a well developed brush border (4,800X).

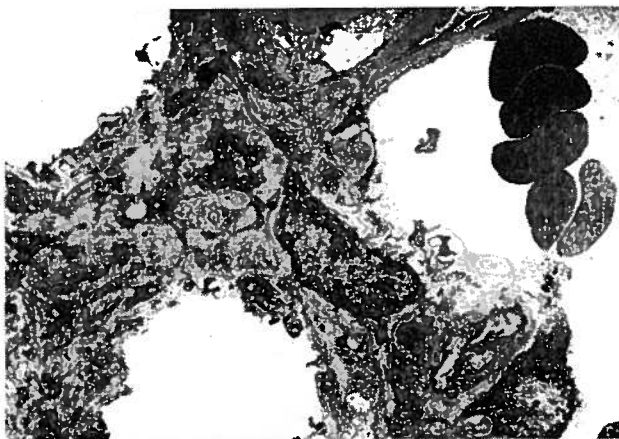


Fig. 6—Glomerular lesions with mesangial reaction and persistent foot processes fusion (4,800X).

port for the hypothesis advanced by Koizumi et al.¹ about the renal toxicity of this chemical. An oliguric ARF occurred and was followed by the recovery of normal renal function

eight days later, although a steroid-dependent nephrotic syndrome persisted.

This case may be a good model for the study of the lesions responsible for ARF induced by a specific toxic mechanism. Most cases of ARF after toxic exposure in man, except that of a deliberate intake, involve several etiopathogenic factors and conclusions about the role of each one are hard to draw². In our patient, there is no indication of the presence of previous renal lesions or other potentially nephrotoxic factors with glomerular lesion and nephrotic syndrome, namely rifampin³ or nonsteroidal anti-inflammatory drugs such as fenoprofen⁴ or tolmetin⁵. So, the light and ultrastructural findings of two renal biopsies may be attributed with a certain accuracy to the action of Maneb. In the first renal biopsy, the lesions were more severe at the tubular level, as is usual with toxic action. Contrary to what is stated in ischemic ARF⁶, the tubular basement membrane was intact and there were signs of early cell regeneration. The absence of an interstitial inflammatory reaction and the scarcity of cellular casts does not suggest backleak of tubular fluid and suggest that reflex vasoconstriction could be the mechanism of oliguria^{2,7}. At the glomerular level, the alterations were not relevant when observed by light microscopy; however, an extensive fusion of epithelial foot processes was seen at electron-microscopical examination. This alteration, that is characteristic of a nephrotic syndrome, had not been previously described after manebe exposure.

In the second renal biopsy, the abnormalities persisted together with an increase in mesangial cellularity and matrix and they were associated to a persistent and steroid dependent nephrotic syndrome. This nephrotic syndrome, not described by Koizumi et al., does not have a clear pathogenesis. There was not any sign of immunologically-induced glomerular lesion such as membranous glomerulopathy or immune-type deposits, in contrast to the findings in cases of nephrotic syndrome associated with many other chemicals used for therapy or other purposes. Morphologically, the observed glomerular lesions look rather like minimal-change disease with mild mesangial cell proliferation, as it occurs commonly in the adult⁸. Nevertheless, this does not invalidate the possibility of an immunologically-mediated lesion, dependent on T-lymphocytes, as was mentioned in other cases of minimal-change disease^{8,9}. Similarly, as regards the other toxics mentioned, like mercury, we cannot exclude the possibility that the tubular lesions found in the first biopsy could be responsible for the antigenic challenge.

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