

*Case Report*

## **Membranous nephropathy from exposure to mercury in the fluorescent-tube-recycling industry**

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### **Introduction**

Mercury is a silvery white liquid metal that is volatile at room temperature due to its high vapour pressure. It exists in different oxidation states and can form a number of compounds. Mercury and its compounds can be absorbed into the human body by inhalation, ingestion, and through the skin. It is toxic when certain threshold values are exceeded. Acute toxicity is due to the inactivation of enzymes by the heavy metal, which leads to interstitial pneumonitis, ulcerative gastro-enteritis, or tubular necrosis, depending on the route of exposure. Long-term mercury poisoning affects mainly the central nervous system and the kidneys. In the latter case the nephrotoxicity is usually manifested as membranous glomerulonephritis (MGN) with nephrotic syndrome.

Since 1920, numerous cases of nephrotic syndrome due to long-term contact with mercury and mercury compounds have been reported. Mercurial diuretics (Mersalyl<sup>®</sup>), teething powders for young children, and mercury-containing ointments for psoriasis were the main sources of exposure in medicine [1,2]. In 1962, MGN was demonstrated by renal biopsy in five cases of nephrotic syndrome due to psoriasis ointments containing mercury [3]. MGN due to skin-lightening creams containing mercury was reported last in 1987 [4]. In industry, mercury is still used in gold mines, in chlor-alkali plants, and in the manufacture of batteries. In daily life, it occurs in technical and control instruments.

Here we report for the first time two cases of membranous nephropathy due to occupational

### **Case 1**

A 49-year-old worker was admitted to our hospital because of suspected mercury intoxication. About 6 months before admission the patient had started work in a factory where fluorescent tubes were recycled, but after 6 weeks he felt weakness, suffered from intermittent headaches, experienced nausea, vomiting, lack of appetite, and insomnia, and noticed changes in his personality such as excitability and depression. There was no personal or family history of renal disease, oedema, hypertension, or psychiatric problems.

Physical examination showed a man of 170 cm height and 73 kg body weight, in balanced hydration, and without pathological signs in lungs, heart, abdomen, or nervous system. Blood pressure was 130/70 mmHg and heart rate was 72 beats per min.

Laboratory investigations revealed decreased total serum protein (5.4 g/dl), increased serum cholesterol (425 mg/dl), and 4+ proteinuria. Urinary sediments showed 0–1 white blood cells, 0–3 red blood cells, and some hyaline casts by phase-contrast microscopy (400×). The 24-h urine protein excretion was 7.7 g, creatinine clearance 124 ml/min. Haemoglobin was 17.6 g/dl, haematocrit 52.4%, platelets 286/nl, and the white blood cell count was 11.2/nl with a normal differential. Serum sodium, potassium, creatinine, and BUN were within normal ranges. Antibodies against nuclear antigens (ANA), mitochondria (AMA), and neutrophil cytoplasmic antigens (ANCA) could not be detected. Serum complement studies showed normal C4 and increased C3 (157 mg/dl). Serum electrophoresis showed a decrease of albumin to 2.7 g/dl (50.5% of normal) and an increase of the alpha-2 fraction (18.5%). An elevation of IgE (266 U/ml) was observed, but IgG (7.1 g/l), IgM (0.83 g/l), and IgA (4.3 g/l) were normal. HBs antigen and antibodies against HBs, HBe, and HCV were not detectable.

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On ultrasonography, the length of the right kidney was 10.3 cm, of the left kidney 10.0 cm, and both kidneys were of normal shape.

Further tests revealed an elevated blood mercury concentration of 11.1 µg/l and an increased urinary mercury excretion of 118 µg/l. Reference values in the non-exposed population are approximately 8 µg/l in blood and 4 µg/l in urine. A mercury-removal test with 2,3-dimercapto-propane-1-sulphonate (DMPS) was performed: oral application of 300 mg DMPS was followed by a 24-h urine collection. The total amount of mercury excreted was significantly elevated at 2208 µg/l, indicating a high body concentration.

## Case 2

A 47-year-old man was admitted to our hospital because of nephrotic syndrome. The patient had started working in the same factory as in case 1 about 6 months before admission. He was personally involved in recycling fluorescent tubes. Six weeks prior to admission he noted painless swelling of both legs and accompanying weakness. He did not complain of other health problems. There was no personal or family history of renal disease, oedema, or hypertension.

Physical examination showed an overweight man (176 cm height and 107 kg body weight), in no distress. Both legs were oedematous up to the knees. There were no pathological findings in the lungs, heart, abdomen, or nervous system. Blood pressure was 150/90 mmHg and heart rate was 82 beats per min.

Laboratory investigation revealed decreased total serum protein (5.6 g/dl), increased serum cholesterol (352 mg/dl), and a 3+ proteinuria. Microscopic examination of urinary sediment showed 0–2 white blood cells, 2–5 red blood cells, and some hyaline casts. The 24-h urine protein excretion was 12.3 g and creatinine clearance was 157 ml/min. Blood cell count, haemoglobin, platelets, serum sodium, potassium, creatinine, and BUN were within normal ranges. ANA, AMA, ANCA, and antibodies against laminin could not be detected. C4 was normal but C3 was increased to 175 mg/dl. An elevation of IgE (1342 U/ml) and a decrease of IgG (3.1 g/l) were noted, but IgM (1.13 g/l) and IgA (1.05 g/l) were within normal limits. Antibodies against hepatitis C were not detectable. Anti-HBc and anti-HBe antibodies were present, whereas HBs-antigen and anti-HBs antibodies were not detectable.

Ultrasonography showed kidneys of 13 cm length and of regular shape.

Mercury concentrations were increased in blood (41.2 µg/l) and urine (158 µg/l). After oral administration of 300 mg DMPS, urinary mercury excretion increased to 1242 µg/l.

## Histological findings

Renal biopsies revealed MGN in both cases. On light microscopy there were no significant pathological

alterations in Bowman's space, the mesangial cells, or the basement membrane. The interstitium was moderately oedematous and hyaline material was present in the tubular lumina. Immunofluorescence revealed granular deposits of IgG and C3 along the glomerular basement membrane. Electron microscopy revealed subepithelial electron-dense deposits and an effacement of the foot processes of visceral epithelial cells.

## Follow-up

The first patient was lost to follow-up and information is available only in case 2. This patient stopped working in the tube-recycling factory. Two years after withdrawal from exposure, mercury concentrations in blood (0.5 µg/l) and urine (0.5 µg/l) had fallen below reference values for non-exposed populations. The 24-h urine protein excretion decreased from 12.3 to 0.32 g and creatinine clearance was 112 ml/min.

## Discussion

Fluorescent tubes contain 10–25 mg metallic mercury vapour per tube, which emits ultraviolet radiation. This vapour is released when the lamps are recycled and can be absorbed by inhalation; 80% is retained in the human body after oxidation to Hg<sup>2+</sup> [5,6].

In these two cases the patients developed MGN about 6 months after starting work in a factory where they were personally involved in recycling fluorescent tubes. Using an atomic absorption method to measure urinary mercury excretion, we demonstrated high concentrations of mercury in their bodies. The urinary concentrations of mercury were 15–20 times higher than reference values for non-exposed populations. MGN has been reported in association with mercury and gold, whereas other precious metals such as silver or titanium do not induce MGN. We therefore concluded that these patients had developed mercury-induced MGN.

In humans, the pathomechanism of mercury-induced MGN has not been elucidated. Experimental studies in rats point to a genetic susceptibility and to polyclonal stimulation of the immune system in mercury-induced MGN. Brown–Norway (BN) rats, Dorus–Zadel black rats, and MAXX rats developed MGN after administration of HgCl<sub>2</sub>, whereas in other strains GN could not be induced by mercury [7,8]. In addition, the exposure of BN rats to Hg vapour induced a membranous nephropathy [9]. The underlying pathogenetic mechanism is characterized by a T-lymphocyte-dependent polyclonal B-cell activation, with subsequent production of autoantibodies against proteins of the glomerular basement membrane (GBM) such as laminin and fibronectin, and also against heparan sulphate proteoglycans [10,11]. It is not

known whether similar mechanisms operate in humans. The results of epidemiological studies in workers exposed to mercury are inconsistent concerning renal function and immune reaction.

We could not demonstrate anti-laminin antibodies in case 2. However, this patient had been admitted at least 8 weeks after exposure to mercury had ceased, and antibody titres may already have decreased below the limit of detection. In addition, antibodies might be not detectable because of low circulating concentrations due to complex building with target antigens in the GBM. Theoretically, polyclonal B-cell activation might result in the production of antibodies against membrane proteins of visceral epithelial cells similar to those in experimental Heymann nephritis (HN). Such antibodies render specificity to epitopes of a glycoprotein on membranes of visceral epithelial cells, designated megalin/gp330. *In-situ* immune-complex formation results in subepithelial immune deposits and proteinuria in HN [12]. However, evidence supporting this hypothesis has not yet been reported in humans.

During follow-up, case 2 patient went into remission with a urinary protein excretion of only 0.32 g/day after withdrawal from exposure to mercury. Similar good results have been reported in gold-induced MGN.

Secondary MGN is commonly associated with infections, malignancies, SLE and drugs such as gold salts and D-penicillamine. The cases reported here emphasize the importance of enquiring into patients' social histories for possible associations.

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