AJKD
Case Report

Mercury-Associated Nephrotic Syndrome: A Case Report and Systematic Review of the Literature

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Kidney injury from mercury is known to cause dose-related tubular dysfunction and idiosyncratic nephrotic syndrome according to various case reports. Motivated by a patient with subacute-onset nephrotic syndrome, histologic features of secondary focal segmental glomerulosclerosis, and concurrent mercury toxicity, we conducted a systematic review to explore renal histologic changes in patients with toxic mercury exposures and nephrotic syndrome. Data were extracted from a patient's clinical record. MEDLINE/Ovid was searched from 1950 to November 2010 using a prespecified search strategy. Two nephrology textbooks and the UpToDate online database also were searched. Inclusion criteria were studies of humans with nephrotic syndrome, nephrotic-range proteinuria, or kidney biopsy results reported. There were no exclusion criteria. We identified 27 other reports of 42 patients with nephrotic syndrome or nephrotic-range proteinuria. Of the 26 individuals, including our patient, who underwent kidney biopsy, histology showed glomerular disease in 21. Of these 20 biopsies, 4 showed minimal change disease and 15 showed membranous glomerulonephritis. Mercury exposure can lead to various glomerular lesions; we emphasize the importance of a careful occupational and dietary history in elucidating a cause for the undetermined nephrotic syndrome.
Am J Kidney Dis. 62(1):135-138.

INDEX WORDS: Mercury; kidney; nephrotic syndrome; kidney biopsy.

Mercury exists in elemental, inorganic, and organic forms and exposure occurs dermally, by inhalation, and by ingestion. Historically, sources of human mercury exposure have included dental amalgam fillings, dietary consumption, occupational exposure, and vaccines. Epidemics have included the mad hatter neuropsychiatric syndrome from fabrics soaked with mercury in the hat industry, poisoning from mercuric chloride used to treat infectious yaws (*Treponema pallidum*) before penicillin, and neurodevelopmental abnormalities (Minamata disease) in Japan from fish contaminated with mercury-containing waste.[1,2] The World Health Organization has issued warnings about the dangers of mercury-containing compounds. The thresholds for allowable levels of mercury have recently been lowered to 0.1 μg per kilogram of body weight per day by the US Environmental Protection Agency.[3]

In the United States, isolated case reports of mercury toxicity caused by inadvertent dermal absorption[4] and ingestion of meat from animals accidentally fed with mercury-treated grain[5] have been reported. In 1974, Wang and colleagues proposed a classification of kidney pathology from mercury.[6]

CASE REPORT

During the course of 1 month, a 60-year-old Jamaican man developed intermittent paresthesias of both hands and fatigue. Investigations identified nephrotic-range proteinuria leading to referral to the renal outpatient service. He had a history of well-controlled hypertension, long-standing Raynaud phenomenon, gout, and a penile implant. His only medication was amlodipine. He worked as a bartender and did not report smoking, drinking, or using recreational drugs. On examination, blood pressure was 140/85 mm Hg. Findings from neurologic, cardiac, respiratory, and abdominal examinations were unremarkable. There was no peripheral edema. One distal interpharangeal joint was acutely inflamed, consistent with gout.

Values for complete blood count, electrolytes, calcium, phosphate, hemoglobin A_{1c}, random glucose, and uric acid were normal. Creatinine level was 1.3 mg/dL, serum urea nitrogen level was 16.8 mg/dL, and albumin level was 3.2 g/dL. Urinalysis showed protein (3+) and trace blood. A 24-hour urine collection showed 6,800 mg of protein. Creatine kinase level was 350 U/L. Results for quantitative immunoglobulins; cryoglobulins; serum and urine protein electrophoresis; serologic tests for hepatitis B, hepatitis C, and human immunodeficiency virus (HIV); antiphospholipid antibody; antinuclear antibody; antineutrophil cytoplasmic antibody; and rheumatoid factor were negative.

Renal ultrasound showed bilateral increased echogenicity and loss of corticomedullary differentiation. Electromyography showed a patchy slowing of conduction in distal sensory and motor fibers consistent with early neuropathy of the upper and lower extremities. Magnetic resonance imaging of the brain showed evidence of

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Received October 4, 2012. Accepted in revised form February 25, 2013. Originally published online April 22, 2013.

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0272-6386/$36.00
http://dx.doi.org/10.1053/j.ajkd.2013.02.372

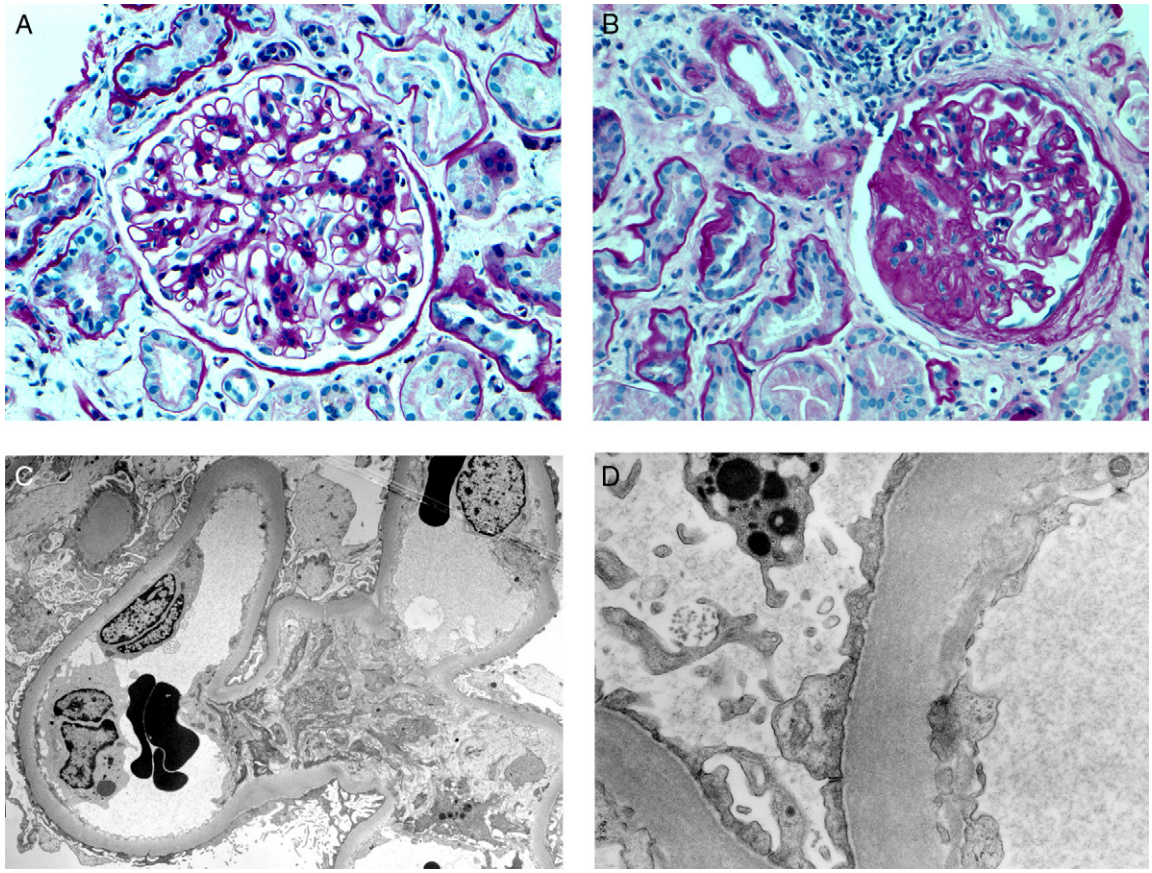

Figure 1. Kidney biopsy. (A) A total of 27% of glomeruli showed capillary wall thickening and mesangial expansion by cells and matrix. (B) Sclerosis and hyalinosis with adhesion to Bowman capsule; moderate interstitial fibrosis, and tubular atrophy. (A, B: Periodic acid–Schiff; original magnification, ×200.) (C, D) Electron microscopy: irregular thickening of glomerular basement membrane and prominent visceral epithelial cell foot-process effacement. (Original magnification, [C] ×2,000; [D] ×12,000.)

chronic microangiopathic disease and several small focal areas of old infarcts.

Over 3 weeks, peripheral edema developed and serum creatinine level increased to 2.2 mg/dL.

Kidney biopsy showed 22% globally sclerotic glomeruli by light microscopy. Twenty-seven percent of glomeruli showed capillary wall thickening and mesangial expansion by cells and matrix (Fig 1A). A single glomerulus showed a segment of sclerosis and hyalinosis with adhesion to Bowman capsule. There also was moderate interstitial fibrosis and tubular atrophy (Fig 1B). Immunofluorescence microscopy was negative. Electron microscopy showed irregular thickening of the glomerular basement membrane and prominent visceral epithelial cell foot-process effacement (Fig 1C and D).

A glucose tolerance test was performed: fasting glucose level was 101 mg/dL, and 2 hours after a 75-g glucose load, was 92 mg/dL (both within the reference range). In the absence of evidence of a secondary cause, we made a provisional diagnosis of idiopathic focal segmental glomerulosclerosis (FSGS) and prescribed prednisone, 1 mg/kg/d, ramipril, and furosemide. One month later, repeated 24-hour urine protein level was 5.3 g. The patient developed steroid-induced diabetes and was started on insulin therapy.

Two months later, the patient was hospitalized for left-leg cellulitis precipitating a hyperglycemic hyperosmolar nonketotic state. His 24-hour urine protein excretion was 6,000 mg. He was discharged to home on decreasing doses of prednisone. Serum mercury level, inadvertently ordered, was 174 (reference range, 0-18) nmol/L. Urinary mercury excretion was 39 (reference, <20) nmol/d. Before this could be investigated further or treated, the patient died suddenly at home. The coroner found his freezer well stocked with freshwater fish and the family confirmed that the patient had eaten freshwater fish many times a week for years. However, the mercury content of the fish was not available for this report.

DISCUSSION

We searched MEDLINE in duplicate from 1950 to November 2010 using the search strategy (exp Mercury compounds or exp Mercury or exp Mercury poisoning) and (exp Kidney diseases), limited to human studies. Inclusion criteria were studies of humans with nephrotic syndrome, nephrotic-range proteinuria, or kidney biopsy results reported; there were no exclusion criteria. We retrieved relevant review articles and reference lists of relevant articles. We also searched reference lists of articles in UpToDate, the *Oxford Textbook of Nephrology*, and *Brenner and Rector's The Kidney*. Two authors (S.P. and S.M.) extracted data for mercury exposure, levels, clinical presentation, and response to treatment from each article, along with verbatim descriptions of all histol-

Table 1. Summary of Histologic Findings in Biopsy Reports of Mercury-Associated Renal Disease, Our Patient and Summary of Systematic Review

Histology	No. (% of total biopsied)
Total patients with biopsies	26
Glomerular diseases	21 (72)
Minimal change disease	4
Alone	2
With ATN and IgG deposition	1
With mild acute interstitial nephritis	1
Membranous glomerulonephritis	15
Alone	12
With ATN	2
With proliferative changes	1
Chronic proliferative glomerulonephritis	1
Focal segmental glomerulosclerosis[a]	1
Acute tubular necrosis[b]	1 (4)
Tubulointerstitial nephritis[b]	4 (15)
Not otherwise classified	1
Eosinophilic interstitial nephritis	3
Alone	2
With eosinophilic material in Bowman space	1

Abbreviations: ATN, acute tubular necrosis; IgG, immunoglobulin G.
[a]Our case, not identified from literature review.
[b]The patients we include here with biopsy findings classified as ATN or tubulointerstitial nephritis were all nephrotic, and reports of their biopsies did not include electron microscopy. We speculate that minimal change disease may have been coincident with the other findings. See Table S1.

ogy. Two nephrologists (C.M.C. and A.S.G.) independently reviewed the histologic information and classified the description in current terminology. All disagreements were resolved by consensus.

The search retrieved 284 articles, of which 27 reports were relevant. For agreement for the decision of relevance, $\kappa=0.87$. Exposures were to skin whitening creams, laxatives, mercury salts, and fluorescent tubes. Of the 42 patients described, 26 underwent kidney biopsy (Table S1, available as online supplementary material). In patients with nephrotic syndrome, histology showed minimal change disease in 4 patients, membranous glomerulonephritis in 15, chronic proliferative glomerulonephritis in one, acute tubular necrosis in one, and tubulointerstitial nephritis in 4 (Table 1; Table S1). (The 2 nephrologists who categorized biopsy results in terms of current classifications agreed exactly on all except 3, which were minor disagreements resolved by consensus). We did not find previous reports of primary or secondary FSGS histology in association with mercury.

Treatment included removal of exposure and a variety of other approaches, including chelation, steroids, and other immunosuppressive treatment. Several of the cases in which there was follow-up improved, but numerical summaries of the prognosis were not possible because of the variation in underlying diagnoses, treatments used, and completeness of follow-up information.

Blood levels of mercury are an indicator of acute intoxication, but do not correlate with clinical toxicity because mercury is concentrated in tissues. A 24-hour urine collection indicates long-term exposure to inorganic and elemental mercury. Organic mercury compounds, such as methylmercury, accumulate in fish and are excreted in small amounts in urine. Elevated urinary levels of mercury therefore may be found in patients consuming large amounts of contaminated fish for many years, as did our patient. Measurement of mercury levels in scalp hair has been suggested, but is not a reliable indicator of long-term exposure, owing in part to short hair in some people and variation in the rate of hair growth.[7]

Environmental and food regulations are widely adopted in the developed world and public education material has been developed. Mercury intoxication is treated with discontinuing the exposure and supportive therapy. Chelation therapy is indicated for those with acute neurologic symptoms and those with toxic levels of mercury. Chelation therapy generally requires several cycles and is most effective for elemental mercury and least effective for methylmercury because of its large volume of distribution. Common chelators include British anti-lewisite (BAL), dimercaptosuccinic acid (DMSA), 2,3-dimercaptopropane-1-sulfonate (DMPS), and penicillamine. Treatment should be monitored with assessment of clinical status and repeated blood and urine mercury levels, and patients should be examined for the side effects of chelators. Mercury-induced nephrotic syndrome generally is reversible after elimination of the source of intoxication, although it may take many months.[8,9]

We recognize an important limitation. Segmental sclerosis was not found in more than one area in the biopsy. Foot-process effacement was widespread, but perhaps not sufficiently diffuse to warrant classification as the diffuse podocytopathy seen in idiopathic primary FSGS. The focal lesion may reflect secondary scarring from a previous unknown process. We treated our patient with high-dose steroids because at that time we believed he had idiopathic primary FSGS with diffuse podocytopathy, based on our interpretation of the histology and the onset of nephrotic syndrome and decline in glomerular filtration rate over a few weeks. He did not respond to this treatment, and if the lesion was purely a secondary or adaptive focal lesion, response would not have been expected. Finally, later he developed diabetes after exposure to steroids. However, shortly after his biopsy, his glucose tolerance was documented to be normal, his

presentation with nephrotic-range proteinuria coincided with the identification of his peripheral neuropathy, and the rate of increase of his creatinine level was unusually rapid for a diagnosis of diabetic nephropathy. Ultimately, it is never possible in a single case report to prove causality.

Our case highlights the importance of connecting all the manifestations of disease (new-onset peripheral neuropathy and nephrotic syndrome, in this case), and taking a thorough dietary history.

ACKNOWLEDGEMENTS

Support: None.

Financial Disclosure: The authors declare that they have no relevant financial interests.

SUPPLEMENTARY MATERIAL

Table S1: Systematic literature review of published case reports of mercury-induced nephrotic syndrome.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2013.02.372) is available at www.ajkd.org.

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