Mercury in natural health products as a cause of membranous nephropathy

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ABSTRACT

Membranous nephropathy is a glomerular disease characterized by diffuse subepithelial immune complex deposition along the glomerular basement membrane. It can be both primary and secondary to malignancy and various drugs. An emerging area of concern is heavy metal exposure from use of largely unregulated natural health products. Here we present a case of biopsy-proven membranous nephropathy due to natural health products contaminated with mercury.

KEYWORDS Membranous nephropathy; mercury; nephropathy; proteinuria

Membranous nephropathy (MN), a glomerular disease characterized by diffuse subepithelial immune complex deposition along the glomerular basement membrane, is the most common cause of nephrotic syndrome in white adults.^{1,2} Clinical features include progressive edema, hypoalbuminemia, and elevated lipid levels.² Mercury has been identified as a cause of MN due to exposure from skin-lightening creams and medications for rheumatoid arthritis.¹ Mercury exposure with subsequent development of MN has also been documented with use of traditional medicines and herbal remedies.³ An emerging concern is the use of natural health products (NHPs), including vitamins and herbal medicines. Some of these products contain toxic heavy metals.⁴ We present a case of MN due to mercury intoxication related to use of NHPs.

CASE PRESENTATION

A 39-year-old white man with known depression was admitted with worsening bilateral lower-extremity edema and abdominal distention that developed over 1 month. He was taking multiple oral herbal supplements daily, including those from India, for approximately 9 months. There were no changes in urine output, fluid intake, or recent illness. He denied use of nonsteroidal anti-inflammatory drugs, illicit drugs, or alcohol and had no personal or family history of renal disease. He reported eating fish approximately once a month. Aside from increased fatigue and irritability, he had

no additional complaints. Examination demonstrated anasarca, clear lungs, and 3+/4+ pitting edema in both legs. No skin rash was noted. Laboratory findings are tabulated in *Table 1*. Renal biopsy yielded 25 glomeruli. Light microscopy revealed mild mesangial hypercellularity and glomerular basement membrane thickening (*Figure 1a, 1b*). Anti-PLA2R and THSD7A immunohistochemical stains were negative. Minimal to focal mild interstitial fibrosis was noted with no evidence of tubulointerstitial nephritis or acute tubular necrosis. Immunofluorescence showed granular staining with IgA, IgG (IgG > IgA), IgM (focal), C1q, C3, and lambda in a mesangial and membranous distribution (*Figure 1c*). Other immunoreactants were negative. Electron microscopy disclosed sparse subepithelial and intramembranous electron-dense deposits of varying intensity. Sparse stage 1 electron-dense deposits without significant basement membrane reaction between deposits were noted (*Figure 1d*).

In light of the initial biopsy results and elevated mercury and arsenic levels, the supplements were discontinued and the patient was started on cyclosporine, which was weaned once the electron microscopy results were available. He was continued on atorvastatin 20 mg daily and apixaban 5 mg twice daily for approximately 8 weeks. The patient's edema resolved after 4 weeks and furosemide was discontinued. At his 12-week follow-up, the blood mercury level, urine protein-to-creatinine ratio, albumin, and lipid profile all returned to the normal range, allowing discontinuation of both the statin and oral anticoagulation.

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Table 1. Laboratory findings

Test	Patient result
Creatinine (mg/dL)	0.8
Urine protein/creatinine ratio	14.29
Albumin (g/dL)	1.4
Total cholesterol (mg/dL)	388
High-density lipoprotein (mg/dL)	65
Low-density lipoprotein (mg/dL)	285
HIV antibody	Negative
Hepatitis C antibody	Negative
Hepatitis B surface antigen	Negative
Phospholipase A2 receptor antibody	Negative
Anti-nuclear antibody	Negative
Blood cadmium (µg/L)	<1.0
Urine cadmium (24 hour) (µg/L)	<1.0
Blood lead (µg/dL)	<2.0
Urine lead (24 hour) (µg/L)	<5.0
Blood arsenic (µg/L)	14.0
Urine arsenic (24 hour) (µg/L)	48.9
Urine arsenic/creatinine ratio (µg/g)	65.2
Blood mercury (µg/L)	22.1
Urine mercury (24 hour) (µg/L)	80.0
Urine mercury/creatinine ratio (µg/g)	>106.7

DISCUSSION

Mercury-induced MN is a well-known but relatively rare entity associated with skin-lightening creams, Indian and Chinese herbal medicines, dental amalgams, and fish consumption. To date, only a few cases have been published. Li et al reported 11 cases of mercury-induced MN in China, of which five cases were due to traditional Chinese medicines, four to skin-lightening creams, and one each to vapor inhalation and occupational exposure to hair dye.¹ Qin et al presented a series of 35 cases of glomerulonephritis related to mercury exposure in a single Chinese center.⁵ The exposures included skin-lightening creams in 20 patients followed in frequency by mercury-containing medications and hair dye in nine and four cases, respectively. The source was not identified in two patients.⁵ In our patient, the use of NHPs from India could be documented. Unfortunately, he was unable to bring in the particular medications he had been taking. No other potential sources of mercury exposure were identified.

Mercury-induced glomerular disease most commonly shows MN with mesangial proliferation and acute tubulointerstitial injury in addition to membrane thickening, with most series reviewed showing predominance of IgG1 on immunofluorescence along with C3 and C1q and negative

serum and tissue anti-PLA2R.^{3,5,6} In contrast to previous reports, Qin et al's series of 35 cases of glomerulonephritis related to mercury exposure found minimal change disease more frequently than MN (21 vs 13 cases, respectively).⁵ In our patient, anti-PLA2R and THSD7A were negative. Granular staining with C3, C1q, IgA, focal IgM, and IgG (IgG > IgA) was present, although no IgG subtyping was able to be performed. Electron microscopy showed sparse deposits of varying intensity in the subepithelial and intramembranous areas consistent with secondary MN.

Treatment of mercury-induced disease starts with discontinuation of inciting exposures. Chelation therapy has been shown to be a useful therapy that causes increased renal excretion with reduced time to resolution of symptoms.^{3,5} In our patient, chelation therapy was not given, as he was improving before the results of the 24-hour urine collection were available. He was started on cyclosporine due to the immune complex deposition and severe proteinuria; however, immunosuppression was weaned when the mercury results and final biopsy readings were available. He improved over the course of about 12 weeks after discontinuation of the offending agents. High serum levels of arsenic were present in blood and urine. Arsenic poisoning can lead to tubulointerstitial nephritis and acute tubular necrosis.⁷ In our patient, the renal biopsy did not show findings consistent with arsenic-related damage.

The market for NHPs is rapidly growing, with many products obtained from international sources that are not subject to strict production standards.⁴ Evaluation of 121 internationally produced NHPs revealed that nearly 10% contained heavy metal levels greater than the established daily limit, with the authors noting that the problem is likely greater in scope, as most patients consume more than one supplement.⁴ Though our patient could not show us the products he was taking, he admitted use of several different NHPs from international markets. Our case highlights the necessity of a thorough review of all medications and NHPs to identify unusual causes of nephrotic syndrome.

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Figure 1. (a) Renal biopsy with viable glomeruli and tubulointerstitial compartments (hematoxylin and eosin, original magnification $\times 100$). (b) Glomerulus with mildly thickened glomerular basement membranes (hematoxylin and eosin, original magnification $\times 400$). (c) Two glomeruli showing granular 2+ staining along the capillary loops (direct immunofluorescence IgM, original magnification $\times 400$). (d) Sparse membranous and intramembranous electron-dense deposit (arrow) (transmission electron microscopy, original magnification $\times 2500$).

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