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Exceptional Case

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Membranous nephropathy due to chronic mercury poisoning from traditional Indian medicines: report of five cases

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ABSTRACT

Mercury contained in traditional medicines can cause chronic poisoning, which can cause membranous nephropathy (MN). We report five cases of nephrotic syndrome caused by MN with evidence of chronic mercury poisoning due to consumption of traditional Indian medicines such as Siddha and Ayurveda, which to our knowledge are the first such reports. All patients were seronegative for antibodies against phospholipase A2 receptor (PLA2R). Two patients, who had severe nephrotic syndrome, had received Siddha medicine for prolonged period and oral chelation with dimercaptopropane-1-sulfonic acid was successful in eliminating mercury, resulting in an improvement in nephrotic state in these patients. We suggest that mercury poisoning should be entertained in patients with anti-PLA2R antibody-negative MN, with history of consumption of traditional Indian medicines.

Keywords: dimercaptopropane-1-sulfonic acid, membranous nephropathy, mercury, nephrotic syndrome, traditional Indian medicine

INTRODUCTION

Membranous nephropathy (MN) is the leading cause of nephrotic syndrome in adults. It is characterized by basement membrane thickening with minimal or no cellular proliferation and the presence of immune deposits on the epithelial side of the glomerular capillary wall [1]. MN most often is primary (idiopathic), which accounts for ~75% of cases, while the remaining cases may be associated with various secondary causes [1].

For centuries, mercury was an essential part of many different systems of medicine and was used as a diuretic, antibacterial agent and laxative. Currently, mercury is no longer used in the allopathic system of medicine due to its recognized toxicity. However, heavy metals including mercury are still being used in several systems of traditional medicines. Chronic heavy metal exposure following environmental or medicinal exposure is an important, but under-recognized cause of renal damage. Renal manifestations due to mercury toxicity are acute kidney injury due to acute tubular necrosis, tubulointerstitial nephritis, and glomerulonephritis due to MN and minimal change disease [2].

We present five cases of nephrotic syndrome due to MN, proven by renal biopsy. All cases were investigated for secondary causes of MN, since they were negative for anti-phospholipase A2 receptor (PLA2R) antibodies and enquiry revealed that they had been consuming traditional Indian medicines such as Siddha and Ayurveda. The association between

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the use of mercury-containing skin-lightening creams as well as Chinese traditional medicines and MN has been described previously [3], but such an association has not been reported previously in patients taking traditional Indian medicines. We present these cases to emphasize the importance of MN caused by mercury contained in traditional medicines, a reversible cause of the nephrotic syndrome, which can be easily overlooked unless a careful drug history is taken.

Case 1 (index case)

A 47-year-old male with a history of diabetes and hypertension for 5 years, well controlled on oral drugs, presented in September 2016, with a history of gradual onset of edema and reduced urine output of 1 week duration. On evaluation, he had anasarca, ascites and no evidence of diabetic retinopathy. The laboratory results at presentation are shown in Table 1. A renal biopsy was done, which showed enlarged glomeruli with widely patent capillary loops. The capillary walls were uniformly thickened (Figure 1A) and silver staining showed fine linear spikes on capillary walls (Figure 1B). Tubulointerstitium was unremarkable. Immunofluorescence showed peripheral granular deposits of immunoglobulin G (IgG) and C3c in the glomeruli suggestive of MN. There was no evidence of underlying malignancy. He was started on a combination of steroid and cytotoxic drug therapy for MN and received oral prednisolone and one intravenous pulse of cyclophosphamide (500 mg/m^2). He received telmisartan intermittently, but did not tolerate it well. On enquiry about the intake of medicines, a month after initial presentation, he admitted to taking Siddha medicine for 6 months for sinusitis, which he had stopped recently before renal biopsy. A chemical analysis of the Siddha medicine consumed by him showed a very high concentration of mercury (132.95 mg/kg) and no trace of lead or arsenic. His urine mercury was markedly elevated (Table 1). He was initiated on oral chelation therapy with dimercaptopropane-1-sulfonic acid (DMPS), available as 100 mg tablets of Dimaval®. He initially received 800 mg of Dimaval daily in three divided doses, which was reduced to 400 mg/day due to gastrointestinal intolerance. He received a total of 8 g (80 tablets) of Dimaval over 3 weeks. There was more than a 100-fold increase in urine mercury excretion while receiving Dimaval, which confirmed the efficacy of the drug to chelate and remove mercury. He had multiple infections such as cellulitis and viral pneumonitis following the initiation of steroid therapy, necessitating hospitalization on several occasions. Oral steroid was given intermittently and irregularly and was eventually discontinued after 3 months. He remained severely nephrotic and developed severe bilateral upper abdominal pain, 4 months after the initial presentation. He was found to have bilateral renal vein thrombosis on computed tomography and he received oral anticoagulation with coumarin for 6 months. He recovered well from renal vein thrombosis and received no further immunosuppression. Serial urine mercury excretion measurements showed a decline and eventual disappearance over a period of 1 year. He showed gradual, but sustained improvement in symptoms. At 18 months, he had no significant leg edema, serum creatinine was 1.2 mg/dL, serum albumin was 3.6 g/dL and urine protein/creatinine ratio (PCR) was 5.5 g/g of creatinine.

Case 2

A 47-year-old female with no comorbidities presented in January 2017, with a history of bilateral pedal edema for 5 months. She had noticed a lump in her left breast in 2011, which she ignored, which was later diagnosed as carcinoma of the breast in 2015. She opted for Siddha medicine for carcinoma of the breast, which she took for 12 months starting January 2016. She developed oral ulcerations and bilateral pedal edema 9 months after initiation of the treatment. On evaluation, she was detected to have proteinuria (dipstick 3+) and microscopic hematuria (6–8 red blood cells/high power field). The laboratory results at presentation are shown in Table 1. Renal biopsy showed 20 glomeruli that were enlarged and there was mild increase in mesangial cellularity with underlying patent capillaries and uniformly thickened capillary basement membrane (BM). Eight glomeruli showed segmental endothelial proliferation with infiltration by numerous neutrophils (Figure 2A). Few glomeruli showed segmental sclerosis and one showed partial fibroepithelial crescent (Figure 2B). Immunofluorescence staining showed peripheral fine granular deposits of IgG and C3c and minimal C1q in the glomeruli. Electron microscopy (EM) study showed uniformly thickened BM and subepithelial electron dense deposits (Figure 3) and no electron dense deposits elsewhere, which was consistent with MN.

Based on our previous experience with the index case, we suspected mercury poisoning causing MN, which was confirmed by the presence of very high levels of mercury in the urine (Table 1). The patient received oral prednisolone, which was discontinued after 2 weeks in view of intolerance and uncertainty about the efficacy of steroid in mercury-induced MN. She was initiated on Dimaval at a dose of 300 mg/day and the dose was increased to 400 mg/day, which was well tolerated. She received a total of 12 g of Dimaval over 6 weeks. There was a 20-fold increase in urinary mercury excretion following oral chelation therapy, confirming the efficacy of the drug. The urine mercury had reduced to an insignificant level (2.66 μg/L and 4.79 μg/day) after the completion of Dimaval therapy. There was a significant improvement in nephrotic state after chelation therapy, with improvement in serum albumin to 3.0 g/dL and proteinuria (urine PCR: 0.9 g/g of creatinine).

Case 3

A 41-year-old female presented with leg edema for 4 months in March 2017. She was detected to have hypertension 1 month prior to presentation. She had skin rashes for 10 years with intermittent flares, which were treated with topical Ayurveda medicine. She was evaluated elsewhere and found to have nephrotic syndrome and was started empirically on oral prednisolone. The laboratory results at presentation are summarized in Table 1. Renal biopsy showed features typical of MN. The urine analysis showed a mildly elevated mercury level (Table 1). She was advised to stop topical Ayurveda medicine and steroid was stopped. She was counselled about chelation therapy in case nephrotic syndrome did not improve. However, after initial evaluation, there was no follow-up.

Case 4

A 48-year-old male, known to have diabetes mellitus for 4 years and hypertension for 1 month, presented with fever and arthralgia and foamy urination in December 2016. He had mild edema on examination. The laboratory results at presentation are shown in Table 1. Renal biopsy showed 28 glomeruli, which showed features typical of MN. The patient gave a history of consumption of Ayurveda medicine for bronchial asthma during the past 2 months. Blood mercury level was mildly elevated at 24 μg/L

Table 1. Summary of cases

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	47	47	41	48	70
Type of alternative medication	Siddha	Siddha	Ayurveda	Ayurveda	Ayurveda
Route of administration	Oral	Oral	Topical	Oral	Oral
Duration of traditional medication	5 months	1 year	10 years	2 months	2 months
Clinical syndrome	Nephrotic syndrome	Nephrotic syndrome	Nephrotic syndrome	Nephrotic syndrome	Nephrotic syndrome
Serum creatinine (normal: 0.6–1.1 for women, 0.8–1.3 for men; mg/dL)[a]	0.9	0.52	0.5	0.7	1.02
Serum albumin (normal: 3.5–5.2 g/dL)[a]	2.1	2.3	3.4	3.4	2.2
Proteinuria[a] (g/g of creatinine)	11.6	10.3	6.21	13.7	8.58
Renal biopsy	MN	MN with focal proliferation and 1/20 fibroepithelial crescent	MN	MN	MN
Immunofluorescence	Peripheral granular deposits of IgG, C3c with lesser amount of C1q	Peripheral granular deposits of IgG, C3c with minimal amount of C1q	Peripheral granular deposits of IgG and moderate amounts of IgA and C3c	Peripheral granular deposits of IgG, C3c and C1q with peripheral and mesangial IgA	No glomeruli
Anti-PLA2R antibody assay	Negative	Negative	Negative	Negative	Negative
ANA	Negative	Positive	Negative	NA	NA
Serology for HBV, HCV, HIV	Negative	Negative	Negative	Negative	Negative
Urine mercury[a] (μg/L) (normal <10 μg/L)	68	183.7	16.88	NA	97.35 (68.15 μg/day)
Blood mercury levels[a] (μg/L) (normal <11 μg/L)	NA	NA	NA	24	NA
Treatment	Oral DMPS	Oral DMPS	None	Tacrolimus	None
Outcomes	Improved	Improved	Lost to follow-up	Remission	Improved

DMPS, dimercaptopropane-1-sulfonic acid; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MN, membranous nephropathy; NA, not available; PLA2R, phospholipase A2 receptor.
[a]At presentation.

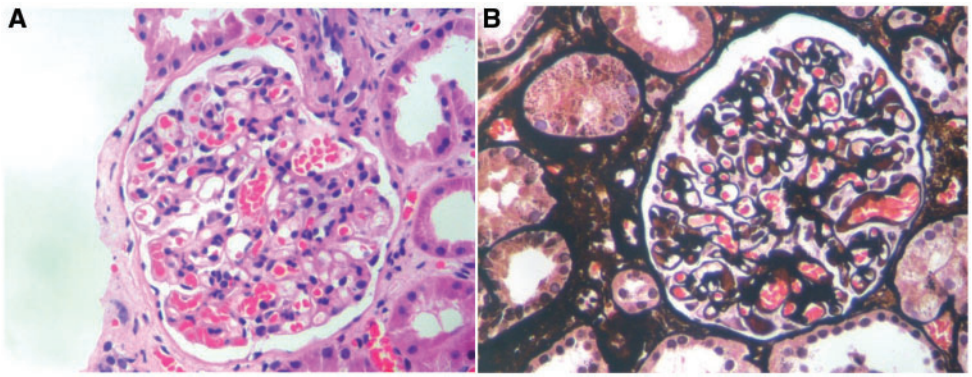

FIGURE 1: Periodic acid–Schiff staining of renal biopsy specimen showing uniformly thickened capillary walls (**A**) and silver staining of renal biopsy specimen from index case showing fine linear spikes (**B**).

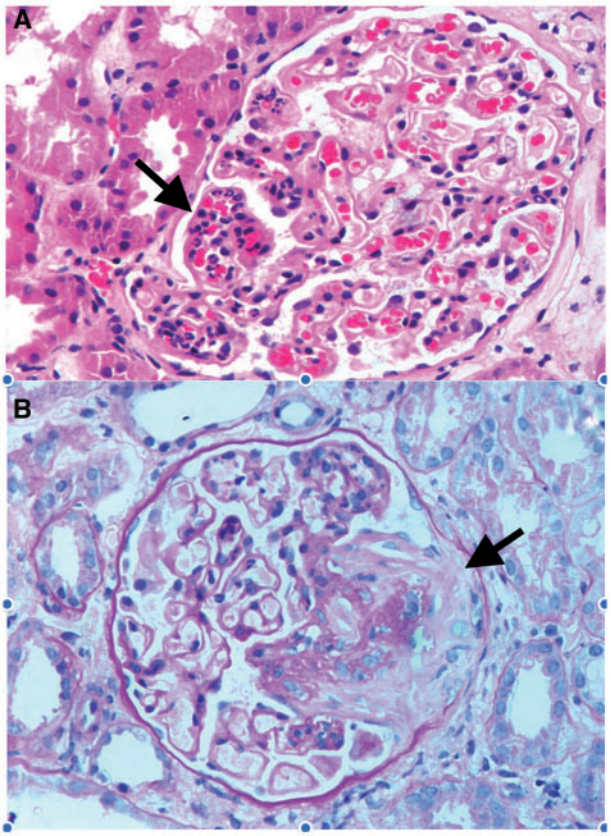

FIGURE 2: Hematoxylin and eosin staining showing segmental endothelial proliferation (arrow) with infiltration by numerous neutrophils and uniform thickening of capillary basement membrane (**A**) and Periodic acid–Schiff staining showing partial fibroepithelial crescent (arrow) from renal biopsy of Case 2 (**B**).

(normal: <11 μg/L). He was advised to stop Ayurveda medicine and was treated with tacrolimus 3 mg/day along with losartan 125 mg/day. At last follow-up in May 2017, his urine PCR was 0.79 g/g creatinine and renal function remained normal.

Case 5

An elderly male aged 70 years presented in May 2017, with complaints of bilateral pedal edema and foamy urination for the past 15 days. He had received Ayurveda medication for bronchial asthma for the past 2 months. He was detected to have hypertension 1 month prior to presentation. The laboratory results at presentation are summarized in Table 1. Renal biopsy showed 18 glomeruli, which showed features consistent with MN. Renal tissue subjected to immunofluorescence did not have any glomeruli. The urinary mercury level was markedly elevated (Table 1). He was treated with losartan 50 mg/day and Ayurveda medicine was discontinued. At last follow-up in June 2017, his urine PCR had reduced to 4.37 g/g creatinine and renal function remained normal.

DISCUSSION

Clinical presentation

Very few cases of mercury-induced MN have been reported in the literature so far. Miller *et al.* [2] reviewed the English literature up to November 2010 and reported 15 cases of mercury-induced MN. Subsequently, Li *et al.* [3] reported a series of 11 cases of mercury-induced MN from China, of which 5 had received traditional Chinese medicine, 4 were due to skin-lightening creams and 1 each due to vapor inhalation containing mercury and hair dye containing mercury. In addition, Priya *et al.* [4] and Chakera *et al.* [5] reported a case each of mercury-induced MN following the injection of mercury and use of skin creams, respectively. We report five cases of mercury-induced MN in patients taking traditional Indian medicines such as Siddha (two patients) and Ayurveda (three patients). The index patient received oral Siddha medicine for sinusitis for 5 months, whereas another received it for breast cancer for 12 months. They developed severe nephrotic syndrome, 5 and 9 months after the consumption of Siddha medicine, respectively. The patient who received topical Ayurveda medicine intermittently, for skin lesions for 10 years, developed a lesser degree of nephrotic state, indicating lower level of toxicity. The other two patients who received Ayurveda medicine for 2 months for bronchial asthma had severe nephrotic syndrome. The timeline to develop mercury-induced MN appears to be variable and probably depends upon the amount of mercury contained in the medicine, in addition to duration of toxicity. Li *et al.* [3] also reported a wide variation in duration of mercury exposure from 2 to 60 months in 11 patients with mercury-induced MN. A chemical analysis of the Siddha medicines consumed by the index case showed a very high concentration of mercury (132.95 mg/kg), which was far above the permissible limit of 0.1 μg/kg [6]. We made efforts to exclude other secondary causes of MN in our patients. Case 2 had breast cancer and positive anti-nuclear antibody (ANA), which raised the possibility of

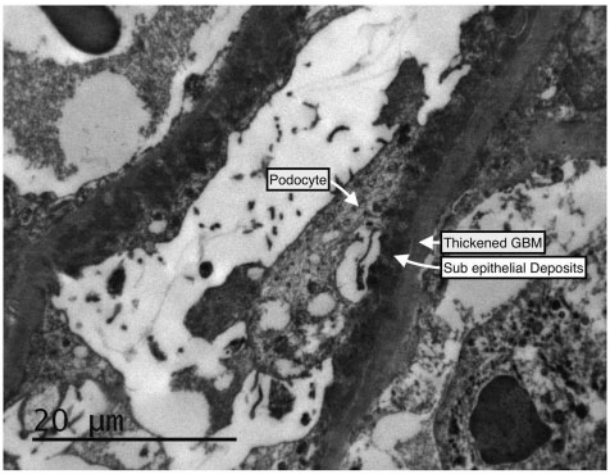

FIGURE 3: EM picture from Case 2, showing subepithelial electron dense deposits.

malignancy-induced MN and lupus nephritis (LN). The absence of anti-dsDNA antibody, full-house immune deposits on immunofluorescence stain and mesangial and subendothelial deposits was inconsistent with LN. Malignancy-related MN could not be excluded, though the time interval between consumption of Siddha medicine and evolution of MN and subsequent improvement with chelation therapy favored mercury-induced MN. ANA was not done for Case 4, and the absence of full-house immune deposits on immunofluorescence did not favor the diagnosis of LN.

Histopathology and pathogenesis

Mercury-induced MN may show mesangial proliferation and acute tubulointerstitial injury on light microscopy, in addition to typical membrane thickening [2, 3]. Case 2 showed focal endothelial proliferation and a rare fibro-epithelial crescent, whereas the rest of the four patients showed typical features of MN on renal histology. Li *et al.* [3] reported that in addition to granular IgG and C3, mercury-induced MN showed deposits of C4 and C1q, which are not common in idiopathic MN. Also, they reported that IgG1 subtype was the predominant IgG deposit as against the commonly observed IgG4 subtype in idiopathic MN. Three of our cases showed weak positive staining for C1q on immunofluorescence and we did not perform subtyping of subepithelial IgG deposits. EM study of Case 2 showed deposits localized to subepithelial space and no deposits in mesangial or subendothelial space. Li *et al.* [3] reported subepithelial deposits on EM study in all 11 patients, of which 5 had additional mesangial deposits, but no subendothelial deposits.

The precise pathogenesis of mercury-induced MN is uncertain. Bariety *et al.* [7] induced MN by several successive subcutaneous injections of mercury chloride in rat experiments. Their findings of subepithelial deposits support the hypothesis of an immune complex disease probably initiated by mercuric chloride. The autoimmune nature of mercury-induced MN is supported by animal experiments. In rat models, mercury chloride was shown to induce autoimmunity due to a T-cell-dependent B-cell polyclonal activation, resulting in production of numerous autoantibodies [8]. In mercury-induced MN rat models, anti-laminin antibodies were eluted from the BM [9]. Anti-PLA2R antibodies were negative in all of our five patients. The discovery of anti-PLA2R antibodies is recent [10] and previous reports of mercury-induced MN did not perform this test, except a recent case report by Chakera *et al.* [5], who reported negative serology for anti-PLA2R antibody. Histochemical staining of renal tissue is more sensitive than serum assay to determine anti-PLA2R-related MN [11, 12]. We did not perform the tissue staining for anti-PLA2R antibodies due to lack of availability. One of our patients had a positive ANA, but negative anti-dsDNA and a similar finding was reported in 4 of 11 cases reported by Li *et al.* [3]. These experimental and clinical observations indicate that mercury causes MN by mechanisms other than antibody formation against PLA2R. However, the nature of autoantibodies in the causation of mercury-induced MN in humans remains unclear.

Treatment

The optimal treatment of mercury-induced MN is unclear. It is essential to withdraw the medicines suspected to contain mercury, which was done in all our cases. It is desirable to analyze the content in order to determine the concentration of mercury to assess the degree of poisoning. The levels in the blood or urine do not reflect the true degree of chronic mercury poisoning, since mercury tends to deposit in the tissues. In case of mild disease, withdrawal of mercury-containing medicines may suffice, whereas in case of severe MN with clear evidence of mercury poisoning, chelation would facilitate the removal of mercury, which may hasten the recovery of MN. A few authors have reported successful use of chelating agents such as DMPS [13] and dimercaptopurine [13, 14] in mercury-induced MN. We demonstrated that oral DMPS markedly increased the excretion of mercury in two of our cases, proving their efficacy. Both of these patients showed clinical improvement after DMPS chelation despite not receiving substantial immunosuppression, which indicated that chelation hastened recovery. Oral chelating agents such as DMPS are the drug of choice in chronic mercury poisoning, which is generally well tolerated. However, it should be used cautiously if renal function is impaired, since these chelating agents are essentially excreted in urine [15]. The outcome in mercury-induced MN is generally good, as indicated in our cases. Li *et al.* [3] reported improvement in proteinuria in all 11 cases and 9 patients reached complete remission on follow-up, after withdrawal from mercury exposure.

Traditional medicines and mercury-induced MN

Mercury has been an ingredient in several traditional medicines such as Ayurveda, Unani, Siddha, Tibetan and Chinese medicines [16–18]. Traditional Indian medicines have been used for millennia in India, and with globalization, several of these traditional medicines are sold over the Internet and have found a global market. However, the drugs sold by traditional medicine manufacturers are not rigorously tested for the contents and their sale is not regulated. Saper *et al.* randomly analyzed Ayurvedic herbs and medicines sold over the Internet in the USA and found that 4.1% of them contained mercury above the permissible limits [17]. The content of mercury was more in rasayan shastra preparations (9.5%) compared with non-rasayan shastra Ayurvedic medicines. However, despite the widespread consumption of traditional Indian medicines by the population, no renal toxicity has been reported thus far and to our knowledge ours is among the first reported cases of traditional Indian medicines containing mercury causing MN. It is possible that it is underreported due to a lack of awareness among physicians and nephrologists. We identified within a span of 24 months, five cases of mercury-induced MN, who were anti-PLA2R antibody negative. We emphasize the need to suspect and evaluate for mercury-induced MN when

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anti-PLA2R antibody is negative and a history of consumption of traditional Indian medicines is present or suspected.

CONCLUSION

We report five cases of mercury-induced MN due to traditional Indian medicines, which to our knowledge is the first such report. We suggest that MN with anti-PLA2R antibody negative cases should be evaluated for mercury-induced MN in patients consuming traditional Indian medicines. We showed that oral chelation by DMPS is effective and should be used as first-line therapy in severe cases of mercury-induced MN.

CONFLICT OF INTEREST STATEMENT

None declared.

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