Kidney Medicine

Complementary and Alternative Medicine Use and Glomerular Disease: A Contemporary Case Series

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Rationale & Objective: Complementary and alternative medicine (CAM) intake is widely prevalent in many parts of India. Heavy metals are known ingredients in some of these formulations. We studied the spectrum of glomerular diseases in patients using CAM.

Study Design: Case series.

Setting & Participants: Patients with proteinuria or unexplained acute kidney injury, who underwent a kidney biopsy between May 2021 and September 2022, and who provided a history of recent CAM intake were included in the study. For patients enrolled prospectively, blood and urine samples were analyzed using mass spectrometry for the presence of mercury, lead, arsenic and cadmium. The CAM formulation, when available, was analyzed using inductively coupled plasma-optical emission spectroscopy.

Results: Twenty-eight patients were enrolled in the study, with a median duration of CAM intake of 4 months (interquartile range, 2-6 months). Heavy metal screening was performed in 17 patients, of whom 15 had elevated urine mercury levels, 10 had elevated blood mercury levels, and 1 had elevated blood and urine arsenic levels. Of the 6 CAM formulations that were analyzed, all had high levels of mercury. Kidney biopsy findings were membranous nephropathy (n = 19), minimal change disease (n = 8), and mesangial proliferative glomerulonephritis (n = 1). Of the 19 patients with membranous nephropathy, 14 were associated with neural epidermal growth factor-like protein 1 (NELL-1). With conservative management alone, 17 patients achieved complete remission.

Limitations: Not all patients underwent blood and urine mercury testing, and only 6 patients provided the CAM samples for analysis. Furthermore, occupational and residential exposure to mercury could not be excluded.

Conclusions: The most common kidney pathology noted in our study was membranous nephropathy, which was predominantly associated with neural epidermal growth factor-like protein 1. A significant proportion of the patients recovered completely after withdrawal of the offending agent and initiation of renin-angiotensin system blockade.

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In India, the use of complementary and alternative medicines (CAM) is commonplace. Heavy metals are known ingredients in some of these formulations and can potentially affect the kidneys. Mercury is noted to be the most common heavy metal in these indigenous preparations, and chronic mercury exposure has been documented to cause minimal change disease and membranous nephropathy.[1-4] Recent reports have suggested an association among consumption of CAM, mercury exposure, and neural epidermal growth factor-like protein 1 (NELL-1)-associated membranous nephropathy.[4]

Here, we report the clinical course and outcomes of different glomerular pathologies noted in patients with a history of CAM intake.

METHODS

We conducted an ambispective observational study at the Institute of Nephrology, Madras Medical College, Chennai, India, between May 2021 and September 2022. The Institutional Ethics Committee of Madras Medical College approved the study protocol (No. 41072023). As the article contains no personally identifiable information and some of the data were collected retrospectively, the requirement for informed consent was waived.

All patients who presented with proteinuria or unexplained acute kidney injury (AKI), had a history of recent consumption of CAM, and who underwent a kidney biopsy were included. The type of CAM, the reason for consumption, and the duration of intake were noted. Kidney biopsy tissue for all patients was processed and reported by a single nephropathologist. Blood and urine samples of the patients were analyzed using inductively coupled plasma mass spectrometry for a panel of 4 heavy metals, including mercury, arsenic, lead, and cadmium. The thresholds that signify a meaningful exposure to mercury vary in the reported literature and range from >10-20 μg/L of urine mercury to >5-20 μg/L of whole blood mercury.[1,5,6] In this study, we used thresholds of >10 μg/L in urine and >5 μg/L in whole blood to signify mercury toxicity. Samples of the specific

PLAIN LANGUAGE SUMMARY

Complementary and alternative medicine (CAM) intake is widely prevalent in many parts of India, and heavy metals are known ingredients in some of these formulations. We describe the clinical spectrum of kidney disease, among patients who had recently ingested CAM. All patients underwent a kidney biopsy, and the most common finding was an entity called "NELL-1-associated membranous nephropathy," which is known to be associated with heavy metal toxicity and CAM intake. Of 17 patients screened for such heavy metals, 15 had greater-than-permissible levels of mercury. Furthermore, 6 patients provided the CAM formulations that they had consumed for analysis: all contained high levels of mercury. Most such patients recovered following withdrawal of the offending CAM agent.

formulation that were consumed, when available, were also analyzed using inductively coupled plasma-optical emission spectroscopy. Testing for heavy metals was done at specialized laboratories that had appropriate accreditation for performing such analyses.

For all patients with a membranous nephropathy pattern of injury, immunostaining for phospholipase A_2 receptor and NELL-1 were performed. A general screen for secondary causes of membranous nephropathy was performed (viral screening for hepatitis B, hepatitis C and HIV (human immunodeficiency virus), testing for anti-nuclear antibody, serum complement levels, chest X-ray, serum prostate-specific antigen, and examination of stool for occult blood). Patients were managed with cessation of the CAM and supportive care. A short course of steroids was administered if deemed refractory, but chelation therapy was not attempted. All patients were followed up regularly to assess response to therapy.

RESULTS

Patient Characteristics

A total of 28 patients were studied. The median age was 46 years (interquartile range [IQR], 39-53), and there was a female preponderance (n = 20, 71%). The median duration of CAM intake was 4 months (IQR, 2-6 months). The most common kidney presentation was nephrotic syndrome (n = 19), with the others presenting as subnephrotic proteinuria (n = 5) and AKI (n = 4). Of the 4 patients who had AKI, all had underlying proteinuria, with 3 patients in the nephrotic range. The AKI was stage 1 in two patients, stage 2 in one patient, and stage 3 in one patient (peak serum creatinine, 2.5 mg/dL). The clinical characteristics of the patients are shown in Table 1.

Table 1. Clinical characteristics of patients with CAM ingestion who underwent for-cause kidney biopsies

Clinical characteristic	Total cohort (n = 28)
Age, y (median [IQR])	46 (39-53)
Female sex (n [%])	20 (71.4%)
Duration of CAM intake (months) (median [IQR])	4 (2-6)
Kidney syndrome (n [%])	
Nephrotic syndrome	19 (67.8%)
Sub-nephrotic proteinuria	5 (17.8%)
Acute kidney injury	4 (14.3%)
Serum creatinine (mg/dL) (median [IQR])	0.8 (0.7-0.9)
Serum albumin (g/dL) (median [IQR])	2.4 (2.1-2.8)

The most common indications for consumption of these medicines were joint pain, asthma, and diabetes mellitus (Fig 1). None of the patients had documentation of their baseline kidney function before the onset of the current illness.

Heavy Metal Screening

Of the 28 patients included in this series, 17 patients underwent screening for heavy metals. Of these, 15 patients were found to have urine mercury levels >10 μg/L, and 10 were found to have blood mercury levels > 5 μg/L (Table 2). There was no evidence of extra-renal manifestations of mercury toxicity in any of the patients. None of them had any known occupational exposure to mercury.

One patient was found to have high levels of arsenic in blood and urine (Table 2). The patient also had elevated levels of mercury in addition to arsenic. Lead and cadmium remained undetectable in all 17 patients who were screened.

Six patients provided samples of the CAM formulations they had been taking. All 6 samples contained high levels of mercury (median, 87.35 mg/kg [IQR, 65.4-132]), but lead, cadmium and arsenic were undetectable. The indigenous formulations submitted for analysis included *swasakalpa* syrup, *madhumega chooranam* and *thirikadugu chooranam*.

Kidney Biopsy Patterns

All 28 patients underwent a percutaneous kidney biopsy. The patterns of injury were membranous nephropathy (n = 19), minimal change disease (n = 8) and mesangial proliferative glomerulonephritis (n = 1) (Fig 2). Additionally, 2 patients had findings of acute tubular injury and acute tubulointerstitial nephritis on biopsy, and both of these patients had AKI at presentation. Among patients with membranous nephropathy, tissue staining for phospholipase A_2 receptor using direct immunofluorescence was negative in all patients. Fourteen patients (73.7%) were positive for NELL-1 on immunohistochemistry (Fig 3). Work-up for other secondary causes of membranous nephropathy were negative for all patients.

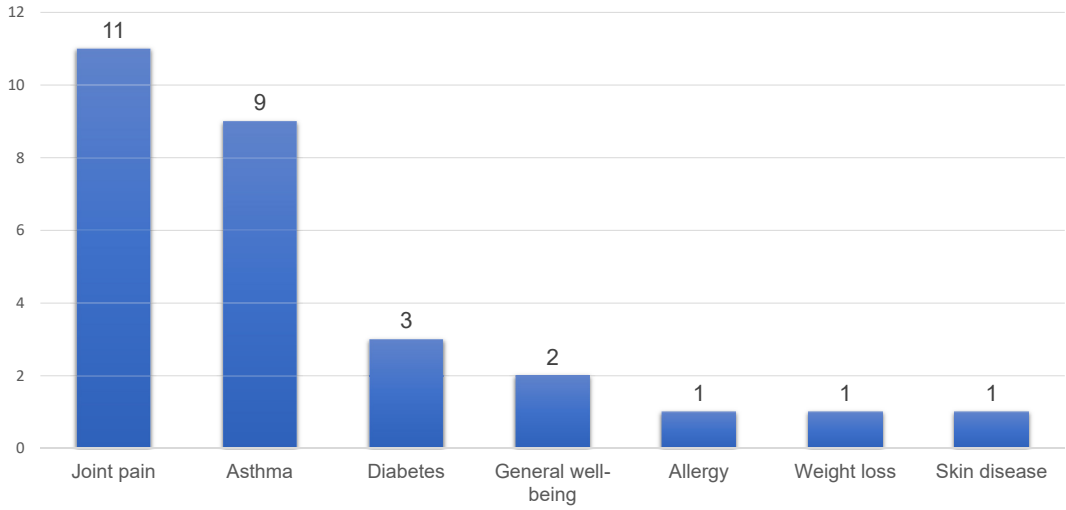

Figure 1. Indications for complementary and alternative medicine (CAM) intake.

TREATMENT

All patients were advised to stop further intake of CAM. Patients were initially managed conservatively, with renin-angiotensin system blockade, and 17 patients (60.71%) achieved complete remission. The median time to achieve remission was 4 months (IQR, 2.5-8 months) (Fig 4). All 4 patients who presented with AKI had spontaneous resolution of the kidney injury.

Nine patients received oral steroids (0.5 mg/kg/day prednisolone) as nephrotic-range proteinuria persisted despite 12 weeks of conservative management. Steroids were continued until remission was attained, or for a maximum of 4 weeks, followed by a rapid taper over 4-6 weeks. Of the 9 patients, 5 achieved complete remission, and 4 achieved partial remission (Table 3 and Fig 4).

DISCUSSION

Mercury is a toxic metal found in environmental and industrial settings. It exists in metallic, inorganic, and organic forms. Inorganic mercury may be found as mercurous or mercuric ions. The toxicity profile depends on the type of mercury, duration, and dosage. Inorganic forms of mercury are commonly used in CAM, and these ions have a tendency to accumulate in kidneys.[1-4,7] The accumulation of inorganic mercury predominantly occurs

Table 2. Heavy metal screening of 17 patients

S. No.	Age	Sex	Duration of CAM Intake	Urine Mercury Level (μg/L)	Blood Mercury Level (μg/L)	Urine Arsenic Level (μg/L)	Blood Arsenic Level (μg/L)	Light Microscopy Pattern	NELL-1 Status
1	39	F	3 months	50	15.53	48.64	Neg	MN	Positive
2	42	F	2 months	28	Neg	Neg	Neg	MN	Positive
3	47	F	5 months	8.92	Neg	Neg	Neg	MN/ATIN	Negative
4	46	F	18 months	109.5	Neg	Neg	Neg	MN	Positive
5	44	F	9 months	12.7	18	69.85	>10	MN	Positive
6	65	M	20 days	50	16	Neg	Neg	MN	Positive
7	21	F	12 months	29.23	Neg	Neg	Neg	MN	Positive
8	45	M	48 months	50	15.5	Neg	Neg	MN	Positive
9	63	F	1 month	35.24	10	Neg	Neg	MN	Positive
10	40	F	5 months	31	12.4	Neg	Neg	MN	Positive
11	48	F	36 months	8.92	Neg	Neg	Neg	MN	Negative
12	55	F	3 months	50	19.7	Neg	Neg	MCD	-
13	46	F	2 months	10	10	Neg	Neg	MCD	-
14	30	F	5 months	50	19	Neg	Neg	MCD	-
15	54	M	5 months	18.3	19.3	Neg	Neg	MePGN/ ATI	-
16	46	F	3 months	12.4	Neg	Neg	Neg	MCD	-
17	31	M	10 days	16.2	Neg	Neg	Neg	MCD	-

The reported thresholds for toxicity are >10-20 μg/L of urine mercury, and >5-20 μg/L of whole blood mercury. Normal urinary arsenic levels are <50 μg/L.
Abbreviations: ATI, acute tubular injury; ATIN, acute tubulointerstitial nephritis; MCD, minimal change disease; MePGN, mesangial proliferative glomerulonephritis; MN, membranous nephropathy.

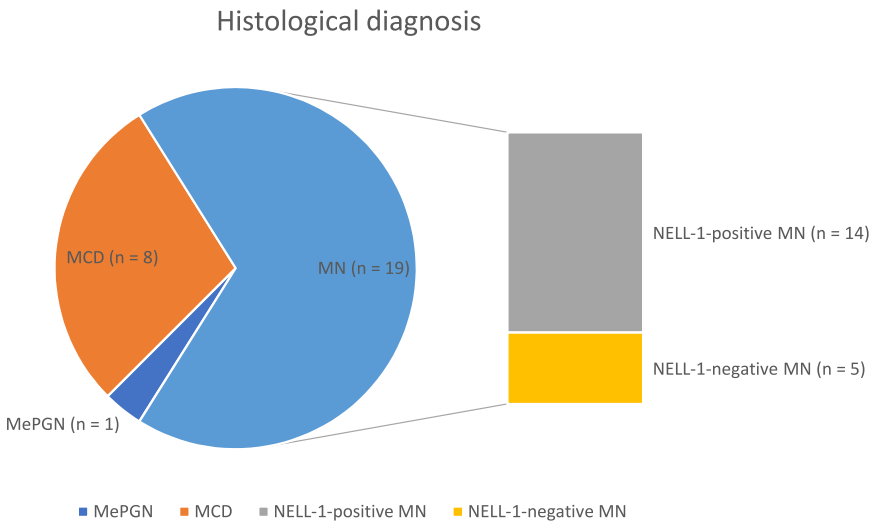

Figure 2. Kidney pathologies associated with the use of complementary and alternative medicine (CAM). MCD, minimal change disease; MePGN, mesangial proliferative glomerulonephritis; MN, membranous nephropathy; NELL-1, neural epidermal growth factor-like 1 protein.

in the pars recta of proximal tubules. Acute mercury toxicity leads to tubular injury, whereas chronic exposure leads to proteinuric kidney diseases like membranous nephropathy and minimal change disease.[3,4,7,8]

A large number of occupations linked to mercury exposure have been described by the Centers for Disease Control and the International Labour Organisation.[9,10] Some of the major sectors include those involved in the production of certain chemicals (chlor-alkali, vinyl chloride, and acetaldehyde) and mercury-containing compounds and devices (antiseptics, mirrors, paint, fluorescent lights, and batteries), coal-fired power plants, oil and natural gas processing, dentistry, and health care waste processing. Occupational exposure may occur through inhalation (most common), ingestion, or dermal contact.

A history of CAM consumption should raise suspicion of mercury-related kidney disease, which is confirmed by raised urinary and blood mercury levels. Chemical analysis of these medicines consumed by our patients also showed very high levels of mercury (particularly swasakalpa 132 mg/kg) which is 1,000-fold higher than the permissible limit of 0.1 μg/kg.[1] Mercury is an integral part of the Ayurvedic pharmacopoeia but undergoes various "purification" techniques to purportedly make it safe for therapeutic use.[11]

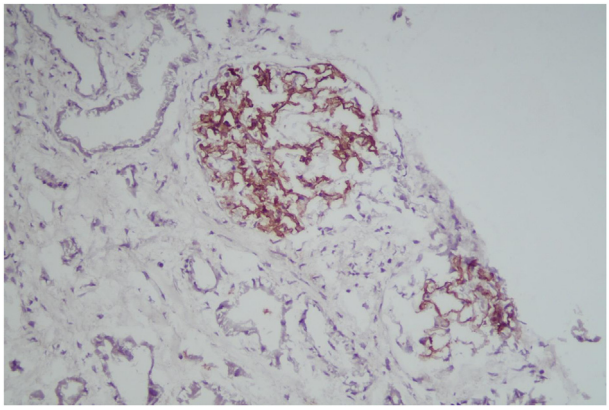

Figure 3. Glomeruli showing NELL-1 positivity on immunohistochemistry.

The association between membranous nephropathy and mercury exposure has been well documented in previous case reports and case series.[1,2,8] However, the specific association with NELL-1 is a more recent discovery. Abraham et al[4] noted that 87.9% of patients with CAM-associated membranous nephropathy were NELL-1 positive in their series. This is similar to our data, in which 73.7% of patients with membranous nephropathy were positive for NELL-1 immunostaining.

The precise mechanism by which mercury intoxication causes glomerulonephritis is unknown. It has been postulated that mercury compounds have immunomodulating activity and abnormal immune responses produce various glomerular lesions.[12] Rat models have shown that mercury can induce autoimmunity through polyclonal B and T cell activation, with subsequent production of various autoantibodies in a dose-dependent manner.[1,3,13,14] In fact, subepithelial immune deposits have been documented in rat models after administration of mercury chloride subcutaneously. It is suggested that mercury acts as a hapten; after binding to proteins on the epithelial aspect of the glomerular basement membrane, autoantibodies are produced that then bind and form subepithelial immune complexes.[2] It has also been hypothesized that prolonged low-level exposure to mercury may induce membranous nephropathy through immune mechanisms, whereas high-level exposure may induce minimal change disease through podocyte injury.[15]

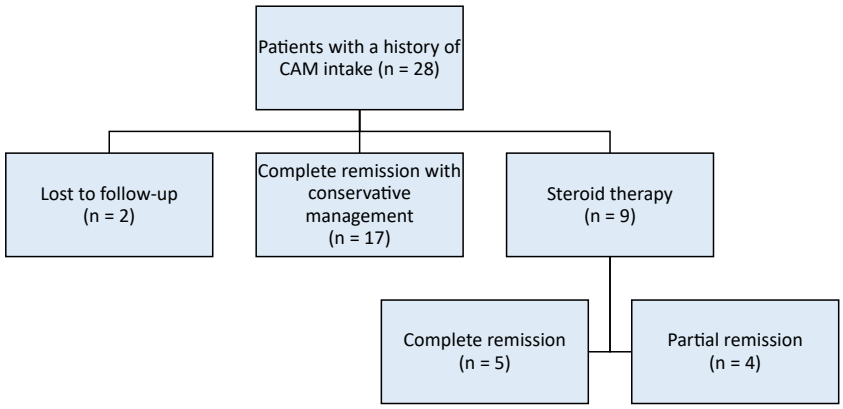

Figure 4. Natural history and response to therapy among patients studied.

The treatment of CAM-induced glomerular disease remains unclear. The first step is to prevent further exposure to mercury. The blood half-life of mercury is about 10 days, and mercury is eliminated by renal excretion. Once the exposure to the offending drug is withdrawn, rapid clearance of mercury occurs, providing a rationale for initial conservative management in mercury-related kidney disease.

Although there is a clear role of chelation therapy in the management of acute mercury intoxication, its relevance in patients with chronic mercury exposure remains controversial. Some authors have used chelation therapy with sodium dimercaptopropane sulfonate in patients with extremely high urinary mercury concentrations (>100 μg/L).[3] However, the preferred agents for chelation are dimercaprol and succimer.[5]

The roles of glucocorticoids and immunosuppression are not clearly defined. Qin et al[15] reported their experience with combined immunosuppression and chelation with sodium dimercaptopropane sulfonate. They observed early remission and a reduced requirement of chelation therapy in those who received immunosuppression. Mattewada et al[16] also found that patients who received steroids remitted early despite having higher blood and urine mercury levels. In our study, steroid therapy was administered when proteinuria continued unabated even after 12 weeks of conservative management with renin-angiotensin system blockade (32.14% of patients), and the clinical response noted emphasizes a potential role for steroid therapy in these patients.

With regard to the patient with arsenic toxicity, it should be noted that arsenic rapidly distributes into the tissues; therefore, blood levels are unreliable. The diagnosis of arsenic toxicity is usually made only in the setting of an elevated arsenic level in a 24-hour urine collection of >50 μg/L.[5] Although arsenic is a known component of

Table 3. Characteristics of Steroid-treated Patients

	Age/ Sex	Duration of CAM Intake	Creatinine at Diagnosis (mg/dL)	Serum Albumin (g/dL)	Spot Urine PCR	Kidney Pathology	Treatment (Full-Dose Steroids, 0.5 mg/kg/d)	Outcome	Time to Remission
Case 1	55/F	3 months	0.6	2.1	3.85	MCD	Full dose 3 weeks, tapered over 2 weeks	CR	3 weeks
Case 2	39/F	3 months	0.5	2.0	7.5	NELL-1 MN	Full dose 4 weeks, tapered over 3 weeks	CR	4 weeks
Case 3	48/F	3 years	1.8	2.8	4.85	MN	Full dose 4 weeks, tapered over 4 weeks	PR	8 weeks
Case 4	42/F	2 months	0.8	2.6	9.1	NELL-1 MN	Full dose 4 weeks, tapered over 4 weeks	CR	6 weeks
Case 5	47/F	5 months	1.2	2.3	5.3	MN	Full dose 4 weeks, tapered over 6 weeks	PR	10 weeks
Case 6	30/F	5 months	0.4	2.1	4.3	MCD	Full dose 3 weeks, tapered over 3 weeks	CR	3 weeks
Case 7	40/F	5 months	0.6	2.8	3.9	NELL-1 MN	Full dose 4 weeks, tapered over 6 weeks	PR	8 weeks
Case 8	38/M	1 month	0.8	1.8	4.7	MCD	Full dose 4 weeks, tapered over 6 weeks	PR	12 weeks
Case 9	44/F	9 months	0.9	2.2	5.8	NELL-1 MN	Full dose 4 weeks, tapered over 6 weeks	CR	10 weeks

Abbreviations: CR, complete remission; MCD, minimal change disease; MN, membranous nephropathy; NELL-1, neural epidermal growth factor-like 1 protein; PCR, protein to creatinine ratio; PR, partial remission.

various CAM preparations, there have been no clear links to the development of glomerulonephritis in the reported literature. Furthermore, there are case reports describing arsenic toxicity secondary to various environmental exposures.[17] It is therefore difficult to link arsenic to the development of the kidney lesions or to the intake of CAM in both of these patients.

Demonstration of high levels of mercury in some of the potential offending formulations and in the blood and urine samples of a significant proportion of patients adds value to our study. However, blood and urine samples of all patients at presentation could not be collected because some of the data were collected retrospectively. Only 6 patients provided samples of the indigenous formulations for analysis. Finally, although patients were questioned about other known sources of mercury exposure, occupational and residential exposures could not be excluded.

In conclusion, the most common kidney pathology noted in patients with a history of intake of CAM was membranous nephropathy, which was predominantly NELL-1 associated. Several of these patients had evidence of mercury intoxication, as confirmed by blood and urine mercury levels. Of the 6 samples that were analyzed, all of them contained higher-than-acceptable levels of mercury. A significant proportion of the patients recovered completely after withdrawal of the offending agent and conservative treatment.

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