Clinical Evidence of Acute Mesoamerican Nephropathy

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Abstract. Mesoamerican nephropathy (MeN), an epidemic of unexplained kidney disease in Central America, affects mostly young, healthy individuals. Its etiology is a mystery that requires urgent investigation. Largely described as a chronic kidney disease (CKD), no acute clinical scenario has been characterized. An understanding of the early disease process could elucidate an etiology and guide treatment and prevention efforts. We sought to document the earliest clinical signs in patients with suspected MeN in a high-risk population in Nicaragua. Physicians at a local hospital identified suspect cases and documented clinical/laboratory data, demographics, and medical histories. Over a 1-year period, physicians identified 255 mostly young (median 29 years), male (89.5%) patients with elevated creatinine or reduced creatinine clearance. Mean serum creatinine (2.0 ± 0.6 mg/dL) revealed a 2-fold increase from baseline, and half had stage 2 or 3 acute kidney injury. Leukocyturia (98.4%), leukocytosis (81.4%), and neutrophilia (86.2%) predominated. Nausea (59.4%), back pain (57.9%), fever (54.6%), vomiting (50.4%), headache (47.3%), and muscle weakness (45.0%) were common. A typical case of acute MeN presented with elevated (or increased ≥ 0.3 mg/dL or ≥ 1.5 -fold from baseline) creatinine, no hypertension or diabetes, leukocyturia, and at least two of fever, nausea or vomiting, back pain, muscle weakness, headache, or leukocytosis and/or neutrophilia. Rapid progression (median 90 days) to CKD was recorded in 8.5% of patients. This evidence can serve as the basis of a sensitive and urgently needed case definition for disease surveillance of early-stage, acute MeN.

BACKGROUND

An unrelenting epidemic of unexplained kidney disease is occurring throughout Central America, extending from Mexico to Panama, mostly along the lowland areas of the Pacific coast.^{1–5} Mesoamerican nephropathy (MeN) emerged decades ago and is believed to have caused more than 20,000 deaths.^{1,4} Yet, the true burden of disease is not well documented, very little is known about the disease process, and the etiology of MeN remains a mystery. MeN is traditionally classified as a chronic kidney disease (CKD) of unknown etiology and is presumed asymptomatic until an elevation in serum creatinine triggers CKD diagnosis; however, interviews with MeN patients and physicians who treat MeN suggest otherwise—that there are clinical signs associated with an early disease process, before CKD.^{6,7} Documenting clinical characteristics at the earliest possible signs of MeN would enhance an urgently needed understanding of the clinical course of disease and shed light on clinical events leading to CKD, potentially leading to effective treatment strategies and windows where interventions could mitigate severe disease and prevent death. Until then, treatment and prevention efforts remain hindered, with great consequence to human life.

Since the natural history of MeN is not known, elucidating an acute clinical picture could lend insight into the underlying renal pathology, hint at disease process, and point to possible etiologies. At present, the epidemic investigation lacks the most critical element—a case definition of the acutely ill patient. An evidence-based clinical case definition would allow rapid detection of new cases during the earliest sign of illness

and facilitate targeted diagnostic workups. In turn, investigations focused on case-defined patients could be used to more efficiently identify the etiology and more accurately determine risk factors. Ultimately, information gleaned from these investigations would inform treatment options and prevention efforts to stop the epidemic.

MeN primarily affects young, otherwise healthy men and women who lack classic risk factors for kidney disease, and agriculture workers appear to be the most heavily affected.^{1,8–11} In Nicaragua, where CKD cases have doubled and CKD mortality is four times the global rate, sugarcane workers in the coastal lowlands are viewed as the highest risk population.^{9,12} Both patients and clinicians there have described a febrile illness during the first signs of kidney impairment.^{6,7} In this study, we sought to define the clinical and laboratory features of the early stages of MeN using hospital-based active surveillance of patients with acute renal impairment in a heavily affected population in Nicaragua.

MATERIALS AND METHODS

Study setting and data collection. The surveillance site for our analysis was a private hospital in Nicaragua, located within a large sugar estate, which provides primary health care to all those who work at the estate and their families. During 2015, there were 15,500 workers at the estate, most laboring only during the harvest season (November to May). Because of the ongoing nature of the epidemic, screening to assess renal function is a routine component of both medical care and frequent occupational health screenings.

Hospital physicians used active case surveillance and prospectively identified patients presenting to the emergency department with suspected MeN, defined locally as elevated serum creatinine (> 1.3 mg/dL for males; > 1.1 mg/dL for females) or reduced serum creatinine clearance ($\text{CrCl} < 90$ mL/min,

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estimated using the Cockcroft–Gault equation¹³), since no gold standard of diagnosis exists. Using structured interviews and medical records, clinicians completed case reports that detailed clinical presentation, medical and social history, and demographics for each patient. Clinical findings and medical history included both subjective and objective data; fever was recorded if measured at $\geq 38.0^{\circ}\text{C}$ or if self-reported by the patient. The hospital clinical laboratory staff analyzed blood and urine samples collected on admission, and hematology, blood chemistry, and urinalysis results were recorded. Serum creatinine, recorded as a routine part of annual preemployment occupational health screenings, was also available. The laboratory measured serum creatinine levels using a modified Jaffe assay (Dialab, Wiener Neudorf, Austria), which is traceable to isotope dilution mass spectrometry reference methods; the reference range is set per assay specifications. Data on subsequent clinical diagnoses of CKD were reported at the end of the surveillance period. These data were made available for our analysis.

Analysis. We analyzed clinical and laboratory data, applying a cross-sectional analysis, and used descriptive statistics for aggregate reporting of the acute clinical picture. Univariate associations were assessed by χ^2 test, and we report *P* values, using Fisher's exact if the comparison included a cell value ≤ 5 .

We calculated estimated glomerular filtration rate (eGFR), using serum creatinine levels and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 equation, and also report the Modification of Diet in Renal Disease Study Group (2006) eGFR and Cockcroft–Gault creatinine clearance estimates.^{13–18} Using serum creatinine at preemployment as a baseline measure, we classified acute kidney injury (AKI) stage according to change in creatinine from baseline to emergency department visit (Acute Kidney Injury Network [AKIN] classification system).¹⁸ For patients later diagnosed with CKD, staging was determined using the Kidney Disease Outcomes Quality Initiative guidelines.^{19,20} We used analysis of variance for repeated measures to analyze change in creatinine levels between baseline, AKI, and later CKD diagnosis, as well as change in eGFR from baseline to CKD. We reported χ^2 *P* values for univariate associations. All statistics were done using Stata 14 (StataCorp LP, College Station, TX).

Ethical considerations. This study was reviewed and approved by the Nicaragua Ministry of Health, Baylor College of Medicine Institutional Review Board (H-36498), and by the Medical Director of Hospital Alfredo Pellas Chamorro in Nicaragua, who waived informed consent for this data analysis. This study was partly funded by El Comité Nacional de Productores de Azúcar de Nicaragua. Neither the funding foundation nor the estate that served as our study site had any influence on this report.

RESULTS

From February 27, 2015 to February 29, 2016, local physicians identified and recorded data on 255 workers with MeN, which equates to 1.6% of the 2015 employment roster. We excluded patients from analysis for either missing clinical data ($N = 7$) or $\text{CrCl} > 90 \text{ mL/min}$ at the time of evaluation ($N = 1$). Thus, we describe the clinical features of 247 potential cases of acute MeN, prospectively identified during 1 year of active surveillance.

Most patients were male (89.5%) and young (29.0 years; 18–68; Table 1). Most (182/245; 74.3%) lived in the rural village

adjacent to the sugar fields and labored in the sugarcane fields (212/246; 86.2%). Comorbidities, particularly classic risk factors for kidney disease, were exceedingly rare: only 3.3% ($N = 8$) had any history of hypertension and four patients (1.7%) were diabetic. Body mass index (BMI) was mostly normal; 10.6% had $\text{BMI} \geq 30$. One patient was > 60 years of age. A prior episode of elevated creatinine was recorded for 16 (6.5%) patients, but none had been previously classified as having CKD or MeN. Self-reported use of traditional/herbal medicines, illicit drugs, and “lija” (an unregulated local homemade alcohol) were uncommon (8.5%, 2.1%, and 4.2%, respectively); almost half (47.7%) reported recent alcohol use. Employment status at the time of symptom onset was known for only 29 workers: of these, 10 (34.5%) were actively working at the time their symptoms began, whereas 19 (65.5%) were not.

Clinical presentation. Symptoms typically began 2 days before the hospital visit, and 19.0% (31/163) presented on the first day of symptoms (Table 1). Nearly all (98.8%) patients presented to the hospital because of their acute symptoms, rather than other reasons. Patients were overwhelmingly normotensive (86.5% $< 120/80 \text{ mmHg}$). Over half had fever associated with their illness (54.6%; Figure 1), but those who were febrile at the time of clinical evaluation (39/247; 15.8%) had mostly low-grade fevers (median 38.5°C ; 38.0 – 39.5). Other frequent symptoms were nausea (59.4%), back pain (57.9%), vomiting (50.4%), headache (47.3%), and muscle weakness (45.0%). Interestingly, paresthesia was somewhat common (43.2%) and had a statistical association with hypomagnesia ($P = 0.034$) but not with hypokalemia or hyponatremia. Urinary symptoms (painful or difficult urination and dysuria) were denied by 79.8% of patients.

Leukocytosis (81.4%; $> 10,000 \text{ cells/mm}^3$) and neutrophilia (86.2%; $> 67\%$) were the predominant abnormal hematology findings, and half of patients had lymphopenia (52.6%; Table 2). We also observed depressed hematocrit (58.5%) and hemoglobin (60.9%). Although serum creatinine levels were generally elevated ($2.0 \pm 0.6 \text{ mg/dL}$), 6.9% of patients had normal levels despite reduced creatinine clearance (Table 3). Serum creatine phosphokinase (CPK) was mostly normal (88.3%); however, three patients had $\text{CPK} > 1,000 \text{ U/L}$. About one-third (29.6%) had hyperuricemia (mean $6.1 \pm 1.8 \text{ mg/dL}$). Some (27.1%) patients had elevated blood urea nitrogen (BUN); however, most (55.1%) BUN-creatinine ratios were normal (< 10.0) and only one was ≥ 20.0 . Hypokalemia, hypomagnesia, and hyponatremia were observed in 61.3%, 41.7%, and 10.2% of patients, respectively.

On urinalysis, almost all patients (98.4%) had some degree of leukocyturia: 74.9% had marked leukocyturia ($\geq 15 \text{ cells/field}$), and 34.2% also had leukocytic casts (Table 4). Epithelial cells (93.9%) and erythrocytes (82.1%) in urine were common. Proteinuria was noted in almost half (44.9%) of the patients, but at low levels; of 42 patients with known levels, 59.5% had some degree of albuminuria, but only 38.1% were $\geq 30 \text{ mg/dL}$. Bacteriuria was unremarkable and was associated with epithelial cells in urine specimens ($P = 0.002$) but not with leukocyturia ($P = 0.182$).

AKI classification. When we analyzed baseline serum creatinine, available on 206 patients, we found that most (98.5%) had normal levels at the time of their preemployment health screenings (Table 5). Despite this, the mean baseline eGFR was $100.4 \pm 16.7 \text{ mL/min/1.73 m}^2$ (37.6–133.0), and

TABLE 1
Characteristics of study population

		n/N* (%)
Male		221/247 (89.5)
Age (years)	< 25	65/247 (26.3)
	25–29	69/247 (27.9)
	30–34	49/247 (19.8)
	≥ 35	64/247 (25.9)
Years working sugarcane fields	≤ 5	112/229 (48.9)
	> 5	117/229 (51.1)
Current occupation	Cane cutter	52/220 (23.6)
	Irrigation/drainage worker	49/220 (22.3)
	Seed planter	37/220 (16.8)
	Other field laborer	16/220 (7.3)
	Herbicide/pesticide applicator	11/220 (5.0)
	Pest control worker	9/220 (4.1)
	Hauler of cane/seeds	9/220 (4.1)
	Weed control worker	6/220 (2.7)
	Oven operator	6/220 (2.7)
	Shrimp farm worker	5/220 (2.3)
	Mechanic/construction worker	4/220 (1.8)
	Other	16/220 (7.3)
Currently ever uses	Cigarettes	45/235 (19.1)
	Alcohol	113/237 (47.7)
	Lija	10/238 (4.2)
	Traditional herbs/medicines	20/234 (8.5)
	Illicit drugs	5/235 (2.1)
Past medical history	Anemia	47/240 (19.6)
	Asthma	8/239 (3.4)
	Azotemia	16/240 (6.7)
	Diabetes	4/241 (1.7)
	Gout	4/241 (1.7)
	Hepatitis	3/241 (1.2)
	Hypertension	8/241 (3.3)
	Kidney stones	5/242 (2.1)
	Kidney injury	2/241 (0.8)
	Sexually transmitted disease	3/239 (1.3)
	Pancreatitis	1/238 (0.4)
	Frequent urinary tract infection	37/241 (15.4)
BMI (kg/m ²)	< 18.5	5/237 (2.1)
	18.5–24.9	122/237 (51.5)
	25.0–29.9	85/237 (35.9)
	≥ 30.0	25/237 (10.6)
		Mean ± SD (range) or median (range)
Age (years)		29 (18, 68)
Vitals	Temperature (°C)	37.0 ± 0.8 (36.0, 39.5)
	Height (m)	1.7 ± 0.1 (1.1, 1.8)
	Weight (kg)	68.8 ± 12.4 (45.4, 115.0)
	Blood pressure (mmHg)	Systolic 112.3 ± 13.1 (70, 180)
		Diastolic 73.1 ± 9.2 (60, 120)
	Pulse (beats per minute)	83.4 ± 11.1 (60, 130)
Symptomatic days before acute visit		2 (0, 95)
Number of days taken off work after discharge		7 (1, 28)

BMI = body mass index; SD = standard deviation.

* N = total number of patients with nonmissing data.

only 72.4% had truly normal filtration rates (eGFR ≥ 90 mL/min/1.73 m²) at that point in time (Table 6). Notably, over a 3.5-month period (104 days; 5–344) from baseline to acute illness, creatinine levels increased by 2-fold (2.1 ± 0.7; 0.9–4.3), a statistically significant change from baseline ($P < 0.001$). Using AKIN criteria, we classified 91.7% ($N = 189$) patients as having AKI, with most (92.4%) having no previous known elevated creatinine level; 12.1% had stage 3 AKI.

Characterization of acute MeN. These observations, which document the typical clinical scenario of acute MeN at the time of hospital presentation, served as the evidence for the following proposed case definition of acute MeN in this setting: a patient, without hypertension or diabetes, who presents with serum creatinine that is either elevated (> 1.3 mg/dL

for males; > 1.1 mg/dL for females) or increased (≥ 0.3 mg/dL or ≥ 1.5-fold) from baseline, accompanied by leukocyturia and at least two of the following: 1) fever, 2) nausea or vomiting, 3) back pain, 4) muscle weakness, 5) headache, or 6) leukocytosis or neutrophilia. Of 247 potential cases of acute MeN we analyzed, 91.1% ($N = 225$) meet this case definition.

Treatment and outcomes. Treatment consisted of hospital admission (91.9%; 226/246), intravenous fluids and electrolytes (91.5%; 226/245), and a 1-week (7 days; 1–28) rest period from work (96.7%; 236/244). During hospitalization, a few patients received ranitidine (7.0%; 17/245), acetaminophen (5.3%; 13/245), or allopurinol (5.7%; 14/245), and antibiotics were rarely prescribed (2.0%; 5/245). Renal ultrasounds were not performed as part of the medical evaluations, and no

FIGURE 1. Frequency of symptoms reported during acute episode.

biopsies were performed. No patient in our analysis died during the hospital encounter.

As a follow-up to our surveillance, we discovered that 21 (8.5%) of the 247 patients we analyzed were later diagnosed by hospital physicians as having CKD, with diagnoses 3 months after their acute episodes (90 days later; 1–541). The mean age at CKD diagnosis was $34.8.1 \pm 9.2$ years (23–57), and 14.3% ($N = 3$) were female. Although there was a reduction in serum creatinine (mean decrease 0.4 ± 0.5 mg/dL; -1.6 to 0.6 ; $P = 0.019$) between the acute presentation and time of CKD diagnosis, the residual creatinine level was elevated (1.5 mg/dL; 1.1 – 2.0). The majority (82.4%), but not all, of these CKD cases had been classified as having AKI during their acute episodes. Using KDIGO guidelines, we classified CKD in these patients as follows: 1 (4.8%) stage 1, 9 (42.9%) stage 2, 7 (33.3%) stage 3A, and 4 (19.1%) stage 3B. CKD patients suffered significant reductions in renal function from baseline (median change in eGFR -20.7 mL/min/ 1.73 m 2 ; -64.2 to 17.2 ; $P = 0.010$) over a short period of only 7 months (221 days; 71–713).

DISCUSSION

MeN is a devastating epidemic, mostly afflicting young agricultural workers. It is associated with progressive renal fibrosis, end stage renal disease (ESRD), and premature mortality.^{2,21,22} The etiology of MeN remains undiscovered, limiting identification, treatment, and prevention of new cases. Our findings suggest that patients in the acute phase of MeN experience AKI, accompanied with clinical features of systemic

inflammation, consistent with an acute tubulointerstitial nephritis. Specifically, neutrophilic leukocytosis and leukocyturia were characteristic, whereas proteinuria and hyperuricemia were not. Patients were normotensive, frequently presented with new-onset febrile illness, and generally denied urinary symptoms. These observations are crucial to the development of an evidence-based clinical case definition and served as the basis for the herein described first-ever case definition of acute MeN. We proposed a sensitive case definition to capture as many potential cases as possible, and we urge its prompt application in high-risk areas. To our knowledge, this is the first study to document the early clinical picture of MeN and propose a case definition, which are vital for early case identification, diagnostic workup, epidemiologic investigations, and planning of effective treatment and prevention strategies.

We found that 92% of suspected MeN cases had AKI, with an overwhelming, 2-fold increase in serum creatinine from baseline; 12% had more advanced, stage 3 AKI. This staging assumes that baseline creatinine measurement accurately reflected baseline renal function, which we found was mostly normal. In practice, staging often relies on assumed baseline functioning, in the absence of serial laboratories, and remains useful to indicate AKI severity, since more severe stages carry higher risk of death.²³ Furthermore, since mortality rates are particularly high in lower income countries, characterizing AKI in resource-limited settings afflicted by the MeN epidemic is an urgent public health need.^{24,25}

As a disruptive event producing renal dysregulation, AKI frequently progresses to CKD and ESRD.^{26,27} Our study

TABLE 2
Clinical laboratory findings—hematology

Clinical laboratory findings - Hematology			Total no. of nonmissing values, <i>N</i>	<i>n</i> (%)
Leukocytes (cells/mm ³)	Normal	≤ 10,000	247	46 (18.6)
	High	> 10,000		201 (81.4)
Neutrophils (%)	Low	< 52	247	4 (1.6)
	Normal	52–67		30 (12.2)
Lymphocytes (%)	High	> 67	247	213 (86.2)
	Low	< 21		130 (52.6)
Eosinophils (%)	Normal	21–35	230	97 (39.3)
	High	> 35		20 (8.1)
Platelets (cells/mm ³)	Normal	≤ 4	212	213 (92.6)
	High	> 4		17 (7.4)
Hematocrit (%)	Low	< 150,000	246	2 (0.9)
	Normal	150,000–500,000		204 (96.2)
Hemoglobin (g/dL)	High	> 500,000	138	6 (2.8)
	Low	< 38.8 male, < 34.9 female		144 (58.5)
Malaria blood smear	Normal	38.8–50.0 male, 34.9–44.5 female	66	101 (41.1)
	High	> 50.0 male, < 44.5 female		1 (0.4)
Parasitemia	Low	< 13.5 male, < 12.0 female	138	84 (60.9)
	Normal	13.5–17.0 male, 12.0–15.5 female		53 (38.4)
	High	> 17.0 male, > 15.5 female	66	1 (0.7)
	No parasites observed			66 (100)
	Parasitemia			0 (0)
Mean ± SD (range) or median (range)				
Hematocrit (%)			246	37.5 ± 5 (20, 51)
Hemoglobin (g/dL)			138	12.5 (7.9, 19.5)
Leukocytes (count/mm ³)			247	14,130 (4,600, 29,200)
Neutrophils (%)			247	79 (40, 96)
Lymphocytes (%)			247	20 (2, 54)
Eosinophils (%)			230	0 (0, 26)
Platelets (count/mm ³)			212	314,000 (103,000, 598,000)

SD = standard deviation.

demonstrates that this phenomenon also occurs in MeN. Through a combination of incomplete recovery, inadequate therapy, and possibly repeat exposures, MeN-associated AKI can progress to MeN-associated CKD. In our study, 9% of patients developed CKD, most within a matter of months. With scarcity of renal replacement therapy in most areas afflicted by MeN, prompt identification and management of patients with AKI could mediate progression to CKD and reduce the risk of death. For now, in light of the inflammatory process we observed, we suggest that therapy, such as a short course of corticosteroids, may mitigate inflammation and aid in renal recovery.²⁸

It is especially intriguing that 98% of patients were shedding leukocytes in their urine, often with leukocyte casts. Given our predominantly young, male population, it is unlikely that this magnitude of leukocyturia is a consequence of cystitis, prostatitis, or pyelonephritis. Also interesting is a high prevalence of anemia (61%). In the United States, only 5.2% of stage 3 CKD patients have anemia.²⁹ Normal baseline creatinine and overall clinical picture makes low erythropoietin production from chronic kidney damage an unlikely source. However, the clinically apparent systemic inflammation may impact red blood cell lifespan via hepcidin-mediated iron metabolism, stunted progression of erythroid precursor cells, and reduced responsiveness to erythropoietin.³⁰ Further research is needed to understand the underlying causes of anemia in this context. Low-grade bacteriuria was fairly common, but since accompanied by epithelial cells, we suspect contamination during collection rather than pyelonephritis or urinary tract infection. Still, epithelial cell shedding could reflect a, yet unknown, renal pathology.

The few published reports on clinical characteristics of MeN describe that patients often have hyponatremia, hypokalemia,

and hyperuricemia.^{22,31–33} It is important to highlight that those studies that relate characteristics of the chronic phase of MeN (CKD) do not necessarily reflect the acute MeN process. CKD patients in those studies were older, had poorer renal function, and more often had hypertension, compared with our population. Although we noted hypokalemia and hyponatremia in our study, they were not defining features. Importantly, hyperuricemia was not a characteristic of acute MeN, which is in stark contrast to chronic MeN. Even so, the observation of hyperuricemia in one-third of these otherwise healthy, young individuals is higher than expected. Several investigators have proposed that hyperuricemia and consequential hyperuricosuria, cyclic in nature due to repeated hard labor in hot conditions, may be the cause of chronic MeN.^{34,35} Since cases in our analysis typically presented for clinical evaluation 2 days after onset, we cannot assess if the two-thirds with normal uric acid levels experienced a return to normal after onset or never had elevated levels. Further investigations are needed to ascertain if hyperuricemia reported during late-stage disease is a result of chronically impaired filtration or a part of the initial pathogenesis.

The clinical spectrum and systemic inflammatory response we observed lend insight into the cause of MeN. We found that most patients had normal BUN-creatinine ratios, anemia rather than hemoconcentration, nonacidic urine, and normal urine-specific gravity, and even with some evidence of hypovolemia, do not suggest patients were in a state of dehydration and overexertion at the time of evaluation. Although CPK was elevated in 12% of patients, levels were not high enough to reflect acute rhabdomyolysis. Most notably, the systemic inflammation that was distinctly characteristic of patients in our investigation cannot be ignored. These

TABLE 3
Clinical laboratory findings—blood chemistry

			Total no. of nonmissing values, <i>N</i>	<i>n</i> (%)
Creatinine (mg/dL)	Normal	≤ 1.3 male, ≤ 1.1 female	247	17 (6.9)
	Elevated	> 1.3 male, > 1.1 female		230 (93.1)
Glucose (mg/dL)	Low	< 75	228	19 (8.3)
	Normal	75–115		171 (75.0)
	High	> 115		38 (16.7)
Uric acid (mg/dL)	Normal	≤ 7.0 male, ≤ 6.0 female	226	159 (70.4)
	Elevated	> 7.0 male, > 6.0 female		67 (29.6)
Calcium, ionized (mmol/L)	Low	< 1.1	247	33 (13.4)
	Normal	1.1–1.35		198 (80.2)
	High	> 1.35		16 (6.5)
Magnesium (mg/dL)	Low	< 1.9	223	93 (41.7)
	Normal	1.9–2.5		120 (53.8)
	High	> 2.5		10 (4.5)
Potassium (mmol/L)	Low	< 3.5	235	144 (61.3)
	Normal	≥ 3.5		91 (38.7)
Sodium (mmol/L)	Low	< 135	225	23 (10.2)
	Normal	135–145		198 (88.0)
	High	> 145		4 (1.8)
CPK (U/L)	Low	< 52 male, < 38 female	180	15 (8.3)
	Normal	52–336 male, 38–176 female		144 (80.0)
	High	> 336 male, > 176 female		21 (11.7)
BUN (mg/dL)	Normal	≤ 24 male, ≤ 21 female	118	86 (72.9)
	High	> 24 male, > 21 female		32 (27.1)
BUN-creatinine ratio	Low	< 10.0	118	65 (55.1)
	Normal	10.0–20.0		53 (44.1)
	High	> 20.0		1 (0.1)
Mean ± SD (range) or median (range)				
Creatinine (mg/dL)				2.0 ± 0.6 (1.2, 4.2)
Glucose (mg/dL)				96.7 ± 20 (60, 182)
Uric acid (mg/dL)				6.1 ± 1.8 (2.0, 12.0)
Calcium, ionized (mmol/L)				1.2 ± 0.2 (0.4, 3.3)
Magnesium (mg/dL)				1.9 ± 0.4 (0.5, 3.2)
Potassium (mmol/L)				3.7 ± 0.7 (2.0, 5.4)
Sodium (mmol/L)				138.4 ± 4.3 (111, 148)
Creatine phosphokinase (CPK) (U/L)				138 (17, 1668)
BUN (mg/dL)				19 (5.5, 43.8)
BUN-creatinine ratio				9.4 (3.2, 23.3)

BUN = blood urea nitrogen; CPK = creatine phosphokinase.

observations may point to an exogenous etiology, such as an infectious agent or toxin, and suggest that dehydration and overexertion, which perhaps increase susceptibility or contribute to the disease process, are not the sole cause of MeN. Our findings shed light on the early disease process, bringing us closer to understanding an underlying cause.

It is important to consider some limitations inherent in our analysis. First, selection bias against cases who did not seek medical care (including asymptomatic cases) and those who sought care elsewhere is inherent to our design. This means that we cannot speak to the rate of asymptomatic acute MeN, and also means that, since we did not follow patients as a cohort, those who did not present for subsequent follow-up at the hospital would not be included in our analysis of progression to CKD. Together, these would result in an underestimation of both AKI and CKD incidence, and we could have missed fatal cases. Our reliance on creatinine levels means that the disease process in our cases was probably already underway, since rise in creatinine does not occur at biologic onset; however, capturing cases at onset is unlikely, since our understanding of MeN and potential biomarkers is still limited. Even so, we herein characterize MeN at an earlier stage of disease than has been done previously. Surveillance using creatinine also limits the ability of our study, and others, to accurately define renal impairment, due to high variability in

creatinine and considerations such as volemia, catabolic effects, tubular excretion, and muscle mass.^{14,36}

Since we relied on clinical data collected during the course of routine evaluation, some valuable clinical indicators were not available for analysis. For example, C-reactive protein levels could serve as an additional marker of inflammation but were not measured during the clinical encounter. Renal ultrasound could have helped us discern between AKI and CKD; however, in this setting ultrasound is not routinely conducted until advanced disease stages. Most notably, renal biopsies would elucidate the acute pathologic changes, but although biopsy is considered standard-of-care in many settings, access to advanced diagnostics, including biopsy, is exceedingly limited in our study setting. Also owing to our study design, we did not assess risk factors, such as exposures, as part of this study, and it is unknown what exposures may have influenced the acute change between baseline and detection. We also did not have baseline levels of other important laboratory values that might lend more insight into baseline health, and it is unknown at which specific point or how quickly after baseline an acute change in renal function occurred. The lack of retrospective laboratory data limits our ability to distinguish an initial, acute onset of MeN from an acute episode of CKD already underway, as we could not accurately assign CKD status at presentation. CKD is a risk factor for subsequent AKI,

TABLE 4
Clinical laboratory findings—urine analysis

		Total no. of nonmissing values, <i>N</i>	<i>n</i> (%)
Aspect	Transparent	242	40 (16.5)
	Lightly turbid		35 (14.5)
	Turbid		167 (69)
Protein	None	247	136 (55.1)
	Trace		14 (5.7)
	> Trace to < 30 mg/dL		42 (17.0)
	30–99 mg/dL		49 (19.8)
	> 100 mg/dL		6 (2.4)
Glucose	Negative	247	218 (88.3)
	Positive		29 (11.7)
Ketones	Negative	247	232 (93.9)
	Positive		15 (6.1)
Urobilirubin	Negative	247	246 (99.6)
	Positive		1 (0.4)
Bilirubin	Negative	247	241 (97.6)
	Positive		6 (2.4)
Hemoglobin	Negative	247	166 (67.2)
	Positive		81 (32.8)
Microalbumin	Negative	42	17 (40.5)
	< 30 mg/dL		9 (21.4)
	30–99 mg/dL		14 (33.3)
	≥ 100 mg/dL		2 (4.8)
Epithelial cells	None	246	15 (6.1)
	Scarce/few		189 (76.8)
	> Few		42 (17.1)
Erythrocytes	None	246	44 (17.9)
	1 per field		58 (23.6)
	≥ 2 per field		144 (58.5)
Leukocytes	None	247	4 (1.6)
	1–14 per field		58 (23.5)
	≥ 15 per field		185 (74.9)
Casts	Negative	246	136 (55.3)
	Positive		110 (44.7)
Leukocytic casts	Negative	246	162 (65.9)
	Positive		84 (34.2)
Crystals	Negative	246	131 (53.3)
	Positive		115 (46.8)
Amorphous urate crystals	Negative	246	148 (60.2)
	Positive		98 (39.8)
Amorphous phosphate crystals	Negative	246	231 (93.9)
	Positive		15 (6.1)
Bacteria	None	247	12 (4.9)
	Scarce/few		156 (63.2)
	Moderate		66 (26.7)
	Abundant/too numerous to count		13 (5.3)
			Median (range)
Specific gravity	247	1,020 (1,005, 1,030)	
pH	245	6.0 (5.0, 9.0)	

and CKD early stages can occur with normal creatinine levels. However, few patients in our study had any known history of elevated creatinine or prior diagnosis of CKD, and creatinine is measured at least annually at our study site, meaning that the vast majority of patients were experiencing their first known creatinine rise, and we considered them incident cases. Finally, patients in our analysis came from a very specific, high-risk, agricultural community, and it is possible that MeN presents differently in other communities. However, this is also a strength of our study, since our population is notorious as having the highest risk in Nicaragua and are, therefore, monitored closely with respect to renal function. Importantly, this analysis afforded us the opportunity to leverage the knowledge and experience of local clinicians who treat and diagnose MeN on a regular basis and who relate observations that an acute episode of illness is often an antecedent to CKD in those patients.^{6,7}

To improve surveillance, we urge the use of the CKD-EPI equation for estimating GFR, rather than reliance on other estimates or on serum creatinine level, alone. Specifically, the Cockcroft–Gault equation overestimates creatinine clearance, has high variability, and, from our observations, fails to correctly classify some individuals with impaired filtration.³⁶ In our study, local physicians identified cases of acute MeN, 10% of whom had serum creatinine levels within the normal range but reduced creatinine clearance. When we applied the CKD-EPI calculation to baseline creatinine levels, 27% of patients with normal levels had eGFR < 90 mL/min/1.73 m². Creatinine screening is warranted in populations at risk, but early cases may go undetected if renal impairment is defined as having creatinine level above the reference range, particularly since young individuals with “normal” levels could already have impaired filtration and could be suffering a decline in function. Since even slight elevations may be indicative of

TABLE 5
AKI staging

	Total no. of nonmissing values, <i>N</i>	<i>n</i> (%)
AKI stage		
No AKI	206	17 (8.3)
Stage 1		86 (41.8)
Stage 2		78 (37.9)
Stage 3		25 (12.1)
Mean $\pm$ SD (range) or median (range)		
Serum creatinine, baseline screening (mg/dL)	206	1.0 $\pm$ 0.2 (0.6, 2.3)
Serum creatinine ratio (acute:baseline)	206	2.1 $\pm$ 0.7 (0.9, 4.3)
Change in creatinine from baseline (mg/dL)	206	1.0 $\pm$ 0.6 (−0.2, 3.2)
Time from baseline to acute presentation (days)	206	104 (5, 344)

AKI = acute kidney injury.

major functional decline, enhanced surveillance of serum creatinine in high-risk populations could serve as an early detection tool for MeN.

Future studies should validate the findings from this study population in similar and additional settings and broadly field test the sensitive case definition we herein propose. In an ongoing analysis, we will describe risk factors in this population for MeN-associated AKI, CKD, and CKD stage. Focused efforts to identify the etiology of MeN, understand long-term clinical outcomes, and examine factors associated with increased risk and susceptibility are needed. Thus, immediate implementation

of the case definition for prompt detection of acute MeN could enable therapeutic intervention during the initial renal injury, as well as facilitate research by aiding in selection of patients for targeted diagnostics and epidemiologic investigations. Renal biopsies during the acute phase of illness will be extremely beneficial to confirm diagnosis, establish early pathology, and guide etiologic discovery. Community-based surveillance could further identify asymptomatic cases and enhance our understanding of the incidence of acute and chronic MeN in a more diverse population. A retrospective study could reveal if recurrent, acute episodes of AKI occur, if

TABLE 6
Change in eGFR

	<i>n</i>	CKD-EPI (mL/min/1.73m ²)	MDRD (mL/min/1.73 m ²)	Cockcroft–Gault (mL/min)
		<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
eGFR at baseline screening				
≥ 120	206	31 (15.1)	11 (5.3)	46 (23.2)
90 to < 120		118 (57.3)	76 (36.9)	100 (50.5)
60 to < 90		54 (26.2)	115 (55.8)	49 (24.8)
45 to < 60		2 (1.0)	3 (1.5)	2 (1.0)
< 45		1 (0.5)	1 (0.5)	1 (0.5)
eGFR at CKD diagnosis*				
90 to < 120	21	0 (0)	0 (0)	3 (15.0)
60 to < 90		10 (47.6)	7 (33.3)	9 (45.0)
45 to < 60		7 (33.3)	8 (38.1)	7 (35.0)
30 to < 45		4 (19.1)	6 (28.6)	1 (5.0)
	<i>n</i>	CKD-EPI Mean $\pm$ SD (range)	MDRD Mean $\pm$ SD (range)	Cockcroft–Gault Mean $\pm$ SD (range)
eGFR at baseline screening	206	100.4 $\pm$ 16.7 (37.6, 133.0)	89.0 $\pm$ 16.1 (34.5, 138.6)	105.0 $\pm$ 23.6 (39.1, 180.6)
eGFR at CKD diagnosis	21	59.6 $\pm$ 14.5 (35.2, 90.9)	53.4 $\pm$ 12.3 (31.5, 79.7)	67.2 $\pm$ 21.2 (30.4, 110.3)
	<i>n</i>	Mean $\pm$ SD (range) or median (range)		
Serum creatinine, time of CKD diagnosis (mg/dL)	21	1.5 $\pm$ 0.2 (1.1, 2.0)		
Change in creatinine from acute presentation to CKD (mg/dL)	21	−0.4 $\pm$ 0.5 (−1.6, 0.6)		
Change in creatinine from baseline to CKD (mg/dL)	18	0.3 $\pm$ 0.3 (−0.6, 0.9)		
Time from acute presentation to CKD (days)	21	90 (1, 541)		
Time from baseline to CKD (days)	18	221 (71, 713)		

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; MDRD = modification of diet in renal disease; SD = standard deviation.

* CKD diagnosis made by hospital clinicians was reported subsequent to the surveillance period.

systemic inflammation consistently accompanies AKI, and if AKI is a usual antecedent of MeN-associated CKD. Finally, case-control studies (using carefully defined case patients) will more accurately determine risk factors for disease.

In summary, clinical data from patients in new, acute episodes of renal dysfunction in line with MeN document that an initial presentation of AKI, hallmarked by an acute systemic inflammatory response, is characteristic. We also report that in MeN patients, the AKI episode can progress quickly to advanced CKD, presumably characterized by chronic tubulointerstitial nephritis. Our findings align with hypotheses of an exogenous agent as either the initial cause or as a trigger or major contributor to the disease process. Repeated insult and exacerbation by additional factors, such as dehydration and heat stress or nephrotoxic medication taken to alleviate symptoms, are also possible contributors. This epidemic's devastating nature, geographic reach, and resulting public health crisis make discovery of the underlying cause our primary objective toward an overall goal of implementing urgently needed preventive and therapeutic strategies.

Detection of MeN at its chronic stage may just be the tip of the iceberg, representing only a fraction of true MeN cases. The chance to identify MeN as early in the disease process as possible can afford clinicians the opportunity to intervene as early as possible, such as counseling patients on proper kidney health (e.g., diet modifications) and closely monitoring renal function to determine therapeutic and diagnostic needs. Thus, identification of MeN at the earliest possible stage in disease is an immediate need, and we urge that the clinical use of our proposed case definition today will bring us closer to solving the mystery of MeN in the future.

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