# Early detection of acute tubulointerstitial nephritis in the genesis of Mesoamerican nephropathy

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**Mesoamerican nephropathy is a devastating disease of unknown etiology that affects mostly young agricultural workers in Central America. An understanding of the mechanism of injury and the early disease process is urgently needed and will aid in identification of the underlying cause and direct treatment and prevention efforts. We sought to describe the renal pathology in Mesoamerican nephropathy at its earliest clinical appearance in prospectively identified acute case patients in Nicaragua. We considered those with elevated (or increased at least 0.3 mg/dL or 1.5-fold from baseline) serum creatinine, leukocyturia, and either leukocytosis or neutrophilia for inclusion in this biopsy study. Renal tissue was obtained by ultrasound-guided biopsy for examination by light, immunofluorescence, and electron microscopy. All 11 individuals who underwent renal biopsy showed tubulointerstitial nephritis, with varying degrees of inflammation and chronicity. Interstitial cellular infiltrates (predominantly T lymphocytes and monocytes), mostly in the corticomedullary junction; neutrophilic accumulation in the tubular lumens; largely preserved glomeruli; few mild ischemic changes; and no immune deposits were noted. The acute components of tubulointerstitial nephritis were acute tubular cell injury, interstitial edema, and early fibrosis. Chronic tubulointerstitial nephritis included severe tubular atrophy, thickened tubular basement membrane, and interstitial fibrosis. Thus, renal histopathology in Mesoamerican nephropathy reveals primary interstitial disease with intact glomeruli.**

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The epidemic of Mesoamerican nephropathy (MeN), commonly referred to as a chronic kidney disease (CKD) of unknown etiology, emerged during the past few decades and has spread throughout Central America. As a result of this epidemic, CKD has become a leading cause of hospitalization and death in the region.[1–5] At least 20,000 have died due to MeN; however, the toll is likely much higher because surveillance limitations and the lack of a consensus on a case definition or diagnostic criteria mean that the true burden of disease has not been well documented.[3,6,7] MeN most often affects working-age men without hypertension and diabetes mellitus, traditional risk factors for CKD.[1,8,9] Prevention and early treatment to mitigate disease progression are critical needs, as renal replacement therapy is scarcely available in most of Central America.[1,10] However, efforts to define appropriate clinical guidelines are limited by the uncertainty of the etiology of MeN, presenting a public health emergency that requires urgent attention.

Historically, MeN has been characterized as a chronic disease, but the natural history of this inexplicable disease has been inadequately described. The renal pathology in chronic MeN is primarily chronic tubulointerstitial disease with fibrosis, atrophy, and glomerulosclerosis.[11–13] Importantly, renal tissues for these biopsy studies came from patients in various stages of CKD who had endured disease chronicity for unknown time periods before biopsy; thus, it is difficult to know whether the observed pathology reflects a primary mechanism of injury or are secondary manifestations of CKD. In a recent case investigation, we observed that MeN can have an early clinical presentation of acute kidney injury (AKI).[14] AKI is a documented risk factor for CKD, end-stage renal disease, and death, but this clinical progression has not yet

been explored in the context of MeN.[15–17] Without evidence of the renal pathology at the apparent clinical onset of MeN, a critical gap in knowledge about its pathogenesis and pathophysiology persists.

Our objectives were to examine renal tissue from well-characterized patients at the onset of MeN and (i) describe the early-phase acute renal pathology, (ii) suggest a clinical diagnosis based on pathology and clinical data, and (iii) propose a mechanism of injury. Our overarching goals were to discover the etiology of MeN and inform clinical management and prevention efforts.

## RESULTS

From May 30 through July 23, 2016, physicians reported 64 cases of presumed MeN. Eleven of these patients met eligibility criteria, gave informed consent, and underwent renal biopsy. Patients were young (26 years of age [range, 22–36 years]) and male, without obesity, hypertension, or diabetes mellitus (Supplementary Table S1). All patients denied use of antibiotics in the previous 2 weeks; 1 patient reported taking ibuprofen, and 2 took acetaminophen. All 11 patients were treated with i.v. fluids with electrolytes on presentation; 6 received iron and folic acid supplements, 2 received ranitidine, and 5 were given pain relievers (acetaminophen or metamizole); none were treated with antibiotics.

Patients presented with a median serum creatinine level of 2.5 mg/dl (range, 2.0–3.6 mg/dl) 2 days after symptom onset (2 days; range, 0–7), and creatinine clearance of 44.3 ml/min (range, 31.5–62.0) (Table 1). Most (81.8%) patients experienced a febrile illness. All were normotensive (≤130/90 mm Hg) and had signs of systemic inflammation, namely, C-reactive protein (>6 mg/dl) and high white cell counts (16,440 cells/mm$^3$; range, 10,870–28,750). All had neutrophilic leukocytosis, and 45% had lymphopenia. Most (82%) also had marked leukocyturia (>15 cells/field), some ($N = 3$) with leukocyte casts, and all had negative urine culture findings. All patients were shedding erythrocytes in the urine, but erythrocyte casts were not observed. All but 2 patients (82%) had normal uric acid levels. Detailed clinical data are shown in Supplementary Table S2. Blood cultures were not performed.

When we evaluated baseline renal function in these 11 individuals using serum creatinine values from previous health screenings, all baseline levels were within normal limits (1.0 mg/dl; range, 0.9–1.2). The median baseline estimated glomerular filtration rate (99.1 ml/min per 1.73 m$^2$ [77.3 to 120.8]) was normal, although we found an estimated glomerular filtration rate <90 ml/min per 1.73 m$^2$ in 3 patients when we applied the CKD-EPI formula. Creatinine levels at the acute phase (2.5 mg/dl; range, 2.0–3.6) reflected a 2.6-fold-increase (range, 1.8–3.3) over only 4.5 months (137 days after baseline [range, 42–395]). All patients had AKI: 1 (9%) stage 1 AKI, 7 (64%) stage 2, and 3 (27%) stage 3. As a follow-up to our study, we learned that serum creatinine returned to within normal limits (1.1 ± 0.2 mg/dl) in 10 of

**Table 1 | Clinical laboratory findings on initial presentation**

| Clinical laboratory finding | | Total no. of nonmissing values | *N* (%) |
|---|---|---|---|
| Blood chemistry | | | |
| Glucose, mg/dl | | | |
| Normal | 75–115 | 11 | 11 (100) |
| High | >115 | | 0 (0) |
| Uric acid, mg/dl | | | |
| Normal | ≤7.0 | 11 | 9 (82) |
| High | >7.0 | | 2 (18) |
| Creatine phosphokinase (U/l) | | | |
| Normal | 52–191 | 11 | 6 (55) |
| High | 191–336 | | 3 (27) |
| Very high | >336 | | 2 (18) |
| BUN, mg/dl | | | |
| Normal | ≤24 | 10 | 5 (50) |
| High | >24 | | 5 (50) |
| BUN-creatinine ratio | | | |
| Low | <10.0 | 10 | 6 (60) |
| Normal | ≥10.0 | | 4 (40) |
| C-reactive protein, mg/dl | | | |
| Negative | <6 | 10 | 0 (0) |
| Positive | ≥6 | | 10 (100) |
| Hematology | | | |
| Lymphopenia, % | | | |
| No | ≥21 | 11 | 6 (55) |
| Yes | <21 | | 5 (45) |
| Neutrophilia, % | | | |
| No | ≤67 | 11 | 0 (0) |
| Yes | >67 | | 11 (100) |
| Hematocrit, % | | | |
| Low | <38.8 | 11 | 7 (64) |
| Normal | ≥38.8 | | 4 (36) |
| Hemoglobin, g/dl | | | |
| Low | <13.5 | 8 | 4 (50) |
| Normal | ≥13.5 | | 4 (50) |

| | | Mean ± SD (range) or median (range) |
|---|---|---|
| Creatinine, mg/dl | 11 | 2.5 (2.0–3.6) |
| Uric acid, mg/dl | 11 | 6.2 ± 1.5 (2.7–8.5) |
| Creatine phosphokinase (CPK-NAC), u/l | 11 | 180 (59–590) |
| BUN, mg/dl | 10 | 23.4 (16.7–33.0) |
| BUN-creatinine ratio | 10 | 9.6 (5.2–14.8) |
| Leukocytes, count/mm$^3$ | 11 | 16,440 (10,870–28,750) |
| Neutrophils, % | 11 | 77 (73–92) |
| Lymphocytes, % | 11 | 23 (8–27) |
| Hematocrit, % | 11 | 38.1 ± 6.1 (29–54) |
| Hemoglobin, g/dl | 8 | 13.6 (11.3–15.5) |
| Urinalysis | | |

| | Total no. of nonmissing values | *N* (%) |
|---|---|---|
| Protein, mg/dl | | |
| None | 11 | 6 (55) |
| <30 | | 0 (0) |
| 30–100 | | 4 (36) |
| >100 | | 1 (9) |
| Leukocytes per field | | |
| <15 | 11 | 2 (18) |
| ≥15 | | 9 (82) |
| Leukocytic casts | | |
| Negative | 11 | 8 (73) |
| Positive | | 3 (27) |
| Hemoglobin | | |
| Negative | 11 | 6 (55) |