Pathology of Uddanam Endemic Nephropathy

Abstract
In the last decade, pockets of endemic nephropathy have been recognized worldwide, in regions of Central America, Sri Lanka, and India. In India, the nephropathy has been recognized in the Uddanam area of north Andhra Pradesh and has been termed the Uddanam endemic nephropathy (UEN). The disease is distinctive in that besides the geographic distribution, it affects rural populations engaged in farm labor and agriculture, often silent in the initial phase with most patients presenting with advanced renal failure. The renal biopsy findings in all geographic areas including UEN have been one of a chronic tubulointerstitial nephritis with varying degrees of tubular injury, interstitial inflammation, tubular atrophy, and interstitial fibrosis with nonspecific glomerular obsolescence and lack of immune deposits. More recently, the demonstration of dysmorphic lysosomes in renal biopsies has favored a toxic etiology. There are thus many gaps in the understanding of this serious disease prevalent among poorer populations.

Keywords: Chronic interstitial nephritis, CKDu, renal pathology

Introduction
Chronic kidney disease of unknown origin (CKDu) alludes to diverse conditions where the etiology remains unknown. Endemic nephropathy is a kidney disease confined to certain geographic regions, which has characteristic features distinctive from other CKD affecting the general population with hypertension and diabetes. The nomenclatures of many of the endemic kidney diseases whose etiology and epidemiologic features have been well defined have been made distinct entities like Balkan endemic nephropathy. The endemic nephropathy in the state of Andhra Pradesh in South India has been termed the Uddanam endemic nephropathy (UEN) but it is still poorly understood.[1]

Renal biopsies remain an important area of study in endemic nephropathy. The biopsy findings in the other endemic nephropathies have been mainly a tubulointerstitial nephritis (TIN) with some differences in the involvement of the glomerular and vascular compartments. A detailed analysis of these findings in the different geographic areas could give clues to the underlying pathogenesis and clues for early detection in the involved population.

Our Experience
We describe the renal biopsy findings in a few cases from the Uddanam endemic area. The renal biopsy findings in five cases showed features of a chronic TIN. The patients were in the age group of 25–42 years, with serum creatinine values ranging from 1.4 to 2.6 mg/dL. The urine proteinuria was absent to trace and the sediment bland in all. None of them was known diabetics or hypertensives.

The histology in all was similar to the viable glomeruli being essentially normal with no increase in cellularity, segmental lesions, or crescents. A varying degree of ischemic changes and glomerular obsolescence was noted. Tubular atrophy and interstitial fibrosis were the dominant findings in all. The inflammation was again varied being mostly lymphomononuclear and around the atrophic tubules. Interstitial edema was notable in one case with associated mild tubular injury. Vessel changes were absent except for mild intimal fibrosis in one [Figures 1-3]. The changes are summarized in Table 1. Direct immunofluorescence using fluorescein isothiocyanate–labeled anti-IgG, IgM, IgA, C3c, C1q, kappa, and lambda light chain was done in all and showed no significant deposits in the glomeruli or along the tubular basement membrane. Electron microscopic studies were not done in any case. To summarize, the findings were of a chronic

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TIN, and there were no clues to the possible etiology from the above findings.

**Review of Literature of Other Endemic Nephropathies**

Itai-itai\(^1\) (ouch-ouch) in the Jingzu basin of the Toyoma prefecture in Japan was among the first endemic nephropathies described in 1912. The etiology was confirmed as cadmium exposure after nearly 50 years of research. Interstitial fibrosis, tubular atrophy, and glomerular ischemia were the histologic findings described.

The causative agent of Balkan endemic nephropathy,\(^1,2\) first described in 1956, was confirmed as aristolochic acid in 1993. Chinese herbal nephropathy,\(^1,3\) in patients consuming these herbal medications for weight loss, has also been confirmed as due to aristolochic acid contamination in these preparations. The pathology in these two conditions is distinctive with hypocellular interstitial fibrosis and tubular atrophy, which is maximum in the inner cortical labyrinth, decreasing in intensity from the outer cortex. There is also a propensity to develop urothelial tumors of the renal pelvis and ureter in these cases.

The Mesoamerican nephropathy\(^1,4\) in South America is another recently described nephropathy with initial reports appearing in 2002. Albuminuria is low and the urine sediment bland in these cases. The renal biopsy in these cases is again one of a chronic TIN with chronic glomerular ischemic changes. Patients in this group have been normotensive and vasculopathy is minimal on the biopsy.

Reports of the Sri Lankan endemic nephropathy\(^1\) have appeared since the 1990s. About 65% of these patients are reported hypertensive in one study. Persistent albuminuria and albumin: creatinine ratio of >30 mg/g has been the defining feature. Although the predominant pathology here is again tubular atrophy and interstitial fibrosis, varying degrees of glomerular sclerosis, glomerular collapse, and moderate vasculopathy have been described.

There has been no consensus on the etiopathogenesis of endemic nephropathy across the world, also known as Chronic Interstitial Nephritis in Agricultural Communities (CINAC). Heat stress and toxic agrochemicals have been the most propounded etiologies although it is possible that genetic factors, infections, heavy metals, and strenuous labor are also contributory. In a seminal work by Marc De Broe and coworkers at Antwerp, dysmorphic lysosomes have been demonstrated in the proximal tubular epithelium by autofluorescence, silver stains, and light microscopy and electron microscopy from a cohort of 31 biopsies obtained from areas of endemic nephropathy across the world (Personal communication). This change is similar to that seen in calcineurin inhibitor toxicity, and it has been proposed that this finding is strongly indicative of a common toxic insult in CINAC across the world. Further work is necessary to identify the toxin, probably from herbicides and pesticides in use in these places, to identify their mechanism of action and most importantly to institute public health measures on an emergency to see whether the incidence of the disease declines.

A cohort study by Wijkstrom among 11 patients based on assessment of kidney biopsies and biochemical
characteristics in Sri Lanka showed varied results from the pattern seen in Central America. The study conducted in Sri Lanka showed a mixed pattern in the renal morphology contrary to the results obtained from the study done in Central America where the morphology was relatively homogeneous in all cases. MeN-like morphology with varying degree of glomerulosclerosis, glomerular hypertrophy, mild to moderate tubulointerstitial changes, and mild vascular changes was seen in six cases in the Sri Lankan cohort, although glomerular ischemia, a common finding in the previous cohorts, was noted in only two among the six MeN-like cases. Also, segmental sclerosis was absent in this cohort as opposed to the few cases seen in previous studies.[5]

Nanayakkara et al., based on their study of kidney biopsies from CKDu patients in Sri Lanka, concluded that the primary lesion was tubulointerstitial damage accompanied by massive interstitial inflammation in endemic nephropathy.[6]

In the Uddanam area, renal biopsy findings have been like that seen in Mesoamerican nephropathy. A zonal phenomenon was noted in two of the five cases with involvement being more in the inner cortex bordering the medulla. In the small number studied, there was also no distinct correlation between the degree of chronic or acute changes in the tubulointerstitial compartment and the serum creatinine.

Conclusion

While the pathology findings in the newly discovered endemic nephropathies are similar in that they involve the tubulointerstitial compartments, there are also some differences in the zones of involvement, degree of inflammation, and the involvement of glomeruli and vessels.

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Conflicts of interest

There are no conflicts of interest.

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