

Karyomegalic Interstitial Nephritis with Chronic Kidney Disease

Farid Nakhoul MD^{1,2,4}, Ofer Ben Itzhaq MD³ and Evgeny Farber MD^{1,2}

¹Nephrology and Hypertension Division, Padeh Poriya Hospital, Lower Galilee, Israel

²Faculty of Medicine in the Galilee, Bar-Ilan University, Safed, Israel

³Department of Pathology, Rambam Healthcare Campus affiliated with Rappaport Faculty of Medicine, Technion-Institute of Technology, Haifa, Israel

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Karyomegalic interstitial nephritis (KIN) is a rare disease entity that was first described by Burry in 1974 [1-4]. A detailed description of patients with history of recurrent respiratory infections and progressive renal failure was given [4,5]. KIN is characterized by chronic tubulointerstitial nephritis associated with enlarged tubular epithelial cell nuclei, which leads to progressive decline of renal function. The prevalence of this disease is less than 1% [1,3] and its pathogenesis is unclear. The disease has no known treatment.

The patient described here presented with various features including young age, associated glomerulopathy causing non-nephrotic proteinuria, and chronic renal failure [4,5]. In one large series published by Bhandari et al. [3], normal renal function at the time of diagnosis was described. Mutations in *FAN1* lead to a defective DNA damage response (DDR) and karyomegalic interstitial nephritis. Different authors implicate susceptibility to environmental genotoxins and inadequate DNA repair as novel mechanisms contributing to renal fibrosis and chronic kidney disease. In the case presented here, the patient had KIN with chronic kidney disease but no other systemic manifestations. Closed renal biopsy demonstrated chronic tubulointerstitial nephritis with bizarre and dramatic

enlargement of proximal tubule epithelial cell nuclei, the hallmark of karyomegalic nephritis.

PATIENT DESCRIPTION

A 40 year-old woman was referred with asymptomatic proteinuria, glomerular hematuria, and a 10 year history of myalgia and arthralgia with chronic ferropenic anemia that was treated with oral iron. She was admitted to the nephrology department at Poriya Medical Center due to unexplained elevation in plasma creatinine found on routine blood examination (plasma creatinine 1.5 mg/dl), microhematuria, and mild proteinuria 1500 mg/24 hours. There was no family history of kidney or systemic disease. She is the first child of a non-consanguineous marriage. There was no history of drug ingestion like chronic use of non-steroidal anti-inflammatory drugs (NSAIDs), or exposure to mycotoxins or other herbal medicines, and no history of recurrent respiratory symptoms.

On physical examination the patient was without respiratory distress; blood pressure was 130/80 mmHg. There were no systolic murmurs on chest examination, organomegaly, or peripheral edema. Her blood tests revealed hemoglobin 10 g/dl, blood urea nitrogen 33 mg/dl, and serum creatinine 1.7 mg/dl (normal 0.8–1 mg/dl). Her liver function tests revealed normoalbuminemia (3.8 g/dl), and liver enzymes were within normal limits. Laboratory tests, including antinuclear antibody, anti-DNA, complement, rheumatoid factor, hepatitis B surface antigen and hepatitis C virus, were negative. Twenty-four hour

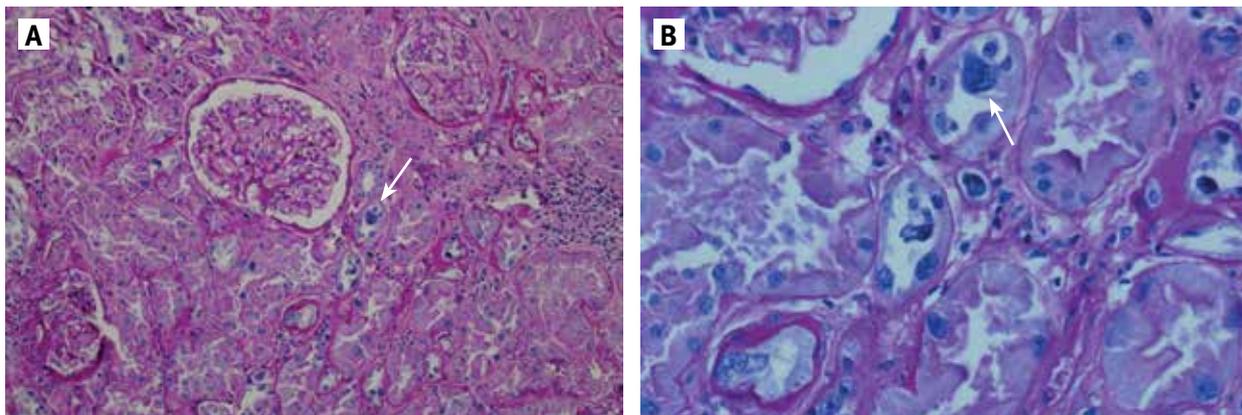
urine protein collection yielded 565 mg, and complete urine sediment examination showed 2+ albumin, 4–6 red blood cells and granular casts. Ultrasound revealed normal sized kidneys with increased echogenicity. Kidney biopsy showed 40 glomeruli, 12 with global sclerosis, 28 were normal. Tubular atrophy and interstitial fibrosis were seen in 25% of the tubulointerstitial area. The dominant pathologic feature was foci of markedly enlarged and hyperchromatic nuclei of some tubular epithelial cells [Figure 1A and B]. These enlarged nuclei were more than three times the size of the normal adjacent tubular epithelial cell nuclei. There were no mitotic figures and no staining for Ki67 proliferation marker in the enlarged nuclei. Immunofluorescence study showed negative stains for immunoglobulin (Ig) G, IgA, IgM, C3, C1q, K, L in the glomeruli. On electron microscopy (EM), no immune deposits in the glomeruli and no podocyte effacement were seen, and glomerular basement membrane was normal.

At her follow-up visit to our outpatient clinic 2 months after her discharge, plasma creatinine was 1.7 mg/dl, and her 24 hour protein collection increased to 1500 mg, without any specific treatment.

COMMENT

KIN is a rare disorder characterized by enlarged tubular epithelial cell nuclei and chronic interstitial nephritis [1-4]. Patients who present renal impairment and extrarenal manifestations are rare. Histologically, the presence of interstitial nephritis together with karyomegaly in the tubular epithelial cells is characteristic

Figure 1. Light microscopy. **[A]** Low magnification of renal cortex showing focal tubuli with markedly enlarged nuclei (arrow) (Hematoxylin and eosin $\times 100$). **[B]** High magnification of markedly enlarged tubular nuclei (arrow) (Periodic acid Schiff $\times 300$)



of this disorder. Karyomegalic cells have been identified in various tissues, such as astrocytes, Schwann cells, intestinal smooth muscle and bile duct epithelium. No clinical significance has been identified with these changes [3]. Transient elevation of liver enzymes was described in other published cases. Pathogenesis of this disease is unclear and remains controversial. Toxins or viral infections have been suggested as a cause of this disorder [2] as well as exposure to herbs or ochratoxins.

All patients described in the literature progressed to renal failure. A familial clustering is known and frequency of human leukocyte antigen (HLA)-A9 and HLA-B35 polypus suggests the possibility of genetic susceptibility. Another genetic defect on chromosome 6, linked to major histocompatibility complex locus, is also suspected. Abnormal deoxyribonucleic acid ploidy and distribution with high ploidy values were described in other cases. Exone sequence study by some investigators identified mutations in *FAN1* as a cause of KIN. The morphological alterations in renal epithelial cells are thought to be the initial damage caused by either chemicals or viral

agents, which in susceptible individuals leads to disruption of cells.

Immunofluorescence and histological findings were negative in a large series as presented by Bhandari et al. [3]. In contrast, our patient presented with proteinuria and mild chronic kidney disease without histological evidence of focal segmental glomerulosclerosis. Since there was no positive family history, drug history or exposure to toxins, this case presents a sporadic occurrence.

KIN is an increasingly recognized entity but it is under-diagnosed. It is important to recognize this entity since it is a progressive disorder that leads to irreversible renal damage [5]. Our patient had both glomerular and tubulointerstitial pathology. Although the common etiologic factors for these lesions are toxins and drugs, our patient on repeated questioning denied any history of drug or herbal medicine intake. This patient also initially presented with normal renal function and on follow-up exhibited gradual deterioration of kidney function.

In summary, we present a rare case of interstitial nephritis and mild renal insufficiency with non-nephrotic range protein-

uria. Kidney biopsy was initially interpreted as chronic interstitial nephritis; however, an expert renal pathologist finally confirmed the diagnosis of karyomegalic interstitial nephritis (KIN). The morphologic changes in this disease are highly characteristic, but the pathologist must be aware of this entity in order to recognize these features.

Correspondence

Dr. F. Nakhoul

Nephrology and Hypertension Division, Poriya Hospital, Tiberias 15208, Israel

email: Fnakhoul@poria.health.gov.il

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“I wish that all of nature’s magnificence, the emotion of the land, the living energy of place could be photographed”

Annie Leibovitz (born 1949), American portrait photographer

“I have found that among its other benefits, giving liberates the soul of the giver”

Maya Angelou (1928-2014), American author, poet, dancer, actress and singer