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Karyomegalic tubulointerstitial nephritis: A rare cause of chronic kidney disease

Ebru Uz¹, Yeter Bayram^{2*}, Hacer Haltas³, Nuket Bavbek¹, Mehmet Kanbay¹, Galip Guz⁴, Ali Akçay¹

¹ Department of Nephrology, Fatih University Medical School, Ankara, Turkey

² Department of Internal Medicine, Fatih University Medical School, Ankara, Turkey

³ Department of Pathology, Fatih University Medical School, Ankara, Turkey

⁴ Department of Nephrology, Gazi University Medical School, Ankara, Turkey

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ABSTRACT

Karyomegalic tubulointerstitial nephritis is a rare disease of uncertain etiology with typical clinical features of slowly progressive renal failure in the third decade of life. Histological findings characterize striking enlarged and hyperchromic nuclei in numerous tubular epithelial cells throughout the nephron accompanied by interstitial fibrosis around atrophic tubules. Herein, we report a case of 30 year-old patient who presented with asymptomatic progressive renal dysfunction in 2009. Renal biopsy revealed chronic tubulointerstitial nephritis and an unusually marked karyomegaly particularly of the tubular epithelium.

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► Implication for health policy/practice/research/medical education:

This case report describes a rare cause of chronic kidney disease that should be considered when a young patient presented as tubulointerstitial nephritis pattern.

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1. Background

Karyomegalic interstitial nephritis (KTN), a rare disease which is characterized by chronic tubulointerstitial nephritis associated with striking enlarged tubular epithelial cell nuclei was first defined in 1979 by Mihatsch *et al.* (1). Although, the pathogenesis of KTN is unclear, the main mechanism is a mitotic block linked to certain MHC genotypes (2, 3); other potential mechanism may be exposure to heavy metal, ochratoxin, or viral patho-

gens (2). This disease has no known treatment and unfortunately progresses to chronic kidney disease (2).

2. Objectives

Herein we report a case of accelerate renal failure due to karyomegalic nephropathy with typical clinical presentation.

3. Case Presentation

A 30-year-old male presented with weakness, loss of weight, postnasal discharge and polyuria, polydipsia, uraemic symptoms of nausea and vomiting. In his past

* Corresponding author at: Yeter Bayram, Alparslan Türkeş Cad. No: 57 06510 Emek/ANKARA, Turkey; Tel: +90-03122035555, Fax: +90-03122035029.
E-mail: dryeter@hotmail.com

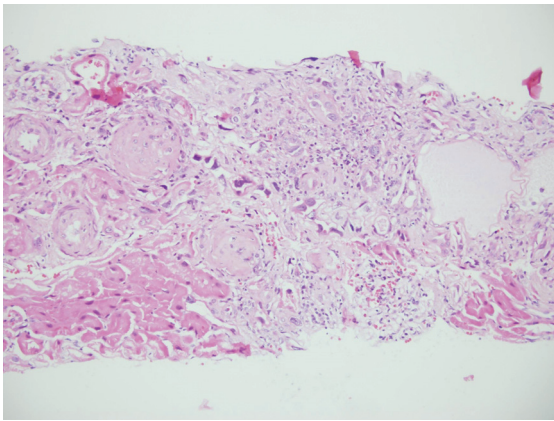


Figure1. The figure shows glomerulosclerosis, interstitial fibrosis and chronic inflammation, tubular atrophy (H&E, x200)

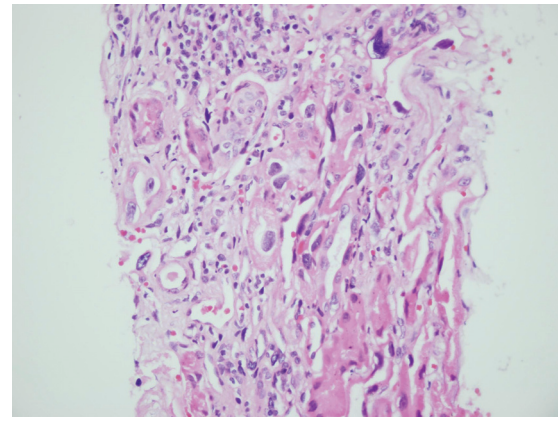


Figure2. Histology of the kidney shows striking nuclear enlargement and hyperchromasia tubular cell nuclei (H&E, x200)

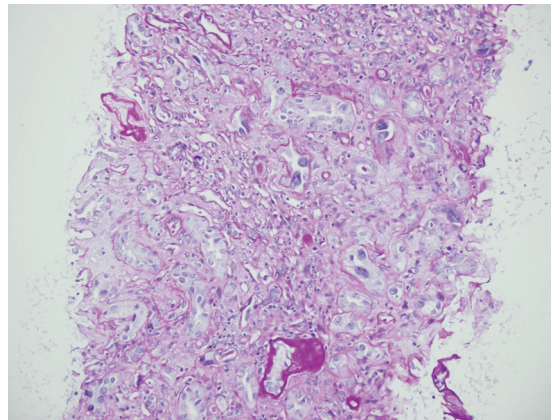


Figure3. Cortical tubules containing enlarged and pleomorphic nuclei and striking tubular atrophy (PAS, x200).

medical history there were recurrent upper-respiratory tract infections during childhood and undescended testis. The patient did not have a significant family history. He denied use of any herbal medicinal products, tobacco, or illicit drug use. There was no known exposure to heavy metals, including lead or bismuth. The patient denied a family history of kidney disease. In his physical examination, pulse rate was 70 beat/minute and arterial blood pressures were 110/70 mmHg, with no pathological signs. Liver function tests were slightly elevated with an AST of 45 U/l and an ALT of 67 U/l. Serum creatinine was 2.7 mg/dl with declined creatinine clearance (28 mL/dak./1.73 m²). Results of urinalysis revealed 426 mg/day of proteinuria. There was no eosinophilia or eosinophiluria. Serum albumin, sodium and potassium levels were normal. He was anemic with a hemoglobin level of 11 g/dL and antinuclear antibodies (ANA), anti-double stranded DNA antibodies and antineutrophilic cytoplasmic antibody (ANCA) titers were all negative. Serum immunoglobulin and complement (C3 and C4) concentrations were within normal limits. Serology for hepatitis B (hepatitis surface antigen) and C (hepatitis antibody) were negative. A renal ultrasound revealed normal kidney size with increased parenchymal echogenicity and thinning

of the renal cortex.

Percutaneous renal biopsy was performed and the biopsy specimen was examined by light microscopy using hematoxylin/eosin (H&E), Periodic acid Schiff (PAS), and Periodic acid silver methenamine (PASM) stains. The sample of renal cortex contained numerous glomeruli. More than half of which were globally sclerosed (*Figure 1*). Some of the viable glomeruli demonstrated minimal enlargement in the mesangial matrix material. Fibrous crescents were observed in 6 glomeruli. The glomerular capillary basement membranes were within normal limits except in a few glomeruli. There was no evidence of amyloid. Many tubular epithelial cells lining the tubules were notable for striking nuclear enlargement with bizarre nuclear shapes, focal intra-nuclear clearing and hyperchromasia (*Figure 2*). A few pleomorphic nuclei showed intranuclear inclusions. In addition, the interstitial area showed regional fibrosis with tubular atrophy and a moderate chronic inflammatory infiltrate which consisted predominantly of lymphocytes and plasma cells (*Figure 3*). Tubulitis was not observed. In immunofluorescence staining IgG, IgA, IgM, C3c, C4, C1q or fibrinogen were not observed. We found low proliferation index in immunohistochemical stain with Ki67

and proliferating cell nuclear antigen (PCNA) within tubular epithelium. Epstein-Barr Virus was not observed with staining. On follow-up controls, serum creatinine levels were found elevated from 2.4 to 4 mg/dl and urinalysis revealed 2+ proteinuria and 10-12 red blood cells/high power field (RBC/hpf). Two weeks later in a clinic follow-up, he remained asymptomatic, serum creatinine remained stabilized at 4.7-4.0 mg/dL and vital signs were stable. At the present time the patient has been worked up for renal transplantation. HLA haplotypes are A1, A32, B63, B50, DR7, and DR13.

4. Discussion

Karyomegalic interstitial nephritis (KTN), a rare disease which is characterized by chronic tubulointerstitial nephritis and associated with striking enlarged tubular epithelial cell nuclei, was described in detail in 1979 by Mihatsch *et al.* (1). Although karyomegalic cells have been identified histologically in several tissues including astrocytes, Schwann cells of peripheral nerves, intestinal smooth muscle, and bile duct epithelium, extra-renal manifestations are clinically uncommon. Transient elevations in liver enzymes are also a common manifestation of the disease (2). The prevalence of this disease remains less than 1% of all biopsies examined. Histological findings consist of bizarre cells with striking enlarged, hyperchromic, vesicular nuclei and prominent nucleoli in numerous tubular epithelial cells may present a clue to the diagnosis (4). Tubular epithelial cells lining the tubules were prominent for striking nuclear enlargement with bizarre nuclear shapes, focal intra-nuclear clearing and hyperchromasia in our patient.

At the present time the pathogenesis of KTN is uncertain and controversial. Toxins or viral infections are suggested to play causative role (1). Exposures to potential environmental cause, herbal, ochratoxin, heavy metal, a history of analgesic for the renal injury were absent in our patient. Typically patients present with a history of recurrent upper respiratory infections and progressive renal failure in the third decade of life (2). In our case, a long history of recurrent upper-respiratory tract infection episodes requiring antibiotics was reported. Moreover, a possible genetic defect in chromosome 6, which

was linked to the major histocompatibility complex (MHC) locus, has been suspected (3). In the literature, Baba *et al.* presented a similar case with karyomegalic interstitial nephritis in 2006 (5). Additionally, Godin *et al.* reported two cases of karyomegalic interstitial nephritis in siblings with ochratoxin and HLA haplotype A9/B35 (6). In our patient, HLA subgroups are A1, A32, B63, B50, DR7, and DR13. In addition, these researchers considered the proliferation markers Ki-67, PCNA and p53 in tissues of patients. Eventually, they decided that a mitotic block could initiate karyomegaly. In our case, Ki67 and PCNA were estimated in the tubular epithelium with low proliferation index. In conclusion, karyomegalic interstitial nephritis is a rarely seen important condition. The clinicians should be alert for karyomegalic interstitial nephritis in the presence of nephropathy in a young patient with symptoms of renal dysfunction, positive urine sedimentation and abnormal liver enzymes with the absence of other environmental factors associated with interstitial nephritis.

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Conflict of interest

None declared.

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