Surgical and Experimental Pathology

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# Karyomegalic interstitial nephritis: diagnosed only when suspected

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## Abstract

**Background:** Karyomegalic interstitial nephritis (KIN) is an uncommon cause of chronic interstitial nephritis that eventually progresses to end-stage renal disease. Overall less than 50 cases have been reported in the literature.

**Case presentation:** We describe an asymptomatic 25-year-old gentleman with a family history of chronic interstitial nephritis who came to check the status of his kidney functions. On evaluation, he was found to have chronic interstitial nephritis which could not be attributed to a specific etiology. Renal biopsy confirmed the diagnosis of KIN.

**Conclusion:** KIN remains underdiagnosed. It is important to recognize this entity because of the familial nature, a wide range of differential diagnoses, and prognostic implications. A high index of clinical suspicion is necessary to perform renal biopsy which remains the gold standard for the diagnosis of KIN.

**Keywords:** Karyomegalic interstitial nephritis, Chronic interstitial nephritis, End-stage renal disease

## Background

Karyomegalic interstitial nephritis (KIN) is an exceedingly rare cause of chronic interstitial nephritis. Before this entity was named, karyomegalic changes were documented in the kidneys [tubules (proximal and distal), collecting ducts and interstitium], non-neoplastic hepatocytes, and pancreatic acinar cells in an autopsy of a young woman who died of hepatocellular carcinoma (Burry 1974). The term "karyomegalic interstitial nephritis" was first published in a study of 3 patients in whom the renal biopsy showed karyomegalic features and chronic interstitial nephritis (CIN). These patients progressed to end-stage renal disease (ESRD) within 4 to 6 years. Apart from the kidneys, biopsies of the liver, colon, bronchus, and lungs revealed similar karyomegalic features especially in the interstitial cells (Mihatsch et al. 1979). In both the aforementioned studies, neither the CIN nor the karyomegaly could be associated with a known etiology. Following these studies, there have been less than 50 cases reported in the literature. We describe a young patient with interesting clinico-pathological features with a brief review of the literature.

## Case presentation

A 25-year-old gentleman came to the renal clinic to know the status of his kidney functions. The patient was asymptomatic but was anxious since his father died of chronic interstitial nephritis of unknown etiology. He was the only child born to a couple of non-consanguineous marriage. Apart from this father, no other family members were affected. The patient had no history of drug, toxin, or native medicine exposure. There was no history of any co-morbid illness. Blood investigations revealed hemoglobin 13.7 g/dL, total leucocyte count 8000 cells/cu.mm, platelet count 265,000/cu.mm, urea 29 mg/dL, serum creatinine 1.6 mg/dL, calcium 9.9 mg/dL, phosphate 3.5 mg/dL and uric acid 6.4 mg/dL. Urine examination did not reveal any proteinuria, hematuria, leukocyturia or abnormal cells, or sediments. The toxicological work-up was negative. Serological tests for ANA, ANCA, dsDNA, AntiGBM, HIV, HBV, and HCV were negative. Serum complements C3 and C4 were within the normal range.

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Abdominal ultrasonography (USG) revealed normal-sized kidneys with increased echos and loss of corticomedullary distinction. The other abdominal organs were within the normal limits. A percutaneous USG guided renal biopsy samples were taken for light microscopy and immunofluorescence studies. Light microscopy revealed an adequate renal biopsy core comprising of cortex and medulla. A total of 56 glomeruli were examined in multiple serial sections of which 14 were globally sclerosed (Fig. 3b). The remaining 42 glomeruli were normal-sized, normocellular with no abnormal changes noted in the Bowman's capsule, parietal epithelial cells, Bowman's space, podocytes, capillary loops, and mesangium. There was a diffuse enlargement of proximal, distal, and medullary tubular epithelial cell nuclei, many of which were bizarre and irregular (Figs. 1 and 2). No viral inclusion was noted. There was moderate tubular atrophy and interstitial fibrosis with lymphomononuclear inflammatory infiltrates (Fig. 3a). Apart from the cortical tubules, no other cells exhibited karyomegalic features. Immunohistochemistry for simian virus 40 (SV40) and cytomegalovirus (CMV) were negative. The arteries, arterioles, and peritubular capillaries were unremarkable. Congo red stain was negative for amyloid deposits. Immunofluorescence did not show any immunoglobulin (IgA, IgG, IgM, Kappa, Lambda light chains) and complement (C3c and C1q) deposits. The overall features were consistent with karyomegalic

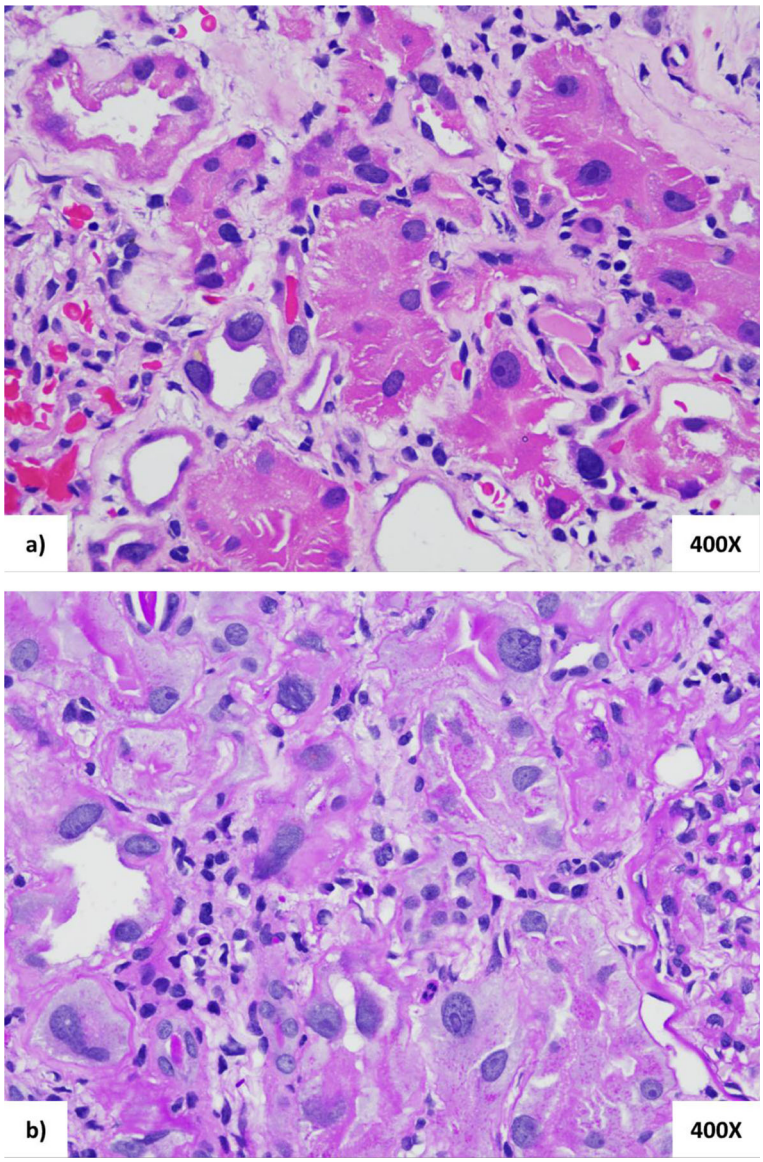


**Fig. 1** **a** H&E and **b** PAS stains demonstrate large, hyperchromatic and pleomorphic nuclei, prominent nucleoli in the absence of intranuclear/intracytoplasmic inclusions suggestive of viral etiology in the cortical tubules

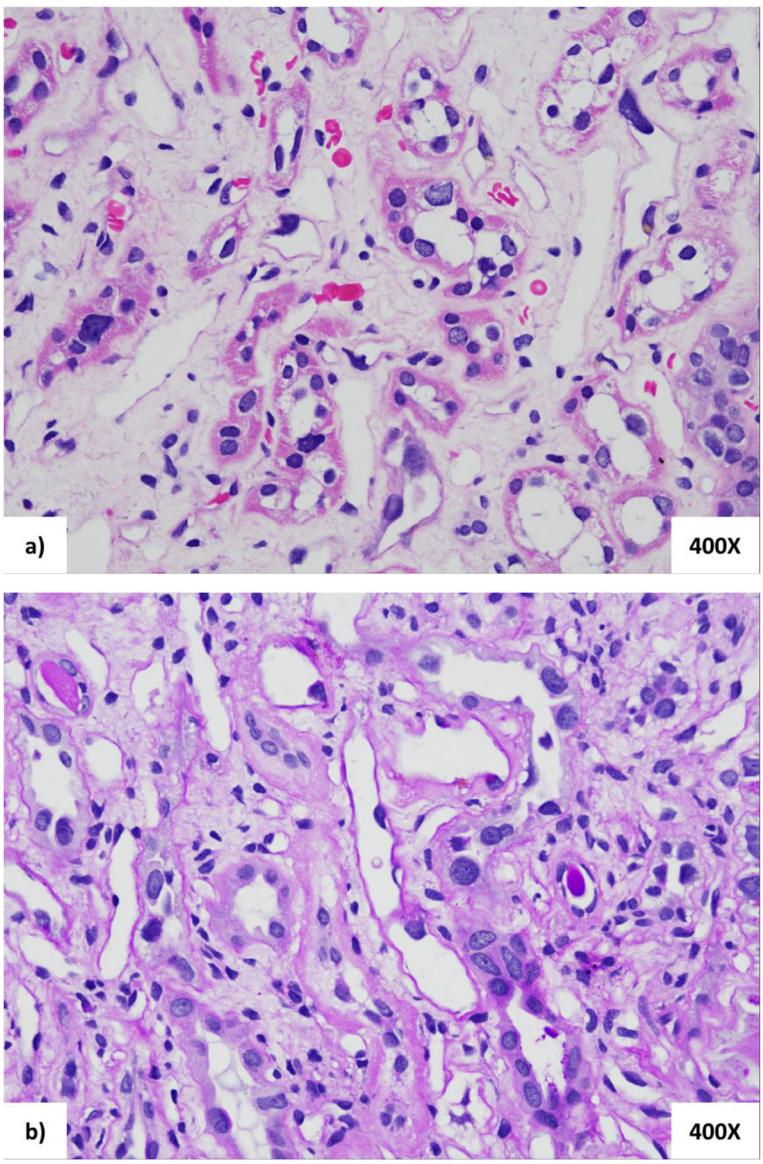


**Fig. 2** **a** H&E and **b** PAS stains demonstrate large, hyperchromatic and pleomorphic nuclei, prominent nucleoli in the absence of intranuclear/intracytoplasmic inclusions suggestive of viral etiology in the medullary tubules

interstitial nephritis (KIN). Since no specific treatment is available for KIN, the patient was counseled regarding the prognosis of KIN and was advised to follow a dietary plan that suits his renal functions. Also, he was cautioned to avoid any toxic substances or drugs that would affect his kidney.

## Discussion

Chronic interstitial nephritis (CIN) most often has a non-specific pattern of kidney injury on biopsy. The diagnosis of idiopathic CIN is made after excluding the secondary causes such as drugs and toxins, infections, immunological conditions, and hereditary disorders (Isnard et al. 2016). The KIN is a specific form of CIN whose clinical presentation ranges from a completely asymptomatic state to non-specific mild to moderate renal dysfunction, absence or mild degree of proteinuria, and/or urinary sediment abnormalities. In most instances, there will not be an absolute indication to perform a renal biopsy because of the non-specific nature of the presentation. The diagnosis KIN needs a high index of clinical suspicion to perform a renal biopsy that typically shows chronic tubulointerstitial nephritis with characteristic "karyomegalic nuclei" i.e. enlargement of tubular nuclei with irregular outlines, coarse chromatin. Immunostains for viral inclusions are typically negative (Law et al. 2020).

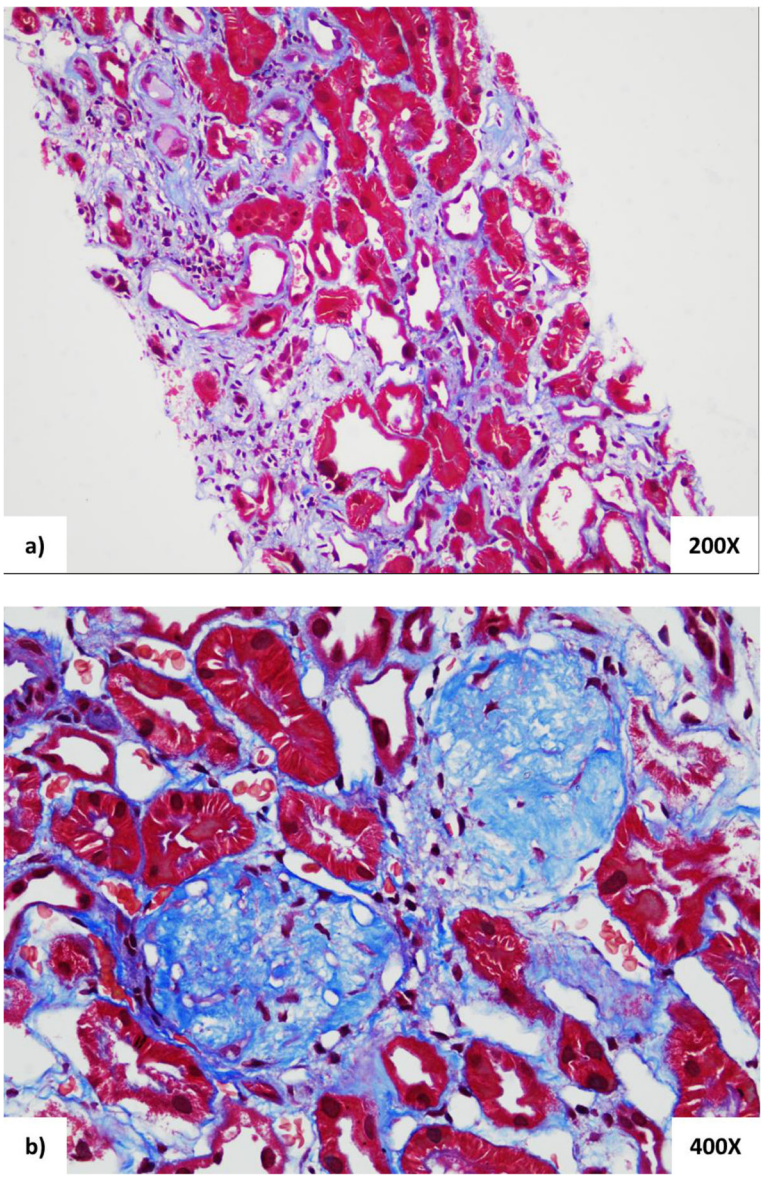


**Fig. 3** Masson's trichrome stain depicts **a** the background interstitial fibrosis and **b** global glomerulosclerosis

The KIN results in slowly progressive renal failure. In most reposts, familial clustering has been documented (Spoendlin et al. 1995). Various studies have shown that KIN is associated with mutations of *FAN 1* (FANCD2/FANCI-Associated Nuclease 1) gene (Zhou et al. 2012). The *FAN1* gene encodes a protein with 5′ flap endonuclease and 5′-3′ exonuclease activity that plays a key role in DNA interstrand cross-link repair. Thus, a mutation in *FAN1* gene results in abnormal ploidy and resultant karyomegalic changes. It has also been hypothesized that mutations in *FAN1* gene and increased frequency of polymorphic variations of HLA A9 and HLA B35 may lead to an increased susceptibility to environmental–genotoxin-induced kidney damage. Apart from the kidneys, karyomegalic changes have been documented in other organs such as the liver, pancreas, colon, bronchus, and lungs. Extrarenal clinical manifestations are either absent or mild that comprise recurrent upper respiratory tract infections and abnormal liver function tests (Isnard et al. 2016).

Certain features make our index case interesting. Most cases reported so far in the literature have been in symptomatic patients. Incidental detection of KIN was mostly in autopsy studies. Our index patient was asymptomatic and KIN was detected in the biopsy that was performed as a result of the patient volunteering for renal function work-up and a high index of suspicion due to positive family history of CIN in the father. The median age of

diagnosis in KIN is usually 33 years (Bhandari et al. 2002), however, our patient was much younger due to early evaluation. Similar to our patient, studies have documented a familial association. With regards to the urine examination, common findings are asymptomatic proteinuria, glycosuria and hematuria, and abnormal sediments (Gupta et al. 2020). The aforementioned findings were not observed in our patient. The urine cytology may reveal large, pleomorphic cells mimicking carcinoma (Palmer et al. 2007). Hence, the presence of any abnormal cells in the urine cytology of a young immunocompetent patient can be a clue to an underlying KIN. In our case, the urine cytology was negative for karyomegalic cells.

In KIN, renal biopsy almost always shows global glomerulosclerosis apart from the characteristic karyomegalic changes in the tubules (Isnard et al. 2016; Zschiedrich et al. 2013; Bhandari et al. 2002; Gupta et al. 2020; Law et al. 2020). These findings are concordant with our case. Three studies and have shown focal segmental glomerular sclerosis (FSGS) in KIN (Radha et al. 2014; Kumar et al. 2019; Mehta et al. 2020). We did not find FSGS in our case. Whether FSGS is a coincidental finding or has an association with KIN is not clear. Further studies are needed to evaluate the association of FSGS and KIN. A recent study has documented the presence of ALECT2 amyloidosis in a case of KIN (Law et al. 2020). Other than this single report there are no cases with concomitant amyloid deposits in KIN.

Other than KIN, karyomegalic changes in renal cells have been reported in different pathologic settings (both in human and experimental animals) such as heavy metal toxicity and CMV infection (Roels et al. 1994). In our patient, toxic and infectious causes had been excluded by toxicologic screen and immunohistochemistry for viral infections.

Extra-renal manifestations have been described in various studies (Burry 1974; Mihatsch et al. 1979; Isnard et al. 2016; Bhandari et al. 2002; Gupta et al. 2020). Approximately 50% of patients have a history of recurrent upper respiratory tract infections and abnormal liver function tests (Isnard et al. 2016). Consistent with this, karyomegalic changes have been described in various extra-renal organs. Our patient did not have any systemic manifestations. However, solely based on the absence of systemic symptoms, we cannot confirm or exclude karyomegalic changes in other organs because the organ-specific biopsies were not done (not indicated) in our case.

## Conclusion

Karyomegalic interstitial nephritis, although described more than 50 years ago remains underdiagnosed. It is important to recognize this entity because of the familial nature, a wide range of differential diagnoses, and prognostic implications. KIN should always be kept in mind when a young immunocompetent patient presents with features of chronic interstitial nephritis. Renal biopsy remains the gold standard for the diagnosis of KIN.

### Abbreviations

ANA: Antinuclear antibodies; ANCA: Antineutrophil cytoplasmic antibodies; DNA: De-oxy ribonucleic acid; dsDNA: Double-stranded DNA; FAN: Fanconi Anemia; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immune-deficiency virus; KIN: Karyomegalic interstitial nephritis; LECT-2: Leukocyte chemotactic factor 2; USG: Ultrasonogram

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### Authors' contributions

GBL conceived the idea. The initial manuscript was written by MS and reviewed by GBL. BN was the treating physician. All the authors read and approved the final manuscript.

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### Availability of data and materials

Not applicable.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Written informed consent was obtained from the patient for participation in the study.

### Competing interests

The authors declare that they have no competing interests.

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## Publisher's Note