

Karyomegalic Interstitial Nephritis: Case Series and Review of Literature

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Abstract Karyomegalic interstitial nephritis (KIN) is a rare cause of hereditary interstitial nephritis, described 45 years ago. Only about 50 cases have been described in English literature so far and none from Pakistan. This disease has an escalated course with a worsened outcome. There are a few potential mimickers of this disease both clinically and histologically, which might lead to a missed diagnosis and hence poor management. We have described here a series of 05 cases of KIN that were diagnosed at our institute for better understanding of this disease entity.

Keywords: *interstitial nephritis, karyomegalic interstitial nephritis, chronic kidney disease, histopathology, kidney transplantation*

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1. Introduction

Karyomegalic nephropathy was first identified in 1974 by Burry in a 22-year-old female who died from liver-cell carcinoma [1]. Mihatsch et al then described the same disorder in 1979 when they reported three patients with similar clinical and pathological findings [2]. From these observations, he proposed a new disease syndrome. Reports of eight additional cases with similar findings have been cited in the literature [3-8].

Classically patients present with a history of recurrent upper respiratory infections and progressive renal failure. Extra-renal manifestations are clinically uncommon, however, karyomegalic cells have been identified in numerous tissues including brain astrocytes, intestinal smooth muscle, Schwann cells of peripheral nerves, and bile duct epithelium. Transient elevations in liver enzymes are also seen [7].

Histologically, the presence of interstitial nephritis in conjunction with atypical big epithelial cells and nuclear enlargement, predominantly of tubular cells, is characteristic. The absence of other factors associated with interstitial nephritis (non-steroidal anti-inflammatory agents and heavy metals) and other glomerular disorders, is suggestive of karyomegalic nephropathy.

KIN has never been reported from Pakistan. We report a series of five cases that were received at Shifa International Hospital. These cases presented with chronic kidney disease and four out of five had a significant family history.

2. Cases Description

2.1. Case 1

A 45-year-old woman of Pakistani origin, known diabetic, presented with deranged renal functions and prolong use of NSAIDs for migraine headache & cervical spondylosis in 2014. Her creatinine level was 1.29 mg/dL. She was labeled as a case of NSAID-induced nephropathy and was managed conservatively. Second time her creatinine was checked in 2016, and it was 1.53 mg/dL with no nephrology follow-up. Later she presented to nephrology clinic in February 2019 for an opinion regarding the rising trend of creatinine (1.53mg/dL) which was found on routine laboratory testing. The patient had no active complaints apart from mild neck pain at the time of presentation. Systemic inquiry was insignificant. She was vitally stable. Her systemic examination was also unremarkable. Her laboratory evaluation showed serum creatinine of 2.3 mg/dL with an estimated glomerular filtration rate of 26 mL/min/1.73m², and gamma-glutamyl transpeptidase and alkaline phosphatase were 3 and 1.5 times the upper normal limit respectively. Urinalysis showed 0.8 g/day of nonselective proteinuria, microscopic hematuria, and aseptic leukocyturia. All her immunological investigations including ANA, ANCA profile, and hepatitis B, C and HIV serology were negative. Complement levels and serum protein electrophoresis was normal. Her renal biopsy was performed to identify the cause of her renal impairment, which showed severe

interstitial fibrosis and tubular atrophy. Numerous tubular cells had nuclear enlargement with irregular outlines, hyperchromatic aspect, and prominent nucleoli. The proliferative index (Ki67) was not significant. These findings were highly suggestive of karyomegalic interstitial nephritis, which was further confirmed by exome sequencing of FAN1 gene showing an identified homozygous frameshift mutation due to a one-base-pair deletion in exon 12 (c.2616delA).

There was a strong history of renal impairment in her family. Her sister and brother had a history of renal impairment which later on progressed to end stage renal disease. Both had renal transplants later on. The detailed history of her brother's renal impairment is mentioned in case 2.

2.2. Case 2

30 years old male patient, who had done masters in International Relations, presented in outpatient department with history of nausea and reduced oral intake for last 1 month. He took homeopathic medications for 1 year for his mild renal impairment in past. Besides this, he had a history of on and off raised blood pressure readings for last 3 years, for which he had never taken any anti-hypertensive medications. His labs at presentation showed creatinine of 8mg/dL, potassium of 6.2mEq/L, bicarbonate of 14mEq/L, and hemoglobin of 5.3g/dL. His ultrasound abdomen showed bilateral grade-3 echogenic kidneys with sizes of 54*25mm and 54*38mm of right and left kidney respectively. His renal biopsy could not be performed due to bilateral shrunken kidneys. He was then started on hemodialysis with 2 packed RBCs transfusion. He remained on hemodialysis for 06 months. During his transplant workup he was incidentally found to have mild mitral stenosis on echocardiogram with a valve area of 4 cm². His living-related renal transplant was performed on 16th April 2007. Donor was her sister. Post-transplant, he was given anti-thymocyte globulin (ATG) and pulse steroids followed by cyclosporine, prednisolone, and mycophenolate mofetil (MMF). Two months post-transplant, he developed cell-mediated rejection which was managed by optimization of immunosuppressants and pulse steroids. Later, he developed fever with bicytopenia for which his cytomegalovirus (CMV) PCR came out to be positive, and he was then managed with valganciclovir and reduction of immunosuppressants. Later on, his creatinine increased from a baseline of 1.4 to 1.7mg/dL, for which his renal biopsy was done in June 2007. It reported mild tubular necrosis involving < 10% of proximal tubules with some bizarre-shaped hyperchromatic nuclei.

BK virus nephropathy was suspected and his MMF was stopped. Despite this intervention, his creatinine increased from 1.7 to 1.89 mg/dL. Then his renal biopsy was reviewed and immunostains for CMV and BK virus were negative. His creatinine kept fluctuating from 1.5 to 2 mg/dL. His subsequent biopsies were planned but not done due to his unpredictable creatinine values. Later on, when his sister presented with impaired renal function in 2019, and sufficient data came out regarding karyomegalic interstitial nephritis, his renal biopsy was then retrospectively followed and he was then diagnosed as a case of karyomegalic interstitial nephritis. Currently

his creatinine is around 1.8 to 1.9 mg/dL after 14 years of renal transplant.

2.3. Case 3

A 22-year-old male of Pakistani origin, presented with complaints of decreased urinary output and deranged renal functions. Past medical history was unremarkable. He did not have any history of steroid or NSAIDs use; however, he had positive family history of chronic kidney disease. His elder brother died of chronic kidney disease as well. His physical examination was unremarkable. Blood pressure was around 120/70 mmHg. On abdominal ultrasound, bilateral mild hydronephrosis was seen. Further workup showed serum creatinine of 2.0 mg/dL and urea of 34 mg/dL. Urine analysis showed few RBCs, no leucocytes and proteins. ANA profile was negative. Renal biopsy showed 16 out of 28 globally sclerosed glomeruli. Moderate tubular damage with enlarged (karyomegalic) tubular epithelial cells with irregular outline, hyperchromatic nuclei, prominent nucleoli. Mild interstitial fibrosis was also seen. Immunostains for CMV and BK virus were negative. Immunofluorescence slides were negative for all antibodies. These findings were highly suggestive of karyomegalic interstitial nephritis.

2.4. Case 4

A 35-year-old male, normotensive patient with no known comorbid presented with unexplained renal impairment. He had a family history of hypertension and diabetes mellitus. Besides this, his clinical examination was unremarkable. On workup, his serum creatinine was 3.2 mg/dL, ANA profile was negative and urine analysis was unremarkable. On ultrasound abdomen, bilateral grade-2 echogenic kidneys were seen. His renal biopsy showed 28 globally sclerosed glomeruli and 1 segmentally sclerosed glomerulus. There was moderate tubular damage and atrophy along with red cell and colloid cast. Tubular epithelial lining cells were enlarged, bizarre with hyperchromatic nuclei. Blood vessels showed moderate intimal thickening and medial hypertrophy. Interstitium had moderate lymphoplasmacytic infiltrates and fibrosis. Immunostains for CMV and SV40 were negative. These findings were favoring the diagnosis of karyomegalic interstitial nephritis.

2.5. Case 5

33 years old unmarried female, a B.COM student, and resident of Chakwal, presented in outpatient department in December 2018 with a history of bilateral intermittent flank discomfort for 6 months. It was associated with mild burning micturition. Besides these complaints, she had a history of frequent episodes of migraine since the age of 13 years. During these episodes, she used to take NSAIDs to relieve pain. There was no other significant past medical history other than the history of some tympanic membrane surgery in her childhood.

Her father had a history of diabetes, ischemic heart disease, and end stage renal disease (ESRD) for which he remained on hemodialysis for 2 years. He died after suffering from a hemorrhagic stroke. Her paternal uncle

was also a hemodialysis patient and died due to cardiac arrest later on. Her twin sister died of some kidney problems at 13 years of age. Her elder sister is a known case of diabetes mellitus for 12 years and chronic kidney disease with serum creatinine of 1.2 mg/dL. Her renal biopsy was not done. Her cousin is also on hemodialysis due to ESRD secondary to some unknown cause.

On examination, her BP was 110/70 mmHg, pulse was 88/min and she was afebrile. She was short heighted with an average built and BMI of 25.5Kg/m². There was no flank tenderness and her systemic examination was unremarkable.

Her laboratory workup showed serum creatinine of 1.6 mg/dL. Her urine R/E showed +1 protein and 4-5 white blood cells per high power field. Her hemoglobin, total leucocyte count, and platelets were normal. Her serum albumin was 4.4 g/dL and ESR was 20mm/hour. All her serological workup including ANA, ANCA, anti-GBM, hepatitis B and C serology, c3 and c4 were negative. Her

abdominal ultrasound showed bilateral small-sized kidneys (Right: 6.6*1.8cm, Left: 6*2.9cm). Renal parenchymal thickness was 1 cm and 0.8 cm and cortical thickness was 4 mm and 4.5 mm in right and left kidney respectively. Renal parenchymal echogenicity was increased and cortico-medullary differentiation was preserved. There was no evidence of cyst, stone, and calcification.

Her renal biopsy was performed to identify the cause of her renal impairment which showed 3 globally sclerosed glomeruli, moderate tubular damage and dilation, with karyomegalic tubular epithelial cells and hyperchromatic nuclei. Immunostains for CMV and BK viruses were negative. Mild focal interstitial inflammation was also seen. Findings were highly suggestive of karyomegalic interstitial nephritis. Currently, her serum creatinine is 1.8 mg/dL. She is on some homeopathic medications only, and consulted nephrologist infrequently.

Figure below shows light microscopic images of all 5 cases.

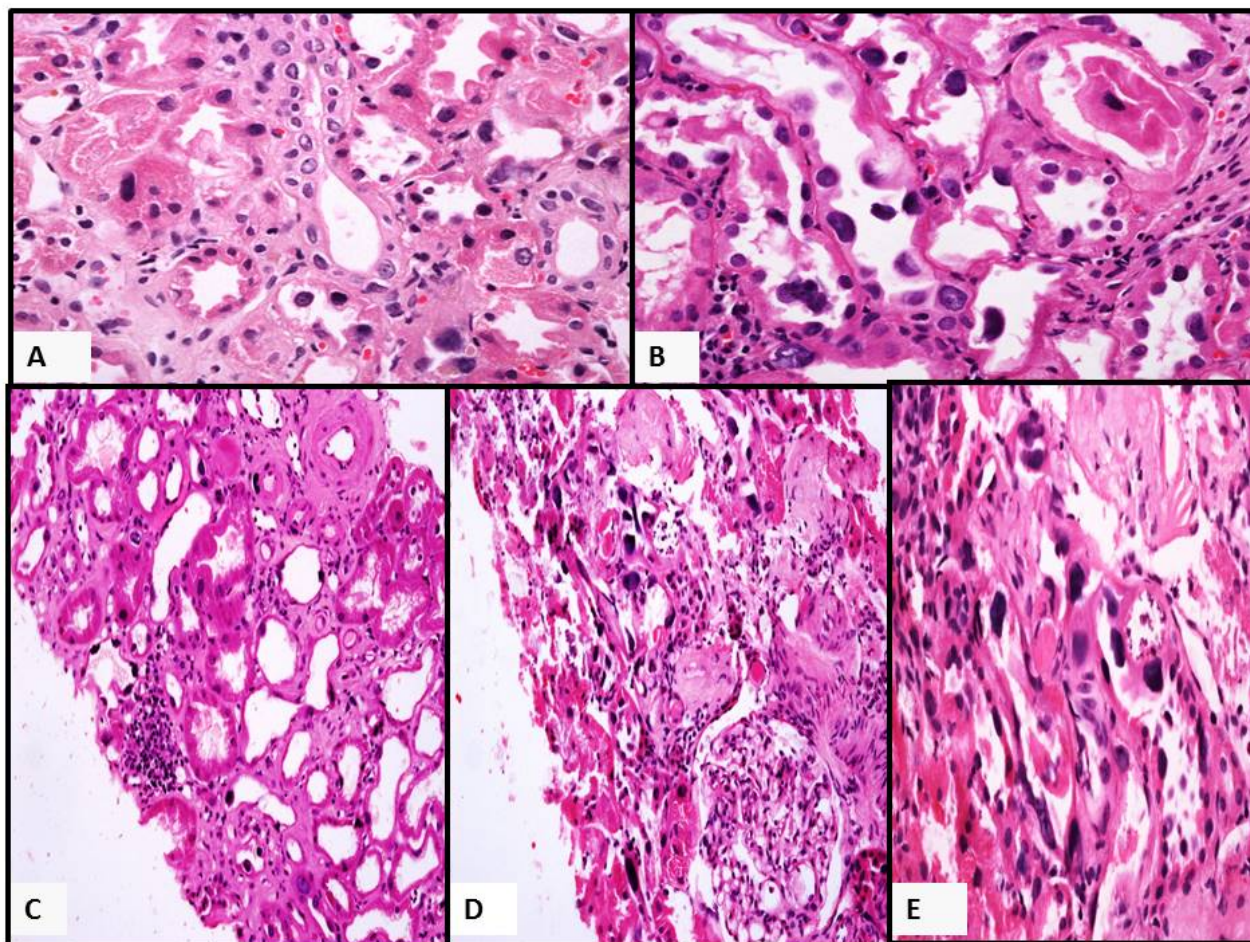


Figure 1. A to E: (A, B, E: H& E x400) and (C,D: H& E x 200) photomicrographs showing cases 1 through 5 displaying mild to moderate interstitial lymphoplasmacytic infiltrates and tubules with large, hyperchromatic nuclei and prominent nucleoli

3. Discussion

Karyomegalic interstitial nephritis is a rare, hereditary cause of chronic kidney disease leading to ESRD at the age of 40 to 50 years [8]. It is associated with an inherited mutation in the FAN-1 gene, which encodes for nuclease enzyme involved in DNA mismatch repair [9,10]. Our case series showed that this disease involved multiple family members, as described in 4 out of 5 case reports. It

is mostly inherited as an autosomal recessive disease [11]. Homozygotes develop slowly progressive renal impairment. Most of the patients present around 20-40 years of age with renal impairment and mild proteinuria [12]. Karyomegalic interstitial nephritis is known to be triggered by nephrotoxic medications, heavy metals, and viral infections. Two of our female patients had a strong history of frequent exposure to NSAIDs for their migraine that might have triggered disease progression. All our

above mentioned patients were diagnosed by characteristic biopsy finding of enlarged, hyperchromatic, pleomorphic nuclei with extensive tubular and interstitial involvement [13].

As this is a progressive disease and there is no specific cure for this disease, aim must be dedicated to halt disease progression. All possible measures must be taken to slow down the natural course of this disease. Genetic counseling and regular screening of all first-degree relatives is the cornerstone of management. The potential role of urine cytology, as a screening tool for the identification of potential donors at risk with positive family history, is still debatable [14,15]. Nephrotoxic medications must be avoided. Regular follow ups must be necessary for control of electrolyte and metabolic abnormalities, blood pressure management, dietary counselling and counselling regarding modality of renal replacement therapy.

As seen from history of case 1, karyomegalic interstitial nephritis can be misdiagnosed as BK virus nephropathy. However, there are some major differences between BK virus nephropathy and karyomegalic interstitial nephritis, which can be clearly distinguished if sought for in a conscious effort [16].

These are highlighted in Table 1.

Table 1. Comparison between Karyomegalic Interstitial Nephritis and BK Virus Nephropathy

	Karyomegalic Interstitial Nephritis	BK Virus Nephropathy
Renal tubules	Viral inclusions: Absent	Intranuclear basophilic viral inclusions: Present
	Large hyperchromatic pleomorphic nuclei with prominent nucleoli	Large nuclei with chromatic clumping present
	Tubulitis: Uncommon	Common
Immunofluorescence	SV40 staining: Negative	SV40 staining: Positive
Interstitialium	Variable interstitial fibrosis, may have chronic interstitial nephritis	Pleomorphic interstitial infiltrates predominantly lymphocytes
Serum PCR	Negative	Positive
Urine PCR	Negative	Positive
Urine cytology	Large pleomorphic tubular cells	Decoy cells

Abbreviations: PCR: polymerase chain reaction, SV40: simian virus 40.

As the usual presentation of this disease is around 20-50 years so potential family donors should be adequately investigated when considering for renal transplant and selected only after exclusion of any disease or genetic abnormality. Medically and physically fit donors above 50 years of age can possibly be chosen as a potential related donor. There is still research going on to identify genes involved in the pathogenesis of karyomegalic interstitial nephritis. Out of potential culprit genes, the FAN-1 gene has been thoroughly studied [9,10]. FAN-1 gene analysis should ideally be done for young potential family donors. According to one case report,

there was recurrence of karyomegalic interstitial nephritis from a related donor 24.7 months post-transplant, which showed that this mutation although clinically silent in a donor, can lead to graft impairment in the recipient [8].

A major obstacle in diagnosing this disease is mild sub nephrotic range proteinuria usually <1g/24hours, mild serum creatinine derangement initially, and usually small-sized highly echogenic kidneys for which biopsy would be difficult with greater chances of post-procedural complications. Although the prevalence of this disease is reported to be only 1% internationally, yet it is not uncommon in our population [11]. Therefore it needs to be more thoroughly recognized, investigated, and addressed.

4. Conclusion

To conclude, karyomegalic interstitial nephritis is a rare disease with a relatively worse prognosis. Its causation, clinical and histological features must be clearly understood to avoid underdiagnosis and mismanagement.

Abbreviations

PCR: Polymerase chain reaction, ESRD: end stage renal disease, NSAIDs: non-steroidal anti-inflammatory drugs, ANA: anti-nuclear antibodies, ANCA: anti-nuclear cytoplasmic antibodies, CMV: cytomegalovirus, BP: blood pressure, ATG: anti-thymocyte globulin, FAN-1: Fanconi anaemia-associated nuclease 1

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