

CASE REPORT

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# Case report: a 58-year-old man with small kidneys and elevated liver enzymes



Jonathan Dash<sup>1\*</sup>, Patrick Saudan<sup>2</sup>, Ariane Paoloni-Giacobino<sup>3</sup>, Solange Moll<sup>4†</sup> and Sophie de Seigneux<sup>2†</sup>

## Abstract

**Background:** The conjunction of hepatitis and renal disease can be seen in several clinical contexts, including karyomegalic nephritis (KIN). Karyomegalic nephritis (KIN) is a rare genetic disease, with less than 50 cases reported, which incidence is probably underestimated. We report here an unusual case presentation of KIN with obtention of several organ biopsies and a novel mutation leading to the disease.

**Case presentation:** A 58-year-old Caucasian without relevant family history presents with advanced chronic kidney disease, elevated liver enzymes and recurrent pulmonary infection. Familial history was negative. Renal biopsy revealed a chronic tubulo-interstitial nephritis with enlarged and irregular hyperchromatic nuclei. Karyomegalic nephritis (KIN) was confirmed by genetic testing with a non-sense mutation and a deletion in the Fanconi anemia associated nuclease 1 (*FAN1*) gene.

**Conclusions:** KIN is a rare disease to be suspected in the presence of renal disease, biological hepatitis and recurrent pulmonary infections, even without a familial history. Diagnosis of this condition is crucial to perform family screening, avoid progression factors, and adapt post-transplantation immunosuppression. Finally, avoiding familial heterozygote donors appears of major importance in this condition.

**Keywords:** Karyomegalic interstitial nephritis, Genetic, Chronic kidney disease

## Specificity of the case

We present here a case of KIN nephritis with recessive inheritance and undescribed mutations. The other specificity of the case relies on the obtention of biopsies from several organs in the same patients, allowing to compare renal and extrarenal lesions.

## Background

Karyomegalic nephritis (KIN) is a rare genetic disease, described in 1974 for the first time. KIN is defined as a systemic disease, with presence of tubular karyomegaly. Less than 50 cases are reported. We report here an unusual case presentation of KIN with obtention of several

organ biopsies and a novel mutation leading to the disease.

## Case presentation

**Initial presentation:** A 58-year-old Caucasian man of Bulgarian origin was referred to our nephrology department because of progressive renal disease without hypertension or diabetes. The patient was previously known for one episode of hepatitis at age 38 of unclear origin, gastro-intestinal specific complaints, and recurrent pulmonary infections. He had no relevant familial or personal history of renal disease. The patient had no consanguinity in his family and reported having potentially being exposed to ionizing radiation in Ukraine during his childhood.

**Initial laboratory:** Serum creatinine level was 245  $\mu\text{mol/l}$ , (eGFR 24 ml/min/1.73m<sup>2</sup>), the urinalysis was bland and proteinuria was of less than 1g, with a minority of

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albumin. Except for a mild metabolic acidosis, no electrolyte disturbance was noted. A moderate elevation of liver enzymes was observed. Viral serology, serum ANCA, ANA immunofixation and free light chain levels were within the normal range.

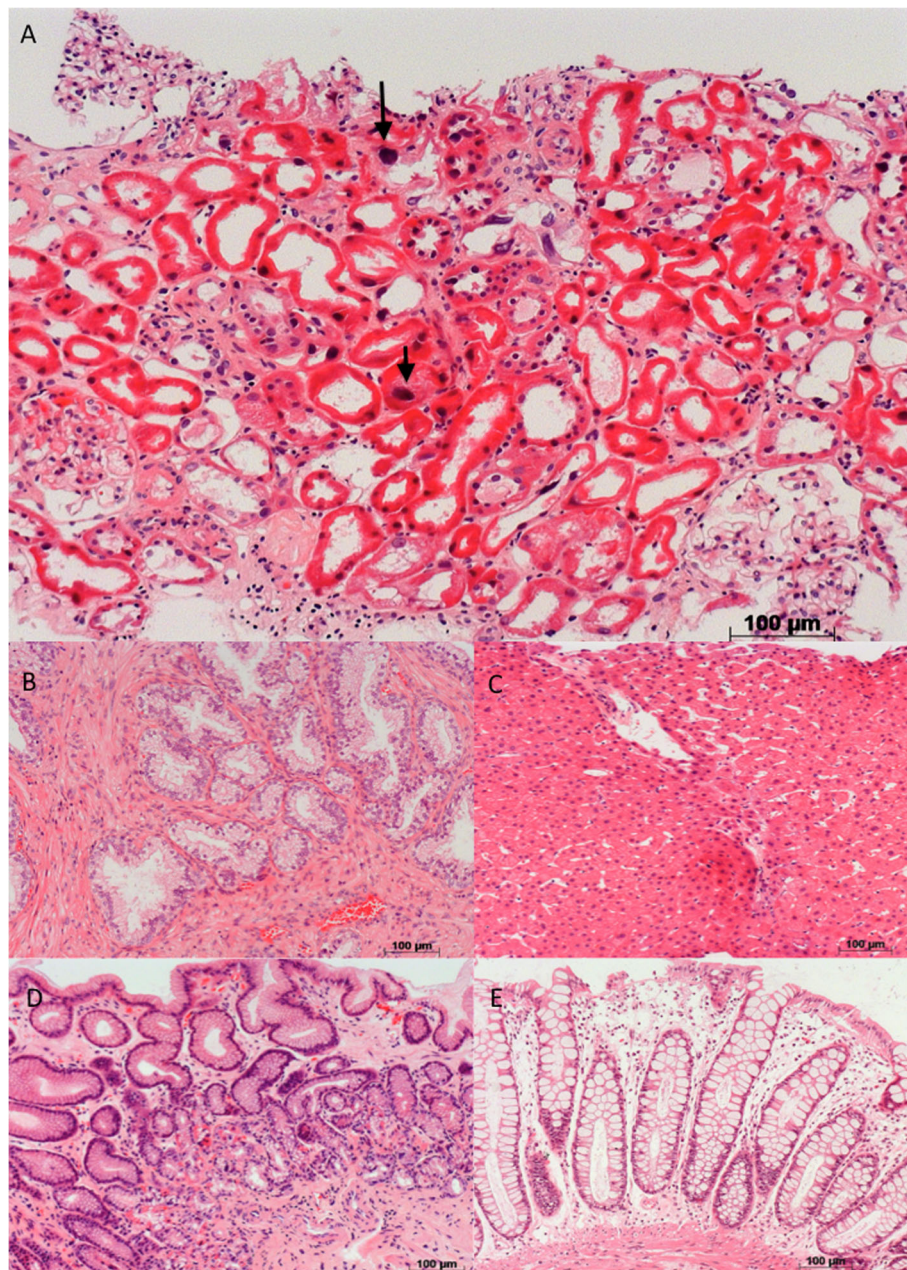
**Additional examinations**

Hepatic ultrasound was normal. A hepatic biopsy performed on account of elevated liver enzymes revealed normal hepatic parenchyma. Given intestinal complaints

and a slightly elevated PSA, the patients underwent gastric, colonic and prostate biopsies which were all normal. Results for all the biopsies are displayed in Fig. 1.

A pulmonary CT scan displayed no specific anomalies, and pulmonary functions were normal.

A kidney ultrasound revealed kidneys of decreased size (Right kidney: 7.7 × 3.5 × 4.3 cm, left Kidney 7.4 × 4.5 × 4.0 cm) with a hyperechoic parenchyma and diminution of the cortico-medullary dedifferentiation. A kidney biopsy was performed and analyzed by light microscopy.



**Fig. 1** Hematoxylin and eosin staining of biopsies from the Kidney **a**, prostate **b**, liver **c**, stomach **d** and colon **e**. The arrows indicate hyperchromatic nuclei

The kidney biopsy revealed 43 glomeruli, among which 23 were sclerosed. The remaining glomeruli were slightly enlarged with mesangial hypercellularity, and non-specific chronic lesions. Interstitial fibrosis including inflammatory cells (lymphocytes and histiocytes) was estimated to be around 40% of the cortical surface. The most notable anomaly was enlarged hyperchromatic nuclei in tubular cells, with irregularities, but without visualization of viral inclusions, together with the presence of tubular atrophy. These anomalies were predominant in the proximal tubules of both the cortex and the medulla. Immunofluorescence studies were negative. Additional staining for virus (CMV, EBV) were negative. Electron microscopy displayed tubular cells with signs of chronic injury, together with enlarged mitochondria in tubular cells and podocytes, but no Karyomegalic nuclei were seen on the available material.

Given the renal histological lesions in a patient with a chronic history of hepatitis and recurrent pulmonary infections, a presumptive diagnosis of Karyomegalic nephritis was retained. Genetic testing of the patient DNA by exome sequencing revealed a non-sense mutation c.1102C > T, p.(Gln368\*) in exon 2 and a deletion c.2616delA, p.(Asp873Thrfs\*17) in exon 12, in the Fanconi anemia associated nuclease 1 (*FAN1*) gene. Both mutations were confirmed by Sanger sequencing. The non-sense mutation had not been reported before, but was classified as pathogenic, the deletion was already reported as pathogenic, and both consequently explaining the phenotype [1]. His son presented only the c.2616delA deletion, arguing for the compound heterozygote mutations. Compound heterozygote mutations as causative for the phenotype and transmitted with an autosomal recessive mode of inheritance have already been reported [1, 2].

The diagnosis of karyomegalic nephritis related to a *FAN1* mutation was retained.

Follow up: Progression towards end-stage renal disease occurred within the following year and the patients was placed on peritoneal dialysis. Peritoneal dialysis was initially difficult because of abdominal pain. A laparoscopy without biopsies was performed and revealed an inflamed peritoneum of unknown cause. The pain spontaneously resolved. The patient was also placed on a kidney transplantation waiting list.

## Discussion and conclusions

Karyomegalic nephritis (KIN) is a rare genetic disease first described in 1974 and named in 1979 by Mihatsch and colleagues describing three cases of the disease [3]. KIN is defined as a systemic disease and has a peculiar specific renal pathology displaying features common to nephronophthisis, with the presence of tubular karyomegaly [3]. Less than 50 cases have been reported and 12 families with an autosomal recessive inheritance are

identified [1]. The role of *FAN1* as a causative mutated gene was reported in 2012 [1]. The *FAN1* protein is required for the repair of DNA interstrand cross-links and repair of DNA damage [1, 2]. Karyomegalic nephritis is usually observed in conjunction with recurrent pulmonary infections and hepatitis, all features presented by the patient [1–3]. Kidney specificity for fibrotic lesions and more pronounced renal karyomegaly than in other organs is possibly related to the expression level of *FAN1* protein, which is highest in the kidney, or to local environmental conditions [1]. Only few case reports have included biopsy of other organs [4]. In the present case, karyomegaly was kidney specific and not apparent in other organs, suggesting a predominance of renal sensitivity due to specific repair mechanism in kidney tubular cells. Participation of ionizing radiation may have promoted the phenotype in our case.

End-stage kidney disease in KIN patients occurs usually in their 50 to 60s. Renal function in our patient declined rapidly and required dialysis. Peritoneal dialysis was implemented and the patient was inscribed on a kidney transplantation waiting list. Few reports are available on the long-term oncologic and infectious risk in these patients when placed under immunosuppression [2]. Pulmonary infections may be limiting in this context [5]. Surveillance and adaptation of immunosuppression are therefore of importance. Familial living donation in this context has to be evaluated carefully and by genetic testing. In a previous report, a recipient with KIN presented a recurrence of KIN after an ABO compatible living-related donor from his sister [6]. Heterozygous carriers might be at increased risk of CKD and a donation in heterozygous carriers should be discouraged.

Clinician have to be aware of the diagnosis of KIN and suspect it in patients with small kidneys, elevated liver enzymes and pulmonary infections. Genetic testing may give the diagnosis if performed in the first place and may avoid the need for hepatic or other biopsies. Genetic diagnosis is also of importance for familial counseling and allograft planning.

In summary, our patient presented with KIN related to a compound heterozygote mutation of *FAN1*. Mutations in this gene should be suspected in individuals with interstitial nephropathy, elevated liver enzymes and recurrent pulmonary infections. The phenotype predominates in the kidney likely because of the specificity of *FAN1* protein expression, or due to possible repeated subclinical injuries to tubular cells. Heterozygous familial donors should be avoided for transplantation.

## Abbreviations

ANA: Antinuclear Antibody; ANCA: Antineutrophil Cytoplasmic Antibodies; CKD: Chronic Kidney Disease; CMV: Cytomegalovirus; DNA: Deoxyribonucleic acid; EBV: Epstein-Barr Virus; eGFR: Estimated Glomerular Filtration Rate;



FAN1: Fanconi anemia associated nuclease 1; KIN: Karyomegalic interstitial Nephritis; PSA: Prostate-specific antigen

#### Acknowledgements

Not Applicable.

#### Authors contributions

All Author contributions are in line with the ICMJE guidelines. JD collected data and wrote the manuscript, PS took care of the patient, collected data and corrected the manuscript, SDS wrote the manuscript, SM performed histological analysis, AG performed genetic analysis and corrected the manuscript. All authors have read and approved the final version.

#### Funding

No funding was obtained for this study.

#### Availability of data and materials

Not Applicable.

#### Ethics approval and consent to participate

Not Applicable.

#### Consent for publication

The patient gave us written consent for publication of his details and images.

#### Competing interests

No one of the Authors has a financial and non-financial competing interest.

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Received: 10 January 2020 Accepted: 11 March 2020

Published online: 27 March 2020

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