

Young-onset Chronic Kidney Disease with Biopsy-proven Chronic Tubulointerstitial Nephritis and a Rare REN Variant, with Coincident Drug-related Erythrocytosis: A Case Report

SAI SANKETH NETHULA¹, RAMA VENKATESHPRASAD², MANIKANTAN SEKAR³,
SUBALAKSHMI BALASUBRAMANIAN⁴, AALAYA HARIDAS⁵



ABSTRACT

Chronic Kidney Disease (CKD) in a young adult with a bland urinary sediment should prompt consideration of a monogenic tubulointerstitial disorder. Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD) is an under-recognised genetic cause, and in ADTKD due to REN the phenotype depends on where the variant lies in preprorenin. This report describes a 23-year-old man with six months of frothy urine who had young-onset CKD (estimated glomerular filtration rate 47-54 mL/min/1.73 m²) with sub-nephrotic proteinuria, hyperuricaemia and a negative immunological screen. He also had absolute erythrocytosis (haemoglobin 20.1 g/dL, packed-cell volume 60.1%) that was JAK2 V617F- and exon-12-negative with a normal erythropoietin and normal oxygen saturation, attributed to prior anabolic-androgenic ("testosterone-boosting") agents and resolving after a single therapeutic venesection and cessation. Renal biopsy showed chronic tubulointerstitial nephritis with negative immunofluorescence, and whole-exome sequencing identified a heterozygous REN variant, c.708A>T (p.Gln236His), in the mature-renin domain - a region associated with later onset and absence of the anaemia that characterises signal-peptide variants. The variant is currently of uncertain significance and family segregation is advised. The case illustrates genotype-phenotype nuance in ADTKD-REN and the value of separating two coincident haematological and renal processes.

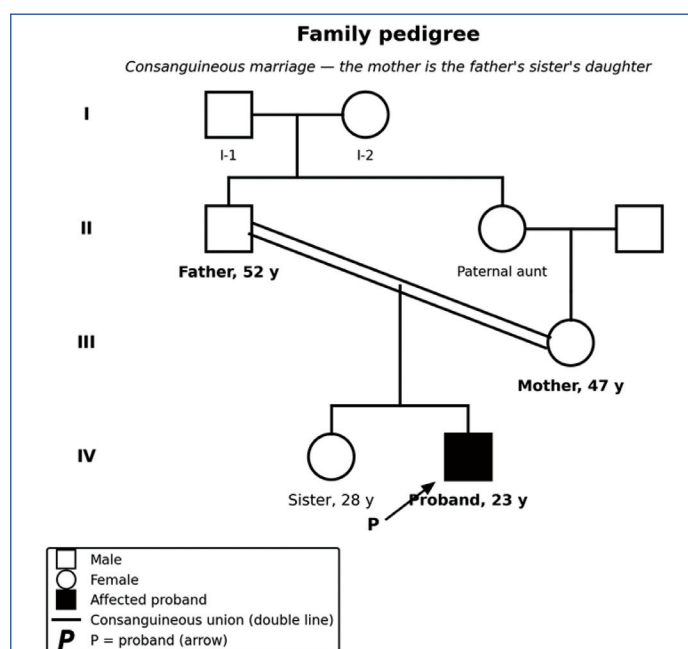
Keywords: Chronic, Erythrocytosis, Hyperuricaemia, Polycythaemia, Renal insufficiency, Renin

CASE REPORT

A 23-year-old man presented with a six-month history of frothy urine, associated with headache, anorexia and intermittent vomiting. There was no haematuria, oedema, fever, arthralgia or use of analgesics or non-steroidal anti-inflammatory drugs, and his past medical history was otherwise unremarkable. On specific enquiry about habits, he reported having taken oral tablets and injectable testosterone-boosting agents, probably anabolic-androgenic steroids of unknown identity and dose, for six to twelve months about two years before presentation and had since discontinued them. He was born of a consanguineous marriage, his mother being his father's sister's daughter, and there was no reported family history of kidney disease. the consanguineous pedigree is shown in [Table/Fig-1].

On general examination, there was no pallor, plethora, hepatosplenomegaly or oedema, and the blood pressure was 150/80 mmHg. Systemic examination, including cardiovascular, respiratory and abdominal examination, was unremarkable.

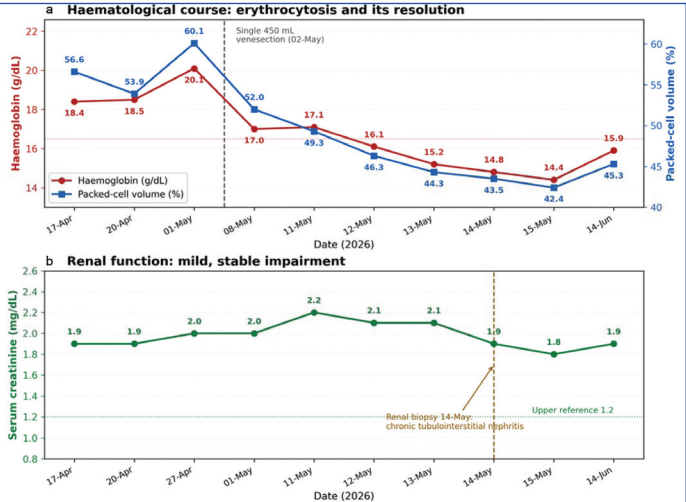
The combination of young-onset renal impairment with an incidentally noted absolute erythrocytosis suggested two parallel problems, and these were investigated together. At an earlier hospital he had been found to have mildly impaired renal function (serum creatinine 1.9 to 2.0 mg/dL), hyperuricaemia (7.3 mg/dL) and proteinuria, with an incidental absolute erythrocytosis; renal biopsy had been deferred because of the erythrocytosis and its attendant bleeding risk, and he had been referred on an angiotensin-receptor blocker and urate-lowering therapy. At the reporting institute the haemoglobin peaked at 20.1 g/dL with a packed-cell volume of 60.1% [Table/Fig-2]. The erythrocytosis was JAK2 V617F- and exon-12-negative, with a normal, non-suppressed serum erythropoietin (13.3 mIU/mL), normal peripheral oxygen saturation and



[Table/Fig-1]: Family pedigree. The proband (arrow, filled square) is a 23-year-old man born of a consanguineous marriage - his mother is his father's sister's daughter (double line denotes the consanguineous union). Square, male; circle, female; filled symbol, affected proband.

normal white-cell and platelet counts, indicating a secondary process [Table/Fig-3]. Renal assessment showed an estimated glomerular filtration rate of 47 to 54 mL/min/1.73 m² (CKD stage G3a), sub-nephrotic proteinuria (urine protein-creatinine ratio 0.84 g/g; 24-hour urinary protein 949 mg), an inactive urinary sediment and a negative

immunological and viral screen [Table/Fig-3]. Ultrasonography showed normal-sized kidneys with increased cortical echogenicity, and the echocardiogram was normal [Table/Fig-4,5].



[Table/Fig-2]: Disease course: (a) Haemoglobin and packed-cell volume; (b) Serum creatinine. In both panels the horizontal axis represents time across the serial measurements of the clinical course, in chronological order from presentation. Numerical data underlying the graphs — Haemoglobin (g/dL): 18.4, 18.5, 20.1 (peak), 17.0, 17.1, 16.1, 15.2, 14.8, 14.4, 15.9. Packed-cell volume (%): 56.6, 53.9, 60.1, 52.0, 49.3, 46.3, 44.3, 43.5, 42.4, 45.3. Serum creatinine (mg/dL): 1.9, 1.9, 2.0, 2.0, 2.2, 2.1, 2.1, 1.9, 1.8, 1.9 (range 1.8-2.2).

Investigation	Result	Reference/interpretation
Erythrocytosis work-up		
Haemoglobin/packed-cell volume (peak)	20.1 g/dL/60.1%	Absolute erythrocytosis
JAK2 V617F mutation	Not detected	Argues against polycythaemia vera
JAK2 exon-12 mutation	Not detected	Argues against JAK2-exon-12 polycythaemia vera
Serum erythropoietin	13.3 mIU/mL	4.3-29.0; normal (not suppressed) - secondary
Peripheral oxygen saturation	Normal	Against hypoxic secondary erythrocytosis
White-cell / platelet counts	Normal (isolated erythrocytosis)	Against a myeloproliferative disorder
Renal and metabolic		
Serum creatinine (range)	1.8-2.2 mg/dL	0.7-1.2; eGFR 47-54 mL/min/1.73 m ² (CKD G3a)
Uric acid	7.3 → 3.95 mg/dL (on febuxostat)	3.4-7.2; initial hyperuricaemia
Serum electrolytes	Na 138-140/K 3.5-4.4/HCO ₃ 24-28	Within/near reference range
Total / indirect bilirubin	3.21/2.48 mg/dL	Unconjugated hyperbilirubinaemia (incidental)
Urinalysis/proteinuria		
Urine protein-creatinine ratio	0.84 g/g	<0.2; sub-nephrotic
24-hour urine protein	949 mg/day	<150; sub-nephrotic
Urine microscopy	Inactive (no dysmorphic RBC/RBC casts)	Bland sediment
Immuno-serology		
ANA/ANCA (MPO, PR3)	Negative/Negative	Against autoimmune/vasculitic disease
Anti-PLA2R antibody	Negative	Against primary membranous nephropathy
Complement C3 / C4	128/32 mg/dL	Normal
HIV/HBsAg / HCV	Non-reactive	-

[Table/Fig-3]: Laboratory investigations and results (erythrocytosis work-up, renal-metabolic panel, urinalysis and immuno-serology). eGFR: Estimated glomerular filtration rate; CKD: Chronic kidney disease; ANA: Antinuclear antibody; ANCA: Antineutrophil cytoplasmic antibody; MPO: Myeloperoxidase; PR3: Proteinase-3; anti-PLA2R = Anti-phospholipase-A2-receptor antibody; RBC: Red blood cell. Reference ranges are those of the performing clinical laboratory; the erythrocytosis and renal results were interpreted using standard diagnostic frameworks [11,13].

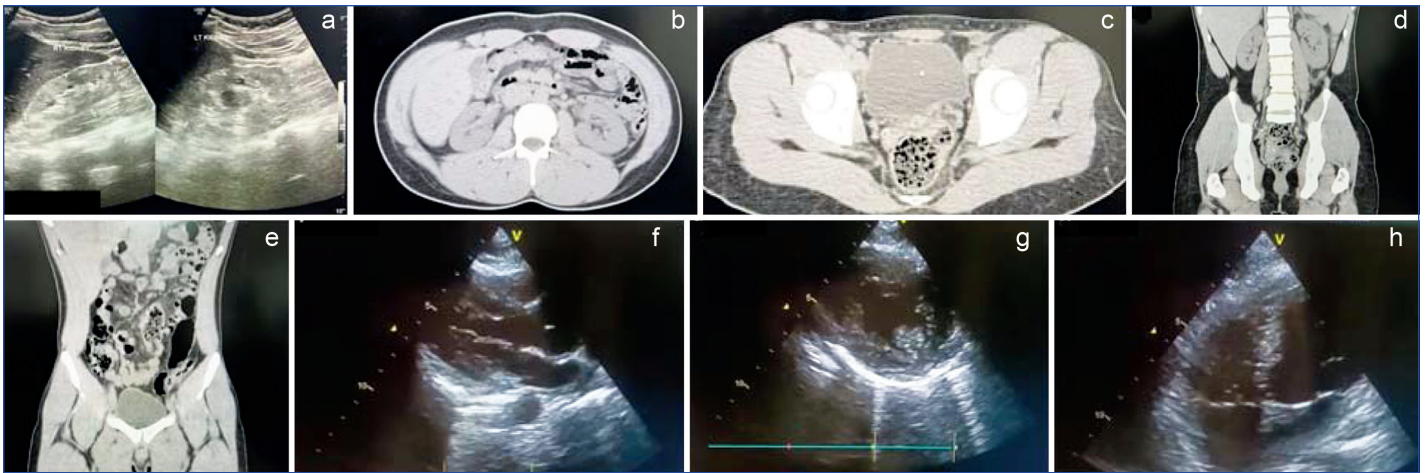
Modality	Findings
Imaging	
Ultrasound kidneys	Normal-sized kidneys (approximately 8-10.7 cm) with increased cortical echogenicity and preserved corticomedullary differentiation.
Echocardiogram	Structurally normal; ejection fraction 62%.
Micturating cystourethrogram/CT-KUB	No vesicoureteric reflux; small right pelvic phlebolith; post-biopsy perinephric changes; incidental emphysematous cystitis.
Renal biopsy (light microscopy + immunofluorescence)	
Glomeruli	Seven sampled; 3 globally sclerosed; remainder with mesangial matrix expansion; no endo-/extra-capillary hypercellularity.
Tubulo-interstitium	Tubular atrophy approximately 50%; interstitial fibrosis approximately 50% with lymphoplasmacytic infiltrate; hyaline casts.
Vessels/immunofluorescence	Medial hypertrophy with myxoid intimal change; immunofluorescence negative for all conjugates.
Impression	Chronic tubulointerstitial nephritis.
Genetics (whole-exome sequencing)	
Gene/variant	REN (NM_000537.4), exon 7: c.708A>T, p.(Gln236His), heterozygous - mature-renin domain.
Classification/disease	Variant of uncertain significance (ACMG); Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD) type 4.
Recommendation	Family segregation testing (advised; pending).

[Table/Fig-4]: Structural imaging, renal histopathology and genetic findings. CT-KUB: Computed tomography of the kidneys, ureters and bladder; ACMG: American College of Medical Genetics and Genomics

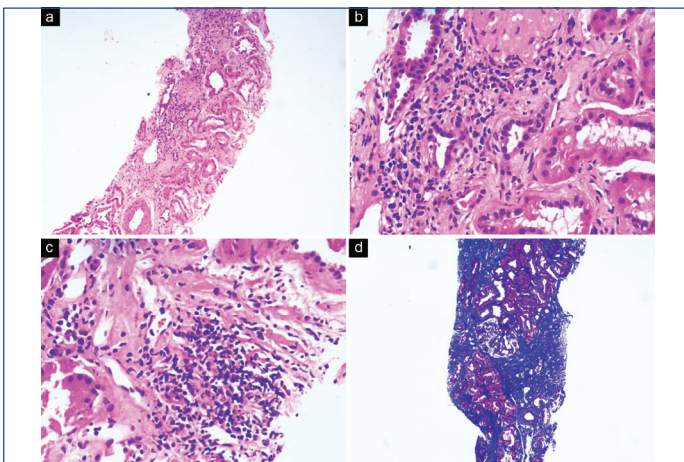
The differential diagnosis for the renal disease included a monogenic tubulointerstitial disorder and chronic interstitial nephritis of other cause, a glomerulopathy being thought unlikely given the bland sediment, while that for the erythrocytosis included polycythaemia vera, hypoxic and erythropoietin-driven secondary causes, and androgen-related erythrocytosis. After a single 450 mL therapeutic venesection, ultrasound-guided renal biopsy showed chronic tubulointerstitial nephritis, with tubular atrophy and interstitial fibrosis each involving approximately 50% of the sampled cortex, a lymphoplasmacytic infiltrate, ischaemic and obsolescent glomeruli and negative immunofluorescence [Table/Fig-6]. Whole-exome sequencing identified a heterozygous REN variant, exon 7 c.708A>T (p.Gln236His), lying in the mature-renin domain, classified as a variant of uncertain significance and associated with ADTKD type 4 [Table/Fig-7]. The final diagnosis was biopsy-proven chronic tubulointerstitial nephritis with a rare mature-domain REN variant (ADTKD-REN), together with a coincident, drug-related secondary erythrocytosis attributable to prior anabolic-androgenic agents.

Molecular characterisation showed that the variant corresponds to chr1:g.204156787T>A (NM_000537.4); it is absent from the 1000 Genomes, gnomAD v2.1 and v3.1, and TOPMed databases, has a minor allele frequency of 0.007% in an internal South Asian database, and lies at a codon conserved across species, and no clinically significant copy-number variants were detected. Under the ACMG framework the variant meets only the PM2 (moderate) criterion and is therefore reported as a variant of uncertain significance, for which parental and family segregation testing is recommended.

Management addressed both problems. The erythrocytosis was treated with a single 450 mL venesection and by ensuring continued avoidance of androgenic agents, and the haemoglobin and packed-cell volume normalised over the following weeks [Table/Fig-2]. Although the androgens had been stopped about two years earlier, the erythrocytosis had persisted until presentation; this is consistent with an androgen-induced upward resetting of the haemoglobin set-point, mediated by increased erythropoietin and suppressed hepcidin, which corrects only slowly, and the prompt resolution after venesection and continued abstinence supported a secondary, reversible process rather than polycythaemia vera. For the renal disease he continued an angiotensin-receptor blocker, oral



[Table/Fig-5]: Supporting imaging (de-identified): a) Ultrasonography of both kidneys; b) Axial computed tomography of the kidneys, ureters and bladder (CT KUB) showing both kidneys; c) Axial CT KUB showing the urinary bladder; d) Coronal CT KUB showing the urinary bladder; e) Transthoracic echocardiography, parasternal long-axis view; f) Parasternal short-axis view; g) Apical four-chamber view.



[Table/Fig-6]: Renal biopsy: a) Low-power (x100) haematoxylin and eosin (H&E); tubular injury with tubular atrophy and interstitial fibrosis; b) H&E, 400x: tubulitis and tubular epithelial injury; c) H&E, 400x: interstitial inflammatory infiltrate; d) Masson trichrome, 200x: confirms interstitial fibrosis (blue). Together the findings are those of an immunofluorescence-negative chronic tubulointerstitial nephritis.

alkali, urate-lowering therapy with febuxostat and a sodium-glucose co-transporter-2 inhibitor. At follow-up the renal function remained mildly and stably impaired (serum creatinine 1.8 to 2.2 mg/dL) and the uric acid normalised to 3.95 mg/dL on febuxostat, while the haematological values remained normal. Family segregation testing was advised to clarify the significance of the REN variant but has not yet been performed. Incidental findings were unconjugated (Gilbert-type) hyperbilirubinaemia and a transient emphysematous cystitis after cystourethrography, which resolved with antibiotics.

DISCUSSION

The CKD in an adolescent or young adult with a bland urinary sediment and normal-sized or small kidneys should raise the possibility of a monogenic tubulointerstitial disorder rather than a glomerulopathy [1]. ADTKD, caused by variants in *UMOD*, *MUC1*, *HNFB*, *REN* and *SEC61A1*, is an under-diagnosed group characterised by tubular atrophy, interstitial fibrosis and slow, familial progression to kidney failure [1-4]. In ADTKD-REN the phenotype depends on where the variant lies in preprorenin: signal-peptide variants present earliest and with near-universal childhood anaemia, whereas prosegment and mature-domain variants present later and with progressively less anaemia [5,6]. Erythrocytosis is not a described feature [7]. In accordance with the CARE guidelines [8], this report describes a young man with biopsy-proven chronic tubulointerstitial nephritis, a rare mature-domain REN variant and a coincident, drug-related erythrocytosis.

This young man had two initially puzzling problems with distinct mechanisms: young-onset chronic tubulointerstitial nephritis harbouring a rare REN variant, and an absolute erythrocytosis of secondary, drug-related origin. Disentangling the two is the central lesson of the case.

REN encodes preprorenin, processed through a signal peptide, a prosegment and the mature-renin peptide; the position of a variant governs both the mechanism of injury and the clinical phenotype [5,6]. Signal-peptide variants misdirect preprorenin and cause the most severe, earliest-onset disease with near-universal childhood anaemia, whereas prosegment and mature-domain variants cause endoplasmic-reticulum retention of (pro)renin with later, milder disease and less anaemia [5,6]. In the largest cohort, childhood anaemia occurred in 91% of signal-peptide, 69% of prosegment and none of the mature-domain patients, who also presented oldest [6]. The patient's p.Gln236His lies in the mature-renin domain, and his complete lack of the disease-defining anaemia is exactly what that correlation predicts - contrasting with signal-peptide cases in whom anaemia is an early clue [9] and mirroring the first mature-protein REN family, who had adult onset and normal haemoglobin [10]. The immunofluorescence-negative chronic tubulointerstitial nephritis, bland sediment, sub-nephrotic

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SNV(s)/INDELs

Gene* (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification ²
REN (-) (ENST00000272190.9) NM_000537.4	Exon 7	c.708A>T (p.Gln236His)	Heterozygous	Tubulointerstitial kidney disease, autosomal dominant, 4 (OMIM#613092)	Autosomal dominant	Uncertain Significance (PM2_M)

Abbreviation : _VS - Very Strong, _S - Strong, _M - Moderate, _Sup - Supporting

Parental testing is recommended, and classification of the variant(s) may change based on segregation analysis.

Genotype-Phenotype correlation is recommended.

COPY NUMBER VARIANTS CNV(s)

No significant CNVs for the given clinical indications that warrants to be reported was detected.

VARIANT INTERPRETATION AND CLINICAL CORRELATION

Variant description: A heterozygous missense variant in exon 7 of the *REN* gene (chr1:g.204156787T>A; Depth: 118x) that results in the amino acid substitution of Histidine for Glutamine at codon 236 (p.Gln236His; ENST00000272190.9) was detected (Table). The p.Gln236His variant has not been reported in the 1000 genomes, gnomAD (v3.1), gnomAD (v2.1) and topmed databases and has a minor allele frequency of 0.00742% in the our internal database. The reference codon is conserved across species.

OMIM phenotype: Tubulointerstitial kidney disease, autosomal dominant, 4 (OMIM#613092) is caused by heterozygous mutations in the *REN* gene (OMIM#179820). Autosomal dominant tubulointerstitial kidney disease-4 (ADTKD4) is a progressive renal disorder characterized by early-onset anaemia and increased serum uric acid with a bland urinalysis and without proteinuria. Although the anaemia tends to improve with age, progressive renal insufficiency results in end-stage kidney disease between 40 and 70 years. Renal ultrasound may show small echogenic kidneys, and biopsy shows tubular atrophy and interstitial fibrosis, sometimes with cysts and secondary glomerulosclerosis (PMID: 18842627).

Due to lack of literature evidence³, this *REN* variation is classified as a variant of uncertain significance and has to be carefully correlated with the clinical symptoms.

The significance/classification of the variant(s) may change based on the genetic testing in parents and other family members.

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[Table/Fig-7]: De-identified whole-exome sequencing report.

proteinuria and hyperuricaemia are all in keeping with ADTKD [1,2]. [Table/Fig-8] compares the case with the reference phenotype and reported cases. Similar cases in the literature support this domain-based interpretation: Clissold RL et al., described a signal-peptide REN mutation presenting with early anaemia after decades of renal disease [9], whereas Schaeffer C et al., reported the first mature-protein REN family with adult onset and normal haemoglobin [10], and the international REN cohort of Zivna M et al., established that mutation location defines distinct clinical subtypes [6]. The patient's mature-domain variant and absence of anaemia fit this pattern, and the comparison is summarised in [Table/Fig-8].

Feature	Signal-peptide (classic)	Reported mature-domain case	Present case
Reference	Zivna M et al., 2009 [5]; Clissold RL et al., 2017 [9]	Schaeffer C et al., 2019 [10]	This report
REN variant / domain	Signal peptide (e.g., p.Leu16del; p.Trp17Arg)	Mature protein (p.Leu381Pro)	Mature protein (p.Gln236His), exon 7
Age at presentation	Childhood/ adolescence (~20 y)	Adulthood (50-65 y)	23 years
Anaemia	Present, early, disproportionate	Absent	Absent (instead erythrocytosis, drug-related)
Hyperuricaemia/ gout	Characteristic	Present	Present (uric acid 7.3 mg/dL)
Urinary sediment / proteinuria	Bland/mild	Bland/mild	Bland/sub-nephrotic (uPCR 0.84)
Histology	Chronic tubulointerstitial nephritis	Chronic tubulointerstitial nephritis	Chronic tubulointerstitial nephritis, IF-negative
Variant classification	Pathogenic	Likely pathogenic	Uncertain significance (segregation pending)

[Table/Fig-8]: The present case compared with the characteristic ADTKD-REN phenotype and representative reported cases.
REN: Renin gene; IF: Immunofluorescence; uPCR: Urine protein-creatinine ratio.

The erythrocytosis required a separate explanation, as it is not part of ADTKD-REN [7]. A myeloproliferative disorder was excluded (JAK2 V617F/exon-12 negative; isolated erythrocytosis), while a normal, non-suppressed erythropoietin and normal oxygen saturation argued against polycythaemia vera and hypoxic or erythropoietin-driven causes, consistent with standard algorithms [11]. Prior anabolic-androgenic “testosterone-boosting” use is the most parsimonious cause: androgens raise the haemoglobin set-point by increasing erythropoietin and suppressing hepcidin, with a normal rather than suppressed erythropoietin being the expected signature [12]. Accordingly, the values normalised after a single venesection and cessation [Table/Fig-1] - a reversible, secondary course rather than polycythaemia vera. The two processes were coincident, not causally linked. A JAK2-negative (secondary) erythrocytosis of this kind, including androgen-related causes, is best approached with the current diagnostic framework for unmutated erythrocytosis [13].

Several practical lessons follow. Young-onset CKD with a bland sediment and immune-negative tubulointerstitial histology should trigger genetic evaluation for ADTKD, which is frequently missed [1,2]. Absence of anaemia does not exclude ADTKD-REN - mature-domain variants spare the erythron [6,10] - so a normal or even elevated haemoglobin should not deter testing when the renal phenotype fits. A variant of uncertain significance must be interpreted with phenotype and family segregation before it drives counselling [14]; this report therefore describes the identification of a rare REN variant, not proof of causation. Finally, unexplained erythrocytosis in a young man warrants a secondary work-up that explicitly asks about androgen and performance-enhancing agents. The variant

met only the ACMG PM2 criterion (absence from population databases), and without functional or family-segregation evidence its classification remains uncertain.

The REN variant remains of uncertain significance; family segregation is pending and functional studies were not performed. Serum/urine protein electrophoresis, free light chains, an arterial blood gas and bone-marrow examination were not undertaken; however, a normal oxygen saturation, a normal non-suppressed erythropoietin, isolated erythrocytosis and a clear reversible cause make polycythaemia vera and hypoxic/paraneoplastic causes unlikely. Follow-up is short. It is emphasised that this report describes the identification of a rare REN variant of uncertain significance, not proof of causation. Family segregation testing, parental and sibling renal-function data, a functional assay, and detailed population-frequency, in-silico and conservation data with formal ACMG criteria are not available, and the negative family history somewhat weakens the case, although incomplete penetrance, unrecognised disease, young untested relatives or unavailable testing may explain it. The variant should therefore be interpreted together with the phenotype and with family segregation before it is used to guide counselling [14].

CONCLUSION(S)

A rare mature-domain REN variant was identified in a young man with biopsy-proven chronic tubulointerstitial nephritis whose phenotype-young-onset CKD, hyperuricaemia, a bland sediment and, characteristic of a mature-domain variant, no anaemia - fits ADTKD-REN, while a coincident erythrocytosis was independently explained by prior anabolic-androgen use and reversed with venesection and cessation. Genetic evaluation should be considered early in young onset tubulointerstitial CKD, and a variant of uncertain significance interpreted with family segregation.

Declarations

Patient consent: Written informed consent for publication of this de-identified case, including the clinical images and pedigree, was obtained from the patient; the pedigree and images are included because they are essential to the scientific message. Written informed consent was also obtained from the patient for the diagnostic and therapeutic procedures described.

Ethics: Institutional requirements for a single de-identified case report were followed.

REFERENCES

[1] Eckardt KU, Alper SL, Antignac C, Bleyer AJ, Chauveau D, Dahan K, et al. Autosomal dominant tubulointerstitial kidney disease: Diagnosis, classification, and management - A KDIGO consensus report. *Kidney Int.* 2015;88(4):676-83.

[2] Devuyst O, Olinger E, Weber S, Eckardt KU, Knoch S, Rampoldi L, et al. Autosomal dominant tubulointerstitial kidney disease. *Nat Rev Dis Primers.* 2019;5(1):60.

[3] Zivna M, Kidd KO, Baresova V, Hulkova H, Knoch S, Bleyer AJ Sr. Autosomal dominant tubulointerstitial kidney disease: A review. *Am J Med Genet C Semin Med Genet.* 2022;190(3):309-24.

[4] Bleyer AJ, Wolf MT, Kidd KO, Zivna M, Knoch S. Autosomal dominant tubulointerstitial kidney disease: More than just HNF1B. *Pediatr Nephrol.* 2022;37(5):933-46.

[5] Zivna M, Hulkova H, Matignon M, Hodanova K, Vyletal P, Kalbacova M, et al. Dominant renin gene mutations associated with early-onset hyperuricaemia, anaemia, and chronic kidney failure. *Am J Hum Genet.* 2009;85(2):204-13.

[6] Zivna M, Kidd K, Zaidan M, Vyletal P, Baresova V, Hodanova K, et al. An international cohort study of autosomal dominant tubulointerstitial kidney disease due to REN mutations identifies distinct clinical subtypes. *Kidney Int.* 2020;98(6):1589-604.

[7] Zivna M, Kidd K, Knoch S, Bleyer AJ. Autosomal dominant tubulointerstitial kidney disease - REN. In: *GeneReviews* [Internet]. Seattle (WA): University of Washington; 2011 (updated 2020).

[8] Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D; CARE Group. The care guidelines: Consensus-based clinical case report guideline development. *J Clin Epidemiol.* 2014;67(1):46-51.

[9] Clissold RL, Clarke HC, Spasic-Boskovic O, Brugger K, Abbs S, Bingham C, et al. Discovery of a novel dominant mutation in the REN gene after forty years of renal disease: A case report. *BMC Nephrol.* 2017;18(1):234.

[10] Schaeffer C, Izzi C, Vettori A, Pasqualetto E, Cittaro D, Lazarevic D, et al. Autosomal dominant tubulointerstitial kidney disease with adult onset due to a novel renin mutation mapping in the mature protein. *Sci Rep.* 2019;9(1):11601.

[11]

McMullin MFF, Mead AJ, Ali S, Cargo C, Chen F, Ewing J, et al; British Society for Haematology. A guideline for the management of specific situations in polycythaemia vera and secondary erythrocytosis. Br J Haematol. 2019;184(2):161-75.

[12]

Bachman E, Travison TG, Basaria S, Davda MN, Guo W, Li M, et al. Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin: Evidence for a new erythropoietin/hemoglobin set point. J Gerontol A Biol Sci Med Sci. 2014;69(6):725-35.

[13]

Gangat N, Szuber N, Pardanani A, Tefferi A. JAK2 unmutated erythrocytosis: Current diagnostic approach and therapeutic views. Leukemia. 2021;35(8):2166-81.

[14]

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-24.

PARTICULARS OF CONTRIBUTORS:

1. Postgraduate Student, Department of Nephrology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.
2. Assistant Professor, Department of Nephrology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.
3. Professor, Department of Nephrology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.
4. Associate Professor, Department of Pathology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.
5. Postgraduate Student, Department of Nephrology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Sai Sanketh Nethula,
200712, 6th Floor, Tower 20C, Prestige Bella Vista, Mount Poonamallee Road,
Porur, Iyyapanthangal, Chennai-600056, Tamil Nadu, India.
E-mail: sanketh77@gmail.com

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- Manual Googling: Aug 20, 2026
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