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Case reports in Frontiers in Nephrology

Edited by
Leopoldo Ardiles, Xuefei Tian and Clay Block

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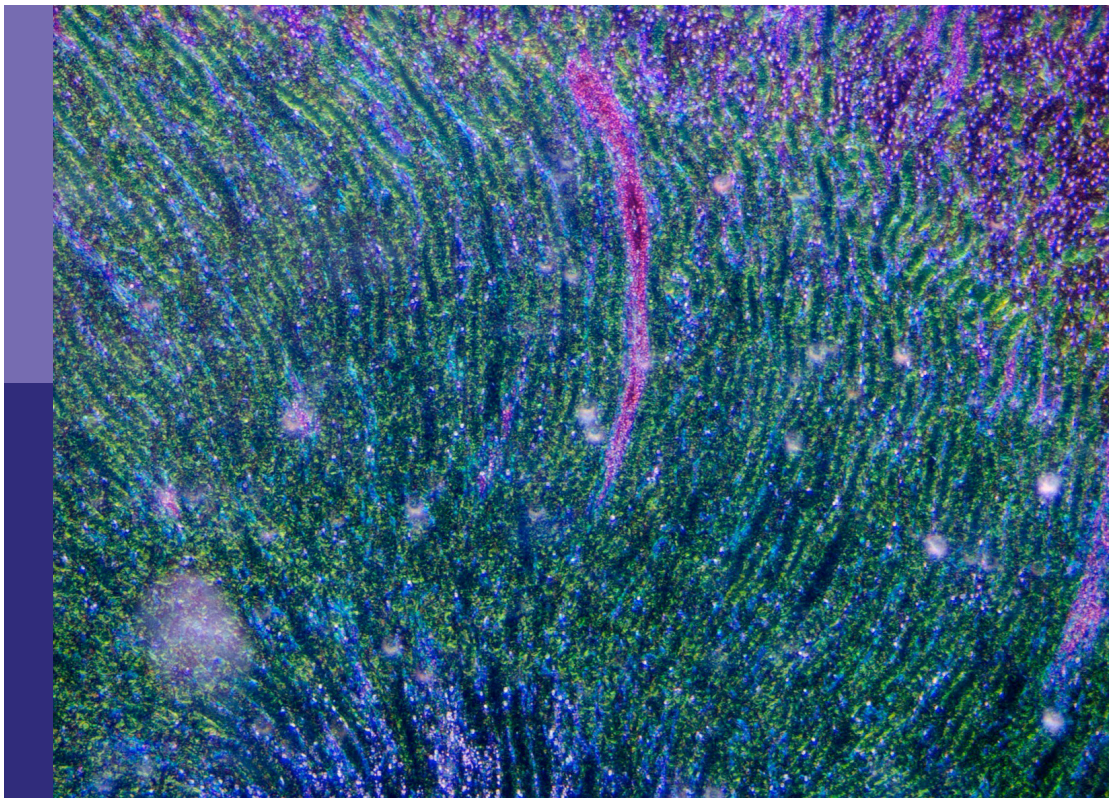

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Case reports in Frontiers in Nephrology

Topic editors

Leopoldo Ardiles — Universidad Austral de Chile, Chile

Xuefei Tian — Yale University, United States

Clay Block — Geisel School of Medicine, Dartmouth College, United States

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EDITED AND REVIEWED BY
Gert Mayer,
Innsbruck Medical University, Austria

*CORRESPONDENCE
Xuefei Tian
xuefei.tian@yale.edu
Leopoldo Ardiles
leopoldoardiles@gmail.com
Clay A. Block
clay.a.block@hitchcock.org

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Editorial: Case reports in nephrology

Xuefei Tian[1]*, Leopoldo Ardiles[2]* and Clay A. Block[3]*

[1]Section of Nephrology, Department of Internal Medicine, Yale School of Medicine, New Haven, CT, United States, [2]Laboratory of Nephrology, Faculty of Medicine, Universidad Austral de Chile, Valdivia, Chile, [3]Nephrology and Hypertension, Geisel School of Medicine at Dartmouth, Dartmouth Hitchcock Medical Center, Lebanon, NH, United States

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Editorial on the Research Topic
Case reports in nephrology

Introduction

Chronic Kidney Disease (CKD) has emerged as a critical public health challenge in the 21st century. According to the World Health Organization, approximately 850 million people globally are affected by kidney disease, with around 130 million suffering from End-Stage Kidney Disease (ESKD) requiring dialysis or kidney transplantation (1). By 2040, CKD is expected to become the fifth leading cause of reduced life expectancy worldwide. This crisis is particularly pronounced in developing countries, where 80% of ESKD patients reside, yet only 10% have access to dialysis or transplantation (2). Beyond its role in precipitating cardiovascular events and metabolic syndrome, CKD imposes a staggering socioeconomic burden, with global expenditures on kidney replacement therapy exceeding $1.5 trillion annually, far surpassing the costs for diabetes and cancer combined (3, 4).

Case reports, by their nature, tend to focus on extreme or rare conditions and would seem to be far removed from a CKD epidemic affecting millions. Osler considered it a duty for the physician to note and publish interesting cases so that similar cases could be recognized. There is now increasing recognition that investigation of the rare or extreme has additional value by generating new hypotheses and/or providing insight into common, but poorly understood pathophysiology (5, 6).

In this crucial context, the recent publication of ten case reports in "Frontiers in Nephrology" provides an essential perspective into the hidden mechanisms of rare kidney diseases and highlights the profound interconnection between clinical practice and translational research. Although we clinicians may not see these exact cases, they inspire us to be more energetic and curious when we encounter their "cousins."

Insights into rare and complex kidney diseases

Case reports often offer the first insights into rare kidney diseases. For instance, Kang et al. documented a case of polycystic kidney disease (PCKD) complicated by xanthogranulomatous pyelonephritis (XGP), highlighting the potential risk of cysts as infection foci. Despite the

absence of a history of urinary tract infection or stones, cysts can lead to urine stasis and bacterial colonization, resulting in granulomatous inflammation. This report suggests that structural kidney diseases such as PCKD and duplicated kidneys might be hidden etiological factors, a mechanism consistent with that proposed by Jang et al. as the "chronic obstruction-immune dysregulation" model (7). This underscores the necessity for enhanced imaging surveillance in patients with structural kidney diseases.

Diagnostic challenges and therapeutic interventions

Kidney diseases often present with non-specific symptoms, making diagnosis challenging. Zhang et al. reported three cases of emphysematous pyelonephritis (EPN), where one patient died due to treatment cessation by the family, while the other two were successfully treated surgically. All patients had diabetes with poor glycemic control, and the primary pathogen was *E. coli*. The authors emphasized the importance of CT diagnosis, antibiotic therapy, glycemic control, and timely surgical intervention. Zhang et al. provided a practical framework for EPN management, stressing CT-guided classification, early drainage, and nephrectomy of non-salvageable kidneys. However, this series also highlighted systemic challenges: small-scale studies hindering protocol standardization, speculative biomarker utility, and socio-cultural influences on outcomes. Future research should prioritize multi-center cohorts to improve risk scoring, evaluate laparoscopic versus open surgery, and explore the prognostic application of biomarkers like IL-6. Additionally, educating patients and families on the severity of EPN could mitigate premature treatment discontinuation.

Advanced diagnostics and multidisciplinary approaches

Leiva et al. highlighted the complexities in managing pregnancy-associated thrombotic thrombocytopenic purpura (TTP) in systemic lupus erythematosus (SLE) patients. With ADAMTS13 activity at just 6% and a "full-house" immunofluorescence pattern on kidney biopsy, the case underscored the intricate interplay between SLE and thrombotic microangiopathy (TMA). This case supports the 2020 International Consensus on TMA (8) and calls for developing pregnancy-safe TTP therapies. The patient's progression to ESKD highlights the chronic kidney damage mechanisms in SLE-associated TMA, necessitating lifelong nephrological monitoring.

Burbano et al. reported a fatal nephrobronchial fistula resulting from xanthogranulomatous pyelonephritis, emphasizing the aggressive nature of advanced XGP involving visceral fistulas. Utilizing enhanced CT and pathological correlations, the study stressed the need for multidisciplinary collaboration in managing complex infections. Despite adherence to standard treatment protocols (antibiotics and nephrectomy), the patient succumbed to multi-organ failure post-surgery. This case aligns with historical findings on XGP's aggressive nature, particularly with visceral fistulas, and suggests anatomical or pathophysiological differences worthy of further investigation.

Errabelli et al. presented a compelling case of pseudo-acute kidney injury (AKI) induced by the CDK4/6 inhibitor abemaciclib. This case highlighted the superior diagnostic capability of cystatin C in identifying renal tubular secretion dysfunction. Their findings directly support the "biomarker stratified diagnostic process" proposed by Vanhoutte et al. (9). They recommend prioritizing cystatin C over serum creatinine to assess kidney function in patients using renal tubular secretion inhibitors.

Genetic insights and personalized medicine

Case reports provide critical evidence for genotype-phenotype correlations in hereditary kidney diseases. Krall et al. identified an *NPHS1* mutation (p.R711S) in the Māori population, presenting a milder disease course compared to the Finnish-type congenital nephrotic syndrome (CNS). This observation suggests that genetic background may influence disease trajectories by retaining some nephrin function or activating compensatory pathways, offering new insights for *NPHS1* genotype-phenotype correlations and gene therapy (10).

Paladugu and Vukkadala discussed compound heterozygous *SLC2A9* variants in South Asian patients with Renal Hypouricemia Type 2 (RHUC2), highlighting the genetic diversity within this group. Integrating whole genome sequencing (WGS) with clinical phenotyping, the study validated the pivotal role of genetic testing in atypical presentations such as low-intensity exercise-induced acute kidney injury (AKI), in alignment with guidelines by Nakayama et al (11). The management strategy emphasized conservative treatment efficacy and called for multi-center clinical trials to evaluate the potential of xanthine oxidase inhibitors in RHUC2. By openly sharing genomic data, the authors promoted global collaborative research on rare kidney diseases.

Ignacio Alarcón et al. reported a novel *ACTN4* gene mutation (c.625_633del), contributing new data to the genetic basis of steroid-resistant nephrotic syndrome. The authors utilized a comprehensive diagnostic approach, integrating clinical history, laboratory tests, imaging studies, kidney biopsy, and whole-exome sequencing. Initially classified as a "variant of uncertain significance" (VUS), the mutation was eventually reclassified as "likely pathogenic." Although there was no recurrence five months post-transplantation, the lack of long-term follow-up data and functional validation experiments highlighted the need for more robust follow-up systems and detailed molecular mechanism studies in hereditary kidney disease research.

Medication safety and toxicity

Case reports play a pivotal role in drug safety monitoring. Zhang et al. detailed a roxadustat overdose, revealing significant short-term hemoglobin elevation followed by a stealthy rise in

serum creatinine over nine months, indicating potential long-term risks. This case enhances toxicological literature on HIF-PHI, underscoring the need for vigilance even with seemingly "safe" overdoses, balancing therapeutic efficacy with potential uncertainties.

Alamilla-Sanchez et al. reported on platinum-induced distal tubular damage, challenging the traditional view of proximal tubular nephrotoxicity predominance. Using urinary calcium-creatinine ratio and fractional excretion of magnesium, the study distinguished Bartter-like from Gitelman-like phenotypes, suggesting a genetic susceptibility hypothesis for chemotherapy-induced nephrotoxicity. This aligns with Nozu et al.'s hereditary tubulopathies classification (12), indicating the need for routine distal tubular function monitoring in chemotherapy patients.

Future directions and broader implications

While case reports are clinically significant, their limitations are apparent. Case reports' inherent evidence level (CEBM Level 4) makes establishing causality challenging. Many case reports remain primarily observational, relying on subsequent studies for mechanism elucidation. Translational research depends on deep collaboration between clinicians and basic scientists, exemplifying "bedside-to-bench" team models. Emerging technologies like patient-specific organoids enable the direct validation of drug toxicity mechanisms *in vitro* (13).

Conclusion

Case reports embody the synthesis of medical humanities and scientific rigor. From precise categorization of pregnancy-associated TTP to expanding etiologies of PCKD complicated by XGP, and from redefining platinum nephrotoxicity mechanisms to delineating population-specific genetic variants, these reports are not merely academic annotations but engines of scientific advancement. They document clinical practice's puzzles and epiphanies, illustrating the interweaving of individual destinies with medical inquiry. Each meticulously documented case may unlock secrets that ultimately redefine medical textbooks. The wisdom garnered from case reports will ultimately catalyze changes in clinical practice. Through this continued accumulation, case reports will harness the necessary force to transform patient care, driven by scientific curiosity and human warmth, paving the way for new horizons in nephrology.

Author contributions

XT: Writing – review & editing, Conceptualization, Writing – original draft. LA: Writing – review & editing, Conceptualization. CB: Writing – review & editing, Conceptualization.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Vincenzo Montinaro,
Ospedale Generale Regionale Francesco Miulli, Italy

REVIEWED BY
Anna Zito,
Ospedale Vito Fazzi, Italy
Bianca Covella,
Ospedale Generale Regionale Francesco Miulli, Italy

*CORRESPONDENCE
Leopoldo Ardiles
leopoldoardiles@gmail.com

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Case report: Thrombotic thrombocytopenic purpura in a pregnant woman with lupus membranous nephropathy: a diagnostic challenge

Marina Leiva[1], Gustavo Navarro[2], J Daniel Carpio[3] and Leopoldo Ardiles[2]*

[1]Department of Nephrology, Hospital Intercultural de Nueva Imperial, Nueva Imperial, Chile, [2]Laboratory of Nephrology, Institute of Medicine, Faculty of Medicine, Universidad Austral de Chile, Valdivia, Chile, [3]Institute of Anatomy, Histology and Pathology, Faculty of Medicine, Universidad Austral de Chile, Valdivia, Chile

A 27-year-old female at 20th week of pregnancy was admitted with edema, foamy urine, but normal blood pressure. Her blood count was normal, she had proteinuria of 3 g/day, creatinine 0.4 mg/dl, albumin 2.4 g/dl, and cholesterol 355 mg/dl. Antinuclear antibodies 1/160, but Anti-DNA, anticardiolipin antibodies and lupus anticoagulant were negative, with normal serum C3 and C4. A renal biopsy showed secondary membranous glomerulopathy, most likely lupus class V pure. Steroids, azathioprine, and aspirin were initiated, up to 28 weeks of pregnancy, when she developed severe hypertension, photopsia, headache, anasarca, extensive bruising of the extremities, severe anemia, thrombocytopenia, and creatinine rose to 2.09 mg/dl with preserved diuresis. A female infant, 1045 grams, was delivered by emergency caesarean section. Following the surgery, she experienced diplopia, dysarthria, bradypsychia, and sensory alterations in the lower extremities, necessitating emergency hemodialysis due to pulmonary congestion. Blood smear revealed schistocytes, LDH elevated at 1148 IU/L, while transaminases and liver function remained normal, suggesting thrombotic thrombocytopenic purpura. ADAMTS13 revealed 6% activity with the presence of inhibitor. Mycophenolate and daily plasmapheresis with fresh frozen plasma replacement yielded unsatisfactory response, unaffected by the addition of methylprednisolone pulses and rituximab. Eventually, intravenous cyclophosphamide was introduced, resulting in complete hematological remission and normalization of ADAMTS13, however dialysis-dependence persisted and four years later, right renal cancer prompted bilateral nephrectomy. After a total follow-up of six years, she remained free of neoplastic recurrence and lupus activity, receiving prednisone and hydroxychloroquine. The differential diagnosis of microangiopathic syndrome in a pregnant lupus patient is discussed.

KEYWORDS

thrombocytopenia, microangiopathic anemia, lupus (SLE), acute kidney injury, ADAMST 13

Introduction

Thrombotic microangiopathy (TMA) is a potentially serious condition characterized by endothelial cell injury. Diagnosis is primarily based on clinical and biological data, which typically involve a classic triad of peripheral thrombocytopenia, mechanical hemolytic anemia, and organ dysfunction, especially in the central nervous system (e.g., altered consciousness, seizures), the kidneys (e.g., acute kidney injury), and the heart (1). TMA is identified by detecting a low platelet count, decreased hemoglobin levels, raised lactate dehydrogenase (LDH) serum levels, undetectable serum haptoglobin, negative direct erythrocyte antiglobulin test, schistocytes in blood smears, or the demonstration of TMA characteristics in kidney or other organ biopsies (1).

Pregnancy and postpartum are high-risk periods for various forms of thrombotic microangiopathy (TMA) with a range of causative factors. These can be classified into two categories: those exclusively observed during pregnancy (e.g. preeclampsia) and those that can also occur in nonpregnant individuals, but pregnancy acting as a trigger. Although clinical overlap exists, management strategies differ considerably (2).

The primary causes of TMA in pregnancy are preeclampsia (PE)/eclampsia and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. These conditions are interrelated but differ in presentation and severity. Acute fatty liver disease, hemolytic uremic syndrome (HUS; a condition where the kidneys are predominantly affected), and thrombotic thrombocytopenic purpura (TTP; with predominant hematological and neurological involvement) are less common. It can be present in severe autoimmune diseases, especially systemic lupus erythematosus (SLE) and catastrophic antiphospholipid syndrome (CAPS) (1).

The approach to pregnancy-related thrombotic microangiopathy (TMA) includes two main objectives. The first is to conduct an immediate ADAMTS13 activity test to confirm or rule out TTP, due to its potential life-threatening risks. The second is the prompt diagnosis of complement-mediated atypical hemolytic uremic syndrome (aHUS) in order to initiate specific treatment (1).

TMA in pregnancy constitutes a medical emergency, with delays in diagnosis and treatment resulting in potentially life-threatening consequences. Maternal complications encompass a range of adverse outcomes such as renal failure, seizure, stroke, pulmonary edema, disseminated intravascular coagulation (DIC), requiring blood transfusion, ICU admission, and mortality. Timely decision-making could be hindered due to the presence of overlapping clinical features and diagnoses across multiple disciplines, such as Hematology, Nephrology, and Maternal Fetal Medicine. Given the causal variability and the incomplete clarity of the specific pathogenic mechanisms in each of the clinical entities responsible for TMA in pregnancy, diagnosing and treating the condition is still challenging (3).

Case report

A 27-year-old woman, previously in good health and 20 weeks into her pregnancy, had normal blood pressure and routine check-ups during her prenatal care at primary health facilities. However, one week prior to hospitalization, she was showing symptoms of edema in her extremities and foamy urine. Upon admission, the patient exhibited a blood pressure of 124/68 mmHg, a heart rate of 80 bpm, and a fetal heartbeat of 140 bpm, alongside severe edema of the lower extremities. The laboratory tests indicated normal blood count, proteinuria of 3 g/24 hours, creatinine of 0.4 mg/dl, uric acid 4.3 mg/dl, albumin of 2.4 g/dl, and total cholesterol of 355 mg/dl. The antinuclear antibodies were positive at a rate of 1/160, while anti-DNA, C3, and C4 complement factors were normal, and the IgG and IgM anticardiolipin antibodies and lupus anticoagulant were negative. A pure nephrotic syndrome was diagnosed, antibodies to the phospholipase A2 receptor (PLA2R) resulted negative and a renal biopsy was performed revealing 1 out of 4 globally sclerotic glomeruli with thickened membranes, mesangial proliferation, protein reabsorption drops in tubules, scant lymphocytic infiltrate, tubular atrophy, and discrete interstitial fibrosis (Figure 1). Immunofluorescence demonstrated a full-house pattern positivity for IgG, IgM, IgA, C3, C1q, fibrinogen, kappa, and lambda light chains, in addition to an IgG weak antinuclear antibody-type extraglomerular reaction (Figure 2). Electron microscopy confirmed the existence of significant, continuous subepithelial, mesangial and subendothelial electrodense deposits also (Figure 1), which were associated with an increase in mesangial matrix and cells. These findings suggested that the patient was experiencing a secondary membranous glomerulopathy, possibly caused by lupus, specifically pure class V; therefore, corticosteroid therapy, azathioprine and hydroxychloroquine, combined with aspirin, were initiated. During the 28th week of pregnancy, she experienced severe hypertension, photopsia and headache, anasarca, extensive bruising of the extremities, severe anemia, and thrombocytopenia. These symptoms were accompanied by a rise in serum creatinine up to 2.09 mg/dl, and elevation of uric acid to 8.0 mg/dl, although diuresis was preserved. Suspecting severe preeclampsia, an infusion of magnesium sulfate was initiated, and an emergency caesarean section was performed, resulting in the birth of a female infant weighing 1045 grams, appropriate for gestational age. During the post-surgery period, the patient exhibited diplopia, dysarthria, bradypsychia, and sensory changes in their lower limbs, with renal impairment necessitating urgent hemodialysis due to pulmonary congestion. The complete blood count revealed schistocytes and an LDH value of 1148 IU/L, with normal transaminases as well as preserved liver function and coagulation tests, normalizing uric acid levels to 4.1 mg/dl. The suspected diagnosis was thrombotic thrombocytopenic purpura (TTP), for which a functional test was conducted to determine the activity of A Disintegrin And Metalloprotease with ThromboSpondin type 1 repeats 13 (ADAMTS13) that showed only 6% activity (normal values ranging from 41-180%) with the presence of an inhibitor (titer not determined). Sodium mycophenolate at a dose of 1 g every 12 hours was initiated, and daily plasmapheresis was conducted with replacement of fresh frozen plasma. However, due to an inadequate response, pulses of methylprednisolone and Rituximab (375 mg/m2) were commenced every week for four weeks while maintaining daily plasmapheresis until 30 sessions were completed.

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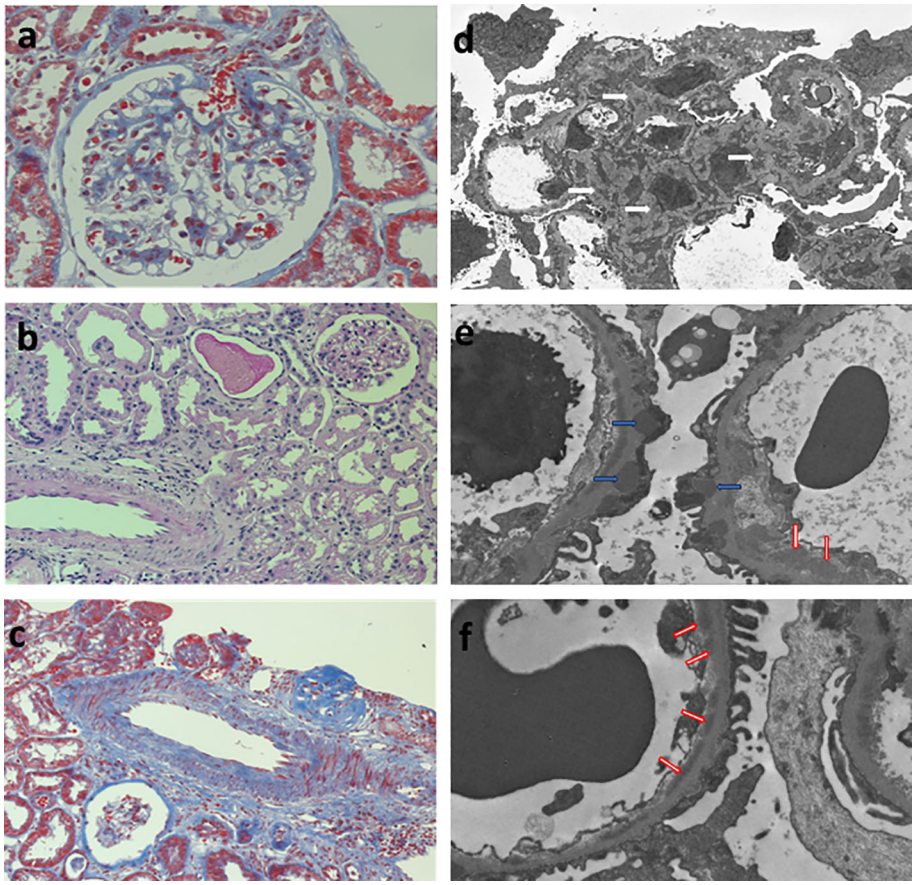

FIGURE 1
Renal biopsy. Left column, light microscopy: **(A)** glomerulus showing mild thickenning of the capillary walls and mesangial hypercelularity (Periodic Acid-Schiff Stain 400x), **(B)** normal tubulointerstitial compartment (Periodic Acid-Schiff Stain 200x), **(C)** normal médium size artery (Masson´s trichromic stain 200x). Right column, glomerular inmune deposits in **(D)** mesangial (white arrows), **(E)** subepithelial (blue arrows), and **(F)** subendothelial (red arrows) localization.

Nonetheless, the patient continued to suffer from severe anemia and thrombocytopenia. Therefore, the treatment was altered to include intravenous cyclophosphamide (three doses of one gram), resulting in complete hematological remission, normalization of anemia, stable platelet counts, and a return to normal ADAMST13 activity (200%) with disappearance of the inhibitor; however, dialysis-dependent renal failure remained persistent (Figure 3).

Four years later, while on stable hemodialysis and undergoing evaluation for kidney transplant candidacy, an ultrasound of the abdomen revealed a mixed solid and cystic tumor measuring 96 x 85 mm in the right kidney. This finding was confirmed by contrast-enhanced computed tomography, which further characterized the lesion as nodular with central necrosis, as well as demonstrating an atrophic appearance and multiple cystic formations in the left kidney. A successful bilateral laparoscopic radical nephrectomy was carried out without any complications, revealing the presence of clear-cell renal carcinoma. In the left kidney, where the renal biopsy was conducted, the findings were indicative of chronic sclerosing nephritis with fibro-cellular crescents and chronic tubulointerstitial involvement, along with moderate to severe arteriosclerosis and arteriolosclerosis. After six years of follow-up, the patient remains on hemodialysis, and there is no evidence of neoplastic disease or lupus activity recurrence; the patient is taking 2.5 mg prednisone and 200 mg hydroxychloroquine.

Discussion

This case exemplifies the challenges in distinguishing a microangiopathic syndrome in a pregnant, formerly healthy young woman, who had recently been diagnosed with lupus, initially affecting only the kidneys not distressing the pregnancy itself, as evidenced by an appropriate fetal growth.

The presence of mesangial proliferation observed in optic microscopy, the full house pattern and antinuclear staining in tubular cells at direct immunofluorescence, and the presence of immune deposits in electron microscopy, including large continuous subepithelial, mesangial, and subendothelial deposits, were suggestive of a secondary etiology for the renal lesion (4). Antinuclear antibodies at an abnormal level, even with negative anti-DNA antibodies and normal serum complement C3 and C4 levels, is a common finding in pure membranous (class V pure) lupus nephropathy (4). While no specific antigen (5) was identified as the cause of the glomerular lesion, the clinical presentation,

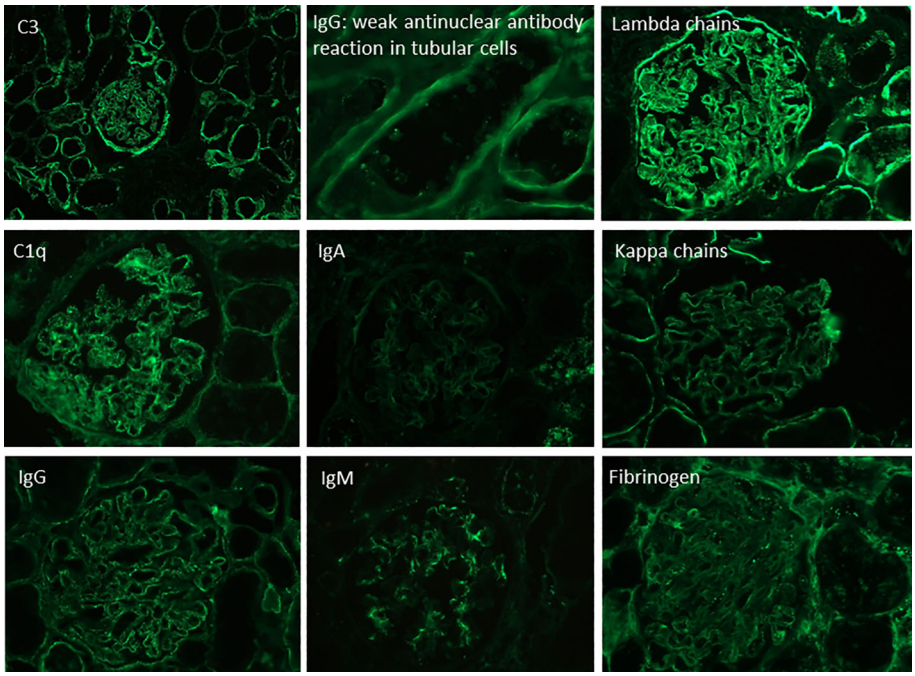

FIGURE 2
Direct immunofluorescence in frozen renal tissue showing a "full house" pattern.

histological features, full-house pattern of immunofluorescence, ultrastructural findings, and subsequent progression strongly support the lupus etiology.

By the 28th week of pregnancy, severe hypertension and neurological symptoms appeared, along with evidence of a microangiopathic syndrome. The most likely diagnosis, based on frequency, was the most severe form of eclampsia, the HELLP syndrome (6), however, our patient's liver enzymes were normal, and the onset of symptoms was somewhat early.

The normality of liver tests, including the absence of jaundice, normal levels of fibrinogen and prothrombin, and the early onset of anemia and thrombocytopenia, suggested that the possibility of an acute fatty liver was unlikely (6, 7). Systemic viral infections, such as disseminated herpes simplex, are exceedingly rare during pregnancy and typically presents during the 3rd trimester without signs of hypertension and is primarily associated with liver-related symptoms (8). VIH (9) was not detected, and the hemodynamic profile was not consistent with septic shock either (10). Given the presence of lupus, the potential for secondary catastrophic antiphospholipid syndrome (11) could not be ignored; however, both anticardiolipin antibodies and lupus anticoagulant factor were found to be absent. The range of thrombotic microangiopathies as a complication of lupus is wide, spanning from laboratory changes without clinical significance or incidental findings in renal biopsies,

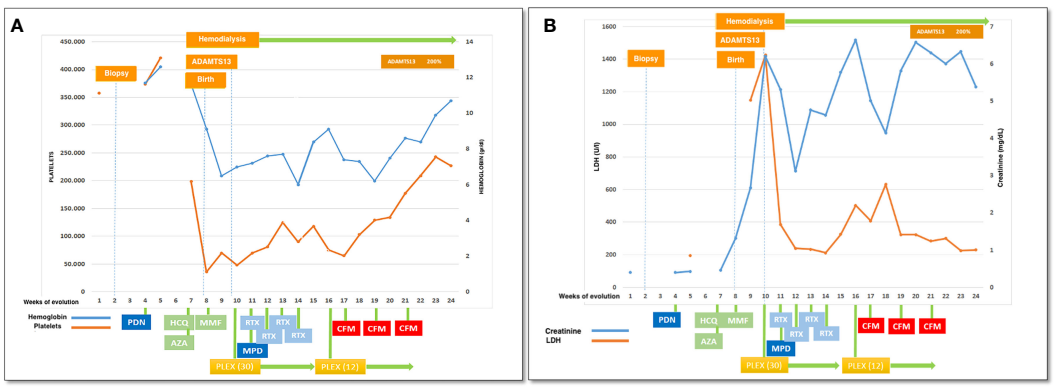

FIGURE 3
Clinical evolution: **(A)** platelets and hemoglobin, **(B)** LDH and creatinine in relationship with therapeutical interventions. PDN, prednisone; HCQ, hydroxychloroquine; AZA, azathioprine; MMF, mycophenolate mophetil; PLEX, plasma exchange (number of sesiones); RTX, rituximab; CFM, cyclophosphamide iv pulses.

to antiphospholipid syndrome or the severe condition of immune-acquired TTP (iTTP) with reduced ADAMST13 activity (12). Indeed, in lupus it is possible to demonstrate antibodies against ADAMTS13 that cannot reduce its activity suggesting that the effectiveness of the antibody and the molecule domain it targets may play a role (13). On the other hand, renal microangiopathic complications are not frequent in pure membranous lupus nephropathy (14). Taking into account all the above, iTTP is life-threatening and requires a combined therapy, including plasmapheresis to remove the antibody and intensive immunosuppression to reduce its production.

The only medication utilized by the patient that may be associated with thrombotic microangiopathy (TMA) was hydroxychloroquine (15), a derivative of quinine, that has not caused a reoccurrence of the phenomenon, even with ongoing use to date.

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are highly uncommon microangiopathic disorders during pregnancy and postpartum (< 1/100000 pregnancies) and, typically, these conditions are reported as either case reports or small case series (6). The pathophysiological basis of these syndromes entails platelet aggregation in the arteriolar and capillary walls, coupled with endothelial injury. Pregnancy-associated hemolytic uremic syndrome (HUS) is a subtype of atypical HUS that manifests more commonly during the postpartum period (16). TTP is a rare condition linked to either an inherited or acquired deficit of ADAMST13, a molecule involved in the cleavage of von Willebrand factor to prevent the survival of sizable multimers that cause a rise in thrombosis and platelet usage in the microvascular network (17). Our patient had severely reduced ADAMST13 activity due to an inhibitor, which was resolved in parallel with the clinical resolution of TMA symptoms, ruling out a genetic or persistent deficiency. The diagnosis of HUS *vs* TTP is typically determined based on the frequent renal complications of HUS and the common neurological symptoms of TTP; nonetheless, overlap between the two disorders is not uncommon (18). In this case, the help of the ADAMST13 information favored TTP, even though an eventual histological change in the renal involvement of her lupus could explain the severe renal damage the patient was facing. Obtaining a new renal histology would have been useful, but the procedure was not feasible due to the patient's condition.

During pregnancy, the maternal-placental immune tolerance phenomenon produces an unresponsive state while maintaining immune system competence. This is accomplished through an increase in innate immunity and a reduction in adaptive immunity (19); when complement dysregulation is present, pregnancy acts as an additional trigger for complement-related disorders.

Initially, therapy was empiric, pending test results, and included plasmapheresis as essential to control thrombotic thrombocytopenic purpura. Upon obtention of the ADAMST13 study results showing a low, inhibitor-dependent, activity, the notion of the presence of severe lupus with autoimmune activity against ADAMST13 was solidified; consequently, the use of cyclophosphamide was validated as a viable solution. But biomarkers may not be available in all facilities and consequently, clinical scores have been formulated for evaluating hospitalized adults suspected of having TTP to determine if the early installation of plasma exchange is warranted while waiting for lab results (20); these clinical tools deserve a validation for their use during pregnancy (21).

It must be acknowledged that an efficient immunosuppressive induction of remission was impossible due to the pregnancy, which limited treatment to steroids and azathioprine, explaining why autoimmune activity persisted, included the production of the ADAMST13 inhibitor. This antibody, at the very least, played a role in causing the microangiopathic phenomenon. Antigen-antibody immune complexes of ADAMTS13 and anti-ADAMTS13 have the potential to activate the classical complement pathway (22).

One could speculate some relationship between the appearance of renal carcinoma and complement dysfunction, given the action of the latter on the immune cells, on the cancer cells and also action on angiogenesis (23), however, assuming the functional alteration was transient, it seems unlikely.

The oncogenic power of immunosuppressive therapy is another possible link between renal cancer and the patient's initial disease. Although mycophenolate mofetil is generally considered safe for use in transplantation therapy (24) cyclophosphamide is an alkylating drug that can cause DNA changes leading to cytotoxicity and mutagenic effects that cannot be repaired if high doses are used for prolonged periods of time, especially in older patients (25); but this is not the case of our patient.

But the presence of neoplasia does not prohibit our patient from undergoing a future transplant. With the demonstration of an inhibitor of ADAMST13, the likelihood of TMA recurring in a subsequent transplant seems unlikely, given sufficient immune suppression. Currently, our center lacks genetic studies on alterations of the complement pathway; however, as the patient desires transplantation once free of tumor disease, we will make efforts to obtain a complete genetic study to assess the risk of recurrence and to evaluate the use of preventive therapy.

The mother's life was saved through emergency treatment that was based on adequate clinical suspicion and confirmed by an accurate exploratory process. Regrettably, it failed to rescue the child and did not restore the mother's kidney function. In a catastrophic scenario such as the one depicted for this patient, objective biomarkers (such as ADAMST13) are crucial for supporting complex therapies.

Data availability statement

The datasets for this article are not publicly available due to concerns regarding participant/patient anonymity. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the patient for the publication of this case report.

Author contributions

ML: Formal Analysis, Validation, Writing – original draft, Writing – review & editing, Data curation. GN: Data curation, Formal Analysis, Writing – review & editing, Conceptualization, Investigation, Visualization. JC: Data curation, Visualization, Writing – review & editing. LA: Conceptualization, Formal Analysis, Investigation, Visualization, Writing – review & editing, Methodology, Supervision, Validation, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Clay Block,
Dartmouth College, United States

REVIEWED BY
Khaled Boubes,
The Ohio State University, United States
Xiangchen Gu,
Shanghai University of Traditional Chinese Medicine, China

*CORRESPONDENCE
Mario Alamilla-Sanchez
silenoz1@hotmail.com

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Chemotherapy-induced tubulopathy: a case report series

Mario Alamilla-Sanchez*, Juan Daniel Diaz Garcia, Valeria Yanez Salguero, Fleuvier Morales Lopez, Victor Ulloa Galvan, Francisco Velasco Garcia-Lascurain and Benjamin Yama Estrella

Department of Nephrology, November 20 National Medical Center (CMN), Mexico City, Mexico

Acquired tubulopathies are frequently underdiagnosed. They can be characterized by the renal loss of specific electrolytes or organic solutes, suggesting the location of dysfunction. These tubulopathies phenotypically can resemble Bartter or Gitelman syndrome). These syndromes are infrequent, they may present salt loss resembling the effect of thiazides (Gitelman) or loop diuretics (Bartter). They are characterized by potentially severe hypokalemia, associated with metabolic alkalosis, secondary hyperaldosteronism, and often hypomagnesemia. Tubular dysfunction has been described as nephrotoxic effects of platinum-based chemotherapy. We present 4 cases with biochemical signs of tubular dysfunction (Bartter-like/Gitelman-like phenotype) related to chemotherapy.

KEYWORDS

tubulopathy, electrolyte abnormalities, onconephrology, platinum, nephrotoxicity

Background

The differential diagnosis of non-proximal tubulopathies (thick ascending loop of Henle and convoluted distal tubule) is closely related to serum potassium concentrations, acid-base status, and blood pressure (1–4). The patient's biochemical phenotype may exhibit any of the following patterns (see Table 1) (3, 4):

1. Hypochloremic metabolic alkalosis, hypokalemia, norm/hypotensive:
   a) Bartter syndrome.
   b) Gitelman syndrome.
   c) EAST/SeSAME syndrome.
   d) Helix syndrome.
2. Hypochloremic metabolic alkalosis, hypokalemia, arterial hypertension:
   a) Liddle's syndrome.
   b) Apparent excess of mineralocorticoids.
3. Hyperchloremic metabolic acidosis, hyperkalemia, normo/hypotension arterial:
   a) Pseudohypoaldosteronism type 1.

TABLE 1 General characteristics of the main distal tubular syndromes.

Syndrome	Molecule and affected site	Potassium	Acid base status	Blood pressure	Others
Bartter	TAL: NKCC2, ROMK, ClC-Ka/b, Barttin, MAGED2	↓	Alkalosis	=/↓	↑ uCa, ↓/= sMg
Gitelman	DCT: NCC	↓	Alkalosis	=/↓	↓ uCa, ↓ sMg
EAST/ SeSAME	DCT: Kir4.1	↓	Alkalosis	=/↓	↓ uCa, ↓ sMg, neurological symptoms
Liddle	CD: ENaC	↑	Acidosis	↑	---
AME	CD: 11β-HSD2	↓	Alkalosis	↑	Growth retardation
PHA-1	CD: ENaC	↑	Acidosis	=/↓	CF-like pulmonary symptoms (AR) Remission after early childhood (AD)
Gordon (PHA-2)	CD: WNK, KLHL, Cul3	↑	Acidosis	↑	Gitelman's "Mirror Syndrome"
dRTA	CD: H V-ATPase, AE1	=/↓	Acidosis	=	↓ uNH4

AME, Apparent mineralocorticoid excess; PHA, Pseudohypoaldosteronism; dRTA; Distal renal tubular acidosis; TAL, Thick ascending limb; DCT, Distal convoluted tubule; CD, Collecting duct; uCA, Urinary calcium; sMg, serum magnesium; CF, Cystic fibrosis; AR, Autosomal recessive; AD, Autosomal dominant; uNH4, urinary ammonium.
= normal. ↑high. ↓low.

4. Hyperchloremic metabolic acidosis, hyperkalemia, arterial hypertension:
    a) Pseudohypoaldosteronism type 2 (Gordon syndrome).
5. Hyperchloremic metabolic acidosis, hypo/hyperkalemia, normotension:
    a) Distal renal tubular acidosis.

Therefore, the examination of urinary concentrations of potassium, chloride, magnesium, and calcium is extremely useful in the differential diagnosis of suspected tubulopathy. We present a series of 4 cases with association of tubulopathies directly related to chemotherapy.

Case presentation

Case 1

A 46 years-old female, with a history of gastric cancer, presented to the emergency department (ED) experiencing progressive muscle weakness and syncope. On admission, no electrocardiographic abnormalities were detected, blood pressure (BP) 122/85 mmHg, heart rate (HR) 84 bpm, Glasgow Coma Scale (GCS) score of 15 points, afebrile. She reported polyuria without dysuria, and diffuse abdominal pain. Cardiopulmonary examination revealed normal findings, with no signs of peripheral edema or hypovolemia. Two weeks before admission, she had completed her last cycle of chemotherapy with oxaliplatin.

Biochemical analysis

Serum creatinine 0.42 mg/dL, sodium 138 mEq/L, potassium 2.78 mEq/L, chloride 105 mmol/L, calcium 7.8 mg/dL, phosphorus 3.8 mg/dL, magnesium 1.1 mg/dL. The following urinary parameters were obtained: urinary calcium-to-creatinine ratio (uCa/uCr) 0.4 mg/mg, potassium 86.8 mEq/L, chloride 56 mEq/L, urinary potassium-to-creatinine ratio (uK/uCr) 200 mEq/g, fractional excretion of magnesium (FEMg) 6%. Venous blood gas: pH 7.53, pCO2 39 mmHg, HCO3 30.7 mmol/L, lactate 1 mmol/L, iCa 0.8 mmol/L. Ultrasound with kidneys of normal size, without nephrocalcinosis. These data reveal renal losses of potassium and magnesium, with hypercalciuria, without evidence of chloride depletion, and evidence of a mixed acid-base disorder: metabolic alkalosis with mild respiratory alkalosis.

Follow-up

An upper endoscopy, prompted by abdominal pain, revealed a gastric tumor that partially obstructed the lumen without active bleeding. Computed tomography evidences multiple ganglia in the retroperitoneum without evidence of urinary tract obstruction. Echocardiography was normal and the syncope was linked to electrolyte disturbance-induced arrhythmia. Oral therapy was prescribed with magnesium and potassium supplements and once the electrolyte disturbances resumed the patient was discharged from the hospital. Upon returning for a follow-up in the outpatient nephrology clinic, mild hypokalemia with normomagnesemia was found. However, due to slight dyspepsia secondary to the potassium supplements, it was decided to add 100 mg of spironolactone daily, resulting in the normalization of electrolytes with suspension of treatment after three months.

Case 2

A 67-year-old male, diagnosed four years ago with diffuse large B-cell non-Hodgkin lymphoma, with a history of autologous hematopoietic stem cell transplantation and received the last dose of the 3rd cycle of R-DHAP (rituximab, cisplatin,

dexamethasone, cytarabine). He presented to the ED due to intense muscle weakness and fatigue. Cardiopulmonary examination revealed normal findings. BP: 100/65 mmHg, HR: 98 bpm, GCS: 15 points, 36°C. Physical assessment showed slightly diminished deep patellar tendon reflexes, with no signs of neurological focalization.

Biochemical analysis

Serum creatinine of 0.92 mg/dL, sodium 145 mEq/L, potassium 2.9 mEq/L, calcium 8.7, phosphorus 1.8, magnesium 1.9 mg/dL. In urinary biochemistry, the following values were found: uCa/uCr 0.01 mg/mg, potassium 7.3 mEq/L, chloride 133 mEq/L, uK/uCr 40 mmol/gr, FEMg 4%. Venous blood gas: pH 7.48, pCO2 37 mmHg, HCO3 29.0 mmol/L, lactate 1.8, iCa 1.07 mmol/L. Renal ultrasound revealed normal kidneys. These data reveal renal losses of potassium and magnesium, with hypocalciuria, no chloride depletion, and mixed metabolic/respiratory alkalosis.

Follow-up

The exclusion of recent administration of diuretics, proton pump inhibitors, laxatives, or any dietary supplement has been confirmed. Treatment was initiated with oral supplementation with potassium and magnesium salts, leading to a gradual normalization of electrolytes. Given the unfavorable prognosis associated with the underlying pathology, the hematology department opted for a referral to palliative care. Unfortunately, the patient was lost to follow-up.

Case 3

A 58-year-old female with squamous cell cancer affecting the middle third of the esophagus underwent endoscopic placement of a metallic prosthesis eight months ago. She received concomitant treatment involving 21 cycles of radiotherapy and four months of chemotherapy with cisplatin. The onset of symptoms occurred a few hours after the last administration of cisplatin, four days before admission. On admission to ED she exhibited generalized weakness, mild bilateral leg edema and progressively hindering her ability to walk. Normal vital signs. BP 130/75 mmHg, HR 89 rpm, GCS 15 points, afebrile.

Biochemical analysis

Serum creatinine 0.31 mg/dL, sodium 137 mEq/L, potassium 2.2 mEq/L, calcium 8.8 mg/dL, phosphorus 4.2 mg/dL, magnesium 0.8 mg/dL. Urinary analysis revealed: uCa/uCr 0.01 mg/mg, potassium 77 mEq/L, chloride 23 mEq/L, uK/uCr 39 mEq/gr, FEMg 26%. Venous blood gas: pH 7.53, pCO2 38 mmHg, HCO3 31.1 mmol/L, lactate 0.9 mmol/L, iCa 1.23. Renal ultrasound revealed normal kidneys. These data reveal renal losses of potassium and magnesium, with hypocalciuria, no chloride depletion, and mixed acid-base disturbance with metabolic alkalosis and respiratory alkalosis.

Follow-up

The initial treatment involved intravenous replacement of potassium and magnesium, followed by a transition to oral supplementation. At discharge, the regimen included potassium salts, spironolactone at 100 mg OD, and magnesium tablets, with gradual normalization of electrolytes and acid-base disturbances. Due to the poor prognosis of esophageal cancer, palliative care was incited. One month later subsequent follow-up at the outpatient nephrology clinic confirmed normal serum electrolyte level and the supplements were suspended. Unfortunately, the patient died shortly after.

Case 4

A 38-year-old female patient with a history of left ovarian dysgerminoma began chemotherapy with BEP (Bleomycin, Etoposide, and Cisplatin), completing five cycles. However, due to cancer recurrence, a second line of therapy with a TIC regimen (Paclitaxel, Ifosfamide, and Carboplatin) was started. During her fifth cycle, routine biochemical analysis revealed various electrolytic imbalances leading to referral to the nephrology department. The patient was asymptomatic. BP 100/60, HR 79, GCS 15 points, 36°C, remaining physical examination was normal.

Biochemical analysis

Serum creatinine 0.63 mg/dL, sodium 142 mEq/L, potassium 3 mEq/L, calcium 9.1 mg/dL, phosphorus 3.8 mg/dL, magnesium 0.88 mg/dL. In the 24-hour urine collection: uCa/uCr 0.37 mg/mg, potassium 87 mEq/L, chloride 34 mEq/L, uK/uCr 43.3 mEq/gr, FEMg 7%. Venous blood gas: pH 7.49, pCO2 38 mmHg, HCO3 30.7 mmol/L, lactate 1.7 mmol/L, iCa 1.18 mmol/L. Renal ultrasound revealed normal kidneys. These data reveal renal losses of potassium and magnesium, with hypercalciuria, no chloride depletion, and mixed metabolic alkalosis with mild respiratory alkalosis.

Follow-up

The patient received oral therapy for the electrolyte disorder. Normalization of potassium and magnesium was evident a few weeks later after dose adjustments, but she continued with low-dose oral supplementation of potassium/magnesium 12 months after diagnosing tubular dysfunction, without receiving more doses of platinum-based chemotherapy.

The biochemical characteristics of the four reported cases are summarized in Table 2.

Discussion

Nephrotoxicity can be defined as any kidney damage caused directly or indirectly by medications. Some examples of commonly associated drugs include nonsteroidal anti-inflammatory drugs, antibiotics, and chemotherapeutic agents (5, 6). Epidemiological studies show that nephrotoxicity is the third most common cause

TABLE 2 Comparison of the 4 cases presented.

Case	Biochemical tubulopathy phenotype	Platinum-based chemotherapy	Electrolyte and acid base disturbances	Urinary ratio and fractional excretion	Tubulopathy status after platinum suspension
1	Bartter-like	Oxaliplatin	↓ sK, ↓ sMg, ↓ sCa Metabolic alkalosis	↑ uCa/uCr ↑ uK/uCr ↑ FEMg	Recovery
2	Gitelman-like	Cisplatin	↓ sK, ↓ sMg Metabolic alkalosis	↓ uCa/uCr ↑ uK/uCr ↑ FEMg	Unknown
3	Gitelman-like	Cisplatin	↓ sK, ↓ sMg Metabolic alkalosis	↓ uCa/uCr ↑ uK/uCr ↑ FEMg	Recovery
4	Bartter-like	Carboplatin	↓ sK, ↓ sMg, ↓ sCa Metabolic alkalosis	↑ uCa/uCr ↑ uK/uCr ↑ FEMg	Persistent

uCa/uCr, Urinary calcium: creatinine ratio; uK/uCr, Urinary potassium:creatinine ratio; FEMg, fractional excretion of magnesium.
↑high. ↓low.

of acute kidney injury (AKI), which has worsened in recent decades due to the more frequent use of medications with renal toxicity, studies indicate a frequency of up to 20% of all patients with AKI (5).

In the present case series report, there were several biochemical data to consider: persistent electrolyte and acid-base imbalances related to urinary loss of potassium and magnesium during subsequent evaluations, coupled with a history of platinum-based chemotherapy. This strongly indicates an acquired tubulopathy. It is crucial to confirm the absence of recent use of diuretics, proton pump inhibitors (PPI), immunosuppressants (e.g., tacrolimus, cyclosporine), antacids, laxatives, anti-EGFR/anti-VEGFR chemotherapy (e.g., cetuximab, pazopanib), or any dietary supplement such as herbal medicine, which may explain renal and/or extrarenal losses of potassium and magnesium. Tubular disorders are frequently underdiagnosed, probably due to the relative absence of specific symptoms that may be related to tubular dysfunction. Additionally, fatigue and mild muscle weakness can easily be associated with the progression of cancer or the administration of any chemotherapy. For this reason, clinician rarely requests a venous blood gas analysis or a urinary electrolyte analysis in this context. Another contributing factor to the low rate of tubular disorder diagnosis is that electrolyte abnormalities are usually managed with intravenous replacement therapy to achieve the desired electrolyte levels, without conducting a concise evaluation to determine whether the etiology is of extrarenal origin or due to a potential tubular dysfunction. This behavior can lead to high morbidity in chronically debilitated patients.

Cancer is associated with multiple fluid and electrolyte disorders. Its appearance can be related to the frequent polypharmacy: PPI, antihypertensives, diuretics, analgesics, and, of course, chemotherapy. In addition, they are frequent users of parenteral nutrition, which can cause serious potassium, phosphorous, and magnesium disorders in the context of refeeding syndrome (7) and may undergo intestinal surgeries that promote malabsorption or severe decrease in food intake, also other serious complications such as tumor lysis syndrome directly affect renal function and the body distribution of electrolytes (8).

Platinum-based drugs have as an important limitation the well-known nephrotoxicity, especially acute kidney injury and electrolyte disorders (9). The damage is mainly located in the proximal tubule (S3 portion), distal duct, and collecting duct (9). The most studied electrolyte alterations include hyponatremia (59%) and hypomagnesemia (27%) (10, 11).

Cisplatin causes dose-dependent nephrotoxicity, the tubular compartment being the most frequently affected. Within the cell, cisplatin behaves as a positively charged electrophilic molecule with high affinity for DNA, resulting in the formation of cross-links between two adjacent guanine residues, which hinders cellular synthesis and replication (12, 13). This can explain structural and functional tubular alterations leading to urinary loss of potassium, magnesium, and calcium, whose abnormalities have a prognostic effect on hospitalized patients, regardless of the cause.

Collins et al., analyzed the electronic reports of more than 911,000 patients, finding a U-shaped association between serum potassium concentrations and mortality, being cumulative for each 0.1 mEq/L change in potassium < 4 mEq/L and ≥ 5 mEq/L; the risk was higher in patients ≥ 65 years, patients with heart failure, chronic kidney disease or diabetes (14). Among patients with chronic kidney disease, where the effect of dyskalemia on mortality has been most strongly investigated, it was reported in a meta-analysis that included 11 clinical studies and 57,234 patients that a serum potassium concentration < 4 mEq/L was associated with a higher risk of all-cause mortality (HR= 1.18, 95% CI: 1.11 – 1.26), and a concentration < 3.5 mEq/L increased the risk of all-cause mortality by 105%(6). Even relatively "off-risk" serum potassium concentrations (e.g., 3.4 mEq/L) may confer an increased risk of cardiovascular complications that should be carefully considered (15).

Magnesium is another relevant cation in cellular physiology with a prognosis impact. The prevalence of hypomagnesemia is 20% in hospitalized patients, especially in patients with oncological and hematological disorders, and is related to longer hospital stay (16), although the incidence approaches 50% in patients in the ICU (17) with higher mortality compared to patients with

normomagnesemia (35% vs 12%, p = 0.01) (18). Extreme values of hypomagnesemia (< 0.3 mmol/L or < 0.75 mg/dL) in hospitalized patients were evaluated by Cheminet et al., finding a prevalence of less than 0.5% (19). Of the 119 patients detected, 84% had a gastrointestinal disorder and 42% had a history of cancer. The most prescribed hypomagnesemia-related drugs were PPIs (70%), immunosuppressants (22%), platinum-based chemotherapy (17%), and diuretics (19%); the association of hypocalcemia (77%) and hypokalemia (51%) was significative (19).

Gitelman and Bartter syndromes are rare inherited tubulopathies that cause hypokalemia, metabolic alkalosis, and hypomagnesemia. Gitelman syndrome is caused by inactivating mutations in the solute transporter family 12-member 3 (SLC12A3) gen; a wide number of these mutations have been reported including nonsense, cut-and-splice site and missense mutations (20). Regarding Bartter syndrome, it is characterized by mutations in the thick ascending limb of Henle's loop, either in NKCC2, ROMK, ClC-Ka/b, Barttin protein, CaSR, or MAGE-D2 (21) (see Table 1). An important characteristic in the differential diagnosis of Bartter phenotype compared to Gitelman is hypercalciuria; currently, the induction test with thiazides is no longer recommended (22). However, a genetic test is a gold standard, especially due to the overlap of biochemical phenotypes (e.g.: Gitelman and Bartter type 3). Unfortunately, genetic testing couldn't be conducted in our institution to determine the coexistence of mutations in the co-transporters. However, the absence of electrolyte and acid-base disorders before the initiation of chemotherapy, along with the temporal association with platinum-based chemotherapy, makes the nephrotoxic effect the most plausible causal factor.

The functional tubular prognosis varies; Panichpisal et al. described the case of a patient with a 20-year follow-up who developed severe hypokalemia with metabolic alkalosis and hypocalciuria related to cisplatin administration. Although the genetic mutation status of the NCC was not determined, it is feasible that the association was causal. The same study documented 12 cases with Gitelman-like syndrome, all with persistent electrolyte abnormalities for up to 6 years (23). Tubular damage and electrolyte abnormalities may be permanent in some patients (24, 25), probably related to the toxic effect on the gene that encodes the sodium/chloride cotransporter and apoptosis of the tubular epithelial cells of the distal segment (23). To date, it is not known whether there are genetic polymorphisms associated with the risk of developing platinum-associated tubulopathy.

Conclusion

Despite the increasing prevalence and incidence of cancer and, therefore, the prescription of new and classic chemotherapy, the diagnosis of electrolyte disorders and especially tubular dysfunction is often an underestimated complication. Its recognition will allow a multidisciplinary management that includes oncologists, nutritionists, geriatricians, and nephrologists for an accurate assessment that improves the long-term results of patients. The relevance of diagnosing these disorders can enhance integrative management, some of which have an ominous prognosis. This holds even if they are in palliative care, as it provides relief for symptoms that can deteriorate the patient's quality of life. Additionally, this is one of the first reports to our knowledge of Bartter phenotype tubulopathy associated with platinum-based chemotherapy.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

MA-S: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. DD: Writing – original draft, Writing – review & editing. VY: Writing – original draft, Writing – review & editing. FM: Writing – original draft, Writing – review & editing. VU: Writing – original draft, Writing – review & editing. FV: Writing – original draft, Writing – review & editing. BY: Writing – original draft, Writing – review & editing.

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EDITED BY
Xuefei Tian,
Yale University, United States

REVIEWED BY
Dagmara Borzych-Duzalka,
Medical University of Gdansk, Poland
Reyner Loza,
Cayetano Heredia Peruvian University, Peru
Cristina Capusa,
Carol Davila University of Medicine and Pharmacy, Romania

*CORRESPONDENCE
Paola Krall
paola.krall@uchile.cl

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Case report: Unveiling a less severe congenital nephrotic syndrome in a Rapa Nui patient with a *NPHS1* Maori founder variant

Paola Krall[1,2]*, Angélica Rojo[3], Anita Plaza[1], Sofia Canals[4], María Luisa Ceballos[2,3], Francisco Cano[2,3] and José Luis Guerrero[2,3,5]

[1]Instituto de Medicina, Facultad de Medicina, Universidad Austral de Chile, Valdivia, Chile, [2]Departamento de Pediatría y Cirugía Infantil Oriente, Facultad de Medicina, Universidad de Chile, Santiago de Chile, Chile, [3]Unidad de Nefrología, Diálisis y Trasplante Renal, Hospital Luis Calvo Mackenna, Santiago de Chile, Chile, [4]Unidad de Lactantes, Hospital Luis Calvo Mackenna, Santiago de Chile, Chile, [5]Programa de Telesalud, Hospital Luis Calvo Mackenna, Santiago de Chile, Chile

Background: Congenital nephrotic syndrome (CNS) is a severe kidney disorder characterized by edema, massive proteinuria, and hypoalbuminemia that manifests *in utero* or within three months after birth. CNS affects 1-3 per 100,000 children, primarily associated with genetic variants and occasionally with infections. Genetic analysis is the first-line method for diagnosis. The most common founder variants have been identified in European populations, often resulting in end-stage kidney disease by 1-2 years of age.

Case-diagnosis/treatment: A female full-term neonate, without prenatal signs of kidney disease, was admitted to Rapa Nui (Eastern Island) Hospital at the age of 2 months due to bronchial obstruction. She presented fever, oliguria, edema, urine protein-to-creatinine ratio (UPCR) 433.33, and hypoalbuminemia (0.9 g/dL). She was transferred to a mainland Chilean hospital following CNS diagnosis. Viral screening detected cytomegalovirus (CMV) positivity in both blood and urine. A kidney biopsy revealed interstitial nephritis and diffuse podocyte damage and the tissue PCR resulted negative for CMV. Interviews with the parents revealed consanguinity, suggestive of hereditary CNS. Genetic analysis identified the Maori founder variant, *NPHS1* c.2131C>A (p.R711S), in homozygosis. The patient received albumin infusions and antiviral therapy, being discharged when she was 5 months old, with improved laboratory parameters evidenced by UPCR 28.55, albumin 2.5 g/dL, and cholesterol 190 mg/dL. Subsequent clinical monitoring was conducted through virtual and in-person consultations. At her last follow-up at 4 years 2 months old, she presented UPCR 16.1, albumin 3.3 g/dl and cholesterol 220 mg/dL, maintaining normal kidney function and adequate growth.

Conclusions: To our knowledge, this represents the first case of CNS in Chile carrying a *NPHS1* variant associated with prolonged kidney survival. As described in the Maori population, the patient exhibited a less severe clinical course compared to classical *NPHS1* patients. Genetic testing for the Maori founder variant in CNS patients related to the New Zealand population, could impact management decisions and potentially prevent the need for nephrectomies.

KEYWORDS

congenital nephrotic syndrome, NPHS1, kidney survival, Maori founder variant, Rapa Nui (Easter Island)

Introduction

Congenital nephrotic syndrome (CNS) is a severe kidney disease that is present at birth or manifests within the first three months of life with clinical signs of edema, massive proteinuria and hypoalbuminemia (1). CNS affects 1-3 per 100,000 newborns, turning this kidney disease into a rare condition, although a higher frequency in specific populations has been described reaching up to 1 in 8,000 in Finland (2). CNS is associated with genetic variants encoding proteins that are expressed in the glomerular filtration barrier, including those found in the slit diaphragm. These genes include nephrin (*NPHS1*), podocin (*NPHS2*), Wilms tumor 1 (*WT1*), Phospholipase C epsilon 1 (*PLCE1*) and Laminin β2 chain (*LAMB2*) (3). However, rare cases of viral-associated glomerulopathies have been described to trigger CNS, reinforcing the need for virus screening (4).

Most of the genetic variants in CNS patients have been detected in *NPHS1*, exhibiting an autosomal recessive inheritance pattern due to homozygous or compound heterozygous combinations (5, 6). As of the current date, over 1200 variants have been documented in *NPHS1*, with approximately 25% classified as either pathogenic or likely pathogenic. The most common *NPHS1* variants, Fin-major and Fin-minor, were identified in Finland as result of a founder effect (7). However, both have been observed in other geographic populations, indicative of a broader involvement of these variants in hereditary CNS (8).

CNS associated with *NPHS1* is a form of steroid-resistant nephrotic syndrome but is treated differently in comparison with patients of infant childhood. The primary objective during the initial evolution of CNS is to manage edema and prevent severe complications such as infections, thrombosis, and/or failure to thrive, which might contribute to morbidity. The clinical course of CNS associated with *NPHS1* usually leads to the requirement of nephrectomy and kidney replacement therapy at 1-2 years of age. Histopathological findings are commonly nonspecific, exhibiting mesangial hypercellularity, glomerulosclerosis, dilated proximal tubules, and diffuse foot process effacement. For this reason, routine kidney biopsy might be replaced by non-invasive molecular diagnosis approaches such as genetic testing (9).

Genetic analysis has become the primary method, offering high detection rates and is strongly recommended to confirm CNS diagnosis, aiding in management, and establishing prognosis (9). If a *WT1* variant is identified, there is a high likelihood to consider a native nephrectomy prior to transplantation (10). Nevertheless, the consideration of aggressive treatment for CNS needs to be analyzed on a case-by-case basis and might benefit of genetic testing, as some patients might require a nephrectomy before transplantation while others have a delayed progression and do not reach end-stage kidney disease by the age of 2 years (11, 12).

In this study, we present a female patient born from a consanguineous couple who was diagnosed with CNS within the first three months of life, representing the first confirmed case from Rapa Nui carrying a known *NPHS1* founder variant associated with prolonged kidney survival.

Case report

A female newborn patient (gestational age 37 weeks, birth weight 2.82 kg) without prenatal evidence of kidney disease was admitted at the age of 2 months at Hanga Roa Hospital in Easter Island (insular Chilean territory) due to bronchial obstruction that was treated with oral steroids and bronchodilator therapy. Shortly after, she developed fever (38°C) with significant shortness of breath that was treated with oxygen supplementation, but in 24 hours she presented decreased diuresis, abdominal distension and swelling in the lower limbs. Chest radiography did not evidence anomalies. Laboratory findings revealed hypoalbuminemia (0.9 g/dL) and proteinuria as urine protein to creatinine ratio (UPCR) 433.33, consistent with a diagnosis of CNS. Her serum creatinine levels were within normal range (0.2 mg/dL). Subsequent treatment involved 20% albumin over 12-hour infusions (2 g/kg/day) to support intravascular volume and reduce extravascular fluid retention when symptomatic hypovolemia was suspected and red blood cells transfusion due to anemia, as evidenced by hemoglobin of 5.9 g/dL.

She was transferred to a major pediatric hospital in mainland Chile at 2 months and 15 days of life. At the initial assessment, the

physical examination confirmed persistence of edema of the eyelids and lower limbs. Laboratory exams upon admission showed hypoalbuminemia (1.5 g/dL), UPCR 156.88, hypocalcemia (6.3 mg/dL) and hypomagnesemia (1.1 mg/dL). The 24-hour urine protein test yielded 8.9 grams (1374 mg/m^2/hr). Ultrasound showed enlarged kidneys, diffuse echogenic parenchyma and limited corticomedullary differentiation.

The treatment regimen consisted of initiation of captopril at a dose of 1.5 mg/kg per administration, given every 8 hours, resulting in a cumulative daily dose of 4.5 mg/kg. Furosemide was administered at 0.5 mg/kg following each albumin infusion or in the presence of severe edema. Furthermore, the patient received a daily oral dose of 4000 IU (25 mcg/kg/day) of vitamin D3 (cholecalciferol) to maintain target serum levels between 30 to 50 ng/mL. In case of low plasma total IgG levels, 450 mg/kg of intravenous normal human immunoglobulins were administered. Additionally, a daily dose of 25 mcg of levothyroxine was provided (equivalent to 100 mcg/m^2/day).

Screening for viral infections yielded a positive result for cytomegalovirus (CMV) in both blood (1748 copies/mL) and urine (59250 copies/mL). Serologic analysis for human immunodeficiency virus, syphilis and toxoplasmosis was negative. Intravenous ganciclovir treatment was given at a dose of 6 mg/kg every 12 hours for 28 days, followed by oral valganciclovir at a dose of 15 mg/kg every 12 hours for the following 6 weeks. After this treatment, the CMV viral load was negative. A kidney biopsy revealed interstitial nephritis and diffuse podocyte damage and the tissue PCR resulted negative for CMV (Figure 1).

Subsequent interviews with the parents revealed a consanguineous relationship, suggestive of hereditary CNS (Figure 2). Genetic analysis conducted by the Laboratory of Nephrology at the Universidad Austral de Chile identified the variant *NPHS1* c.2131C>A (p.R711S) in homozygosis, described as a Maori founder variant, and present in different population databases (Human Gene Mutation Database, gnomAD, ClinVar, dbSNP). The amino acid substitution is located in a highly conserved region across vertebrate species. Both parents were confirmed to be heterozygous carriers of the *NPHS1* R711S variant (Figure 3), prompting genetic counseling about the recurrence in forthcoming gestations considering that the case involved the birth of their first child.

The patient received 20% albumin infusions (2 g/kg/day) and continued antiviral therapy, observing progressive improvement in her general health status. She was discharged when she was 5 months old with favorable laboratory parameters: UPCR 28.55, albumin 2.5 mg/dl and cholesterol 190 mg/dl with indication of treatment with captopril and vitamin D. Clinical follow-up was conducted via telemedicine between Rapa Nui and a nephrologist on mainland Chile during travel restrictions imposed by the SARS-CoV-2 pandemic. This continued until the age of 3 years when in-person visits replaced remote clinical monitoring. At her last visit at 4 years 2 months old, her UPCR was 16.1, albumin 3.3 mg/dL, creatinine 0.27 mg/dL and cholesterol 220 mg/dL (Table 1). She maintained normal kidney function, without swelling, normal blood pressure below the 95th percentile for age, gender, and height, and a normal nutritional status (weight-for-age z-score: +0.41, height-for-age z-score: +1.3, body mass index: 14.7 kg/m^2, body mass index z-score: -0.49). Her body weight was 17.2 kilograms, and she was receiving captopril 12.5 mg three times a day, spironolactone 7.5 mg twice a day and vitamin D 2000 IU once a day.

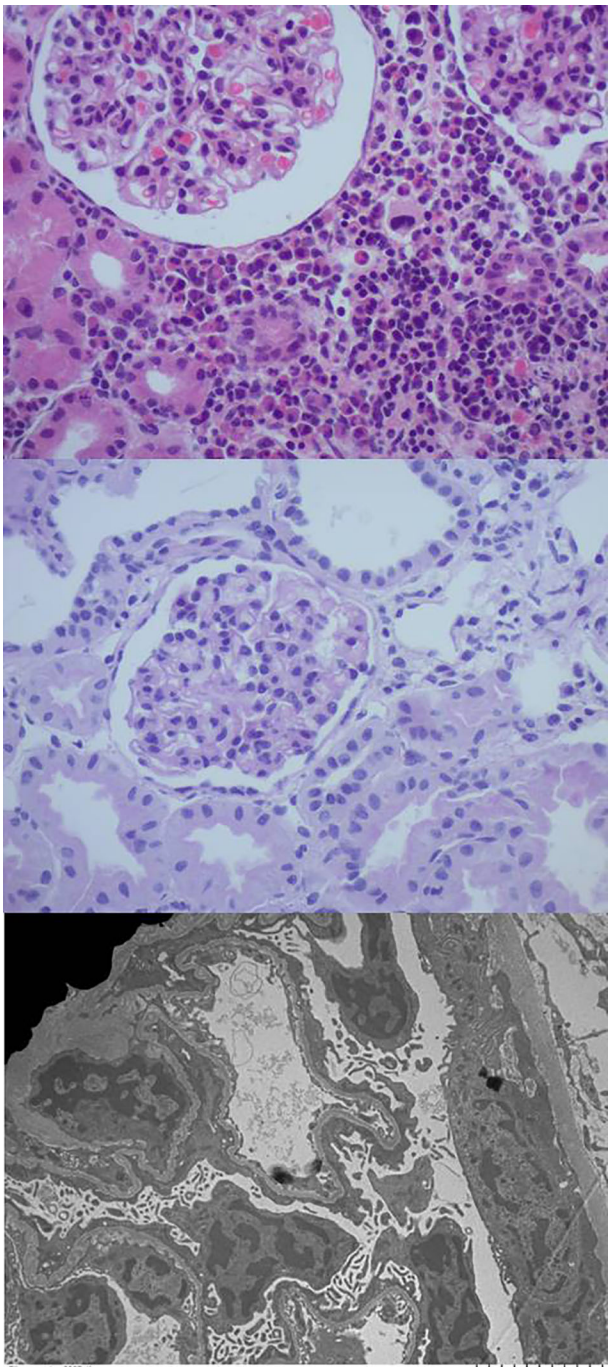

FIGURE 1
The optical microscopy of the kidney biopsy reveals preserved glomeruli with mild mesangial hypercellularity and a mixed interstitial inflammatory infiltrate, while electron microscopy images highlight marked diffuse podocyte damage.

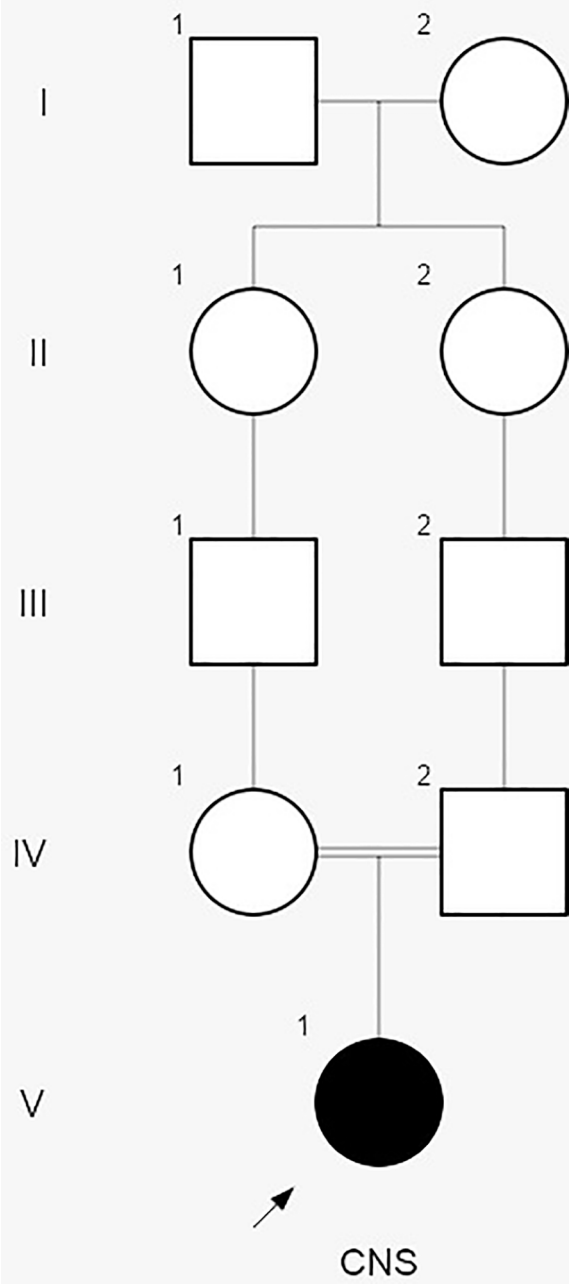

FIGURE 2
The pedigree chart of the Rapa Nui patient diagnosed with congenital nephrotic syndrome (CNS). During the interview with the parents, no family history of kidney disease was reported. However, they disclosed that the patient´s great grandmothers were sisters, suggesting a potential hereditary etiology for CNS.

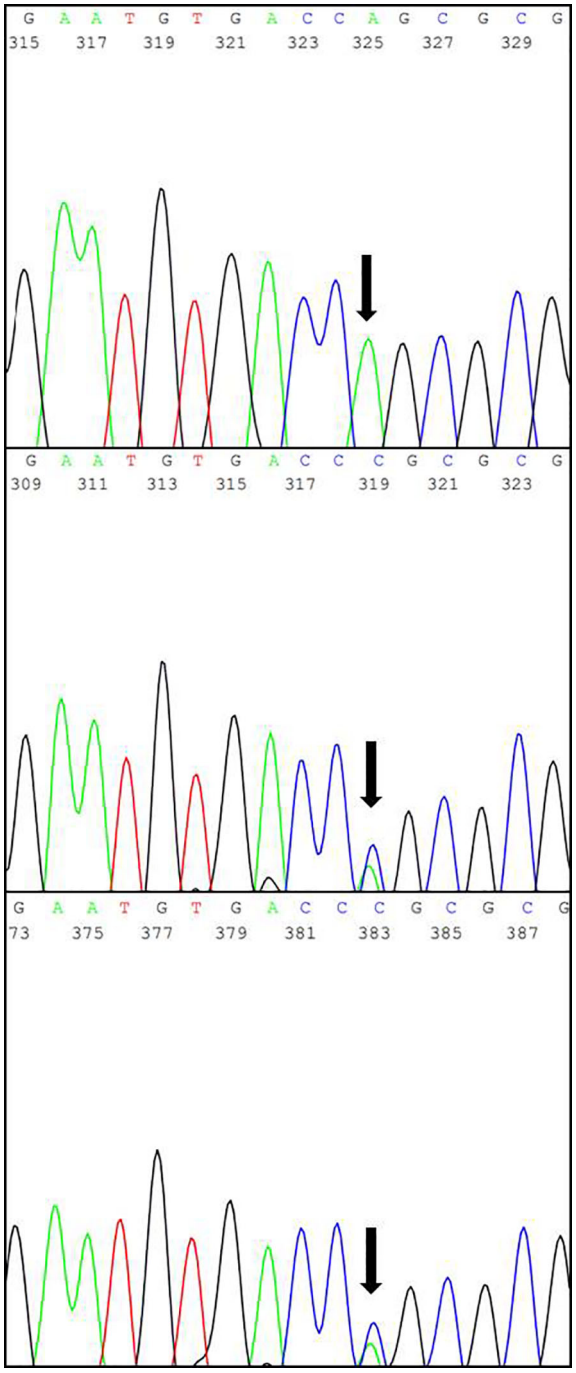

FIGURE 3
The results of Sanger sequencing showing the specific replacement of a cytosine (C) by an adenine (A) within exon 16 in the *NPHS1* gene (marked with black arrow), predicted to cause the missense variant R711S. Top: Patient; Center: Father; Bottom: Mother.

Discussion

Diagnosing patients with CNS involves many difficulties, given their susceptibility to hemodynamic compromise, infections, thrombosis, impaired growth and kidney failure. It is important to address and treat potential complications to reduce their morbidity and mortality. Comprehensive CNS care involves the use of renin-angiotensin system inhibitors, diuretics, anticoagulation, and infection prophylaxis, to maintain intravascular euvolemia, ensure proper nutrition, and preserve both central and peripheral vessels. Routine nephrectomies are not recommended, but they may be considered in cases of severe complications despite optimal conservative treatment (9).

In this article, we describe a newborn patient exhibiting CNS with homozygous status of a *NPHS1* variant and CMV infection. Congenital infections, in particular CMV, *Treponema pallidum*

TABLE 1 Laboratory results by age during the follow-up.

Age	2 months	3 months	4 months	5 months	6 months	8 months	10 months	1 year	3 years	4 years
UPCR	433.33	62	46	28.55	28	9.4	5.9	0.96	6.18	16.1
Serum albumin (g/dL)	0.9	1.7	2.1	2.5	2.6	3.1	3.4	3.4	3.3	3.3
Serum creatinine (mg/dL)	0.2	0.15	0.15	0.15	0.15	0.15	0.22	0.22	0.24	0.27
Serum cholesterol (mg/dL)	127	213	220	190	170	171	170	184	300	220

(syphilis), and occasionally *Toxoplasma gondii*, along with other pathogens, have been linked to rare occurrences of CNS. Although the presence of CMV and cytomegalic inclusions has been observed in the renal tubular epithelial cells in CMV-associated glomerulopathies, the causative role of this virus in the case of glomerulonephritis and nephrotic syndrome remain subjects of ongoing debate (13).

The patient's treatment regimen encompassed the administration of albumin over 12 hour infusions when symptomatic hypovolemia was suspected and red blood cell transfusion to address anemia, alongside antiviral therapy during the postnatal period. Hypocalcemia and hypomagnesemia can be observed in patients with nephrotic syndrome due to proteinuria and tubular dysfunction. Furthermore, hypoalbuminemia can reduce the binding of calcium and magnesium in the blood, worsening their loss. Intravenous and oral calcium and magnesium were administered to the patient until their plasma levels were restored to normal.

Discharge occurred at 5 months of age, marked by favorable laboratory parameters. A therapeutic plan was instituted involving vitamin D supplementation, immunoglobulin therapy, levothyroxine and captopril. At her last visit, the patient was 4 years and 2 months old and maintained normal kidney function, exhibited no signs of swelling, normal blood pressure, and sustained nutritional well-being although she continued to exhibit proteinuria through captopril, spironolactone and vitamin D.

The primary goal is to achieve optimal nutrition and growth, mitigate complications, minimize their impact, and attain adequate weight/height through conservative measures, thereby eliminating the need for nephrectomies (11). This has remained the prevailing situation until now in our patient.

Given the predominant association of CNS with *NPHS1*, genetic analysis in the patient was specifically targeted towards this gene. The concern regarding her prognosis stemmed from the fact that the majority of reported CNS cases with *NPHS1* variants developed a severe clinical course involving Caucasian cohorts. However, in 2013, a retrospective study involving 35 patients with CNS reported a subgroup of patients in New Zealand carrying a previously unknown *NPHS1* variant, R711S, which was interpreted as probably disease-causing (14). The variant was confirmed in homozygosis in 10 individuals. All of them were identified as Maori or Maori-descendent and they appeared to show a better response to pharmacological treatment than Caucasians becoming independent of albumin infusion during their second year of life. Their mean kidney survival was 12.4 years (range: 1 - 37 years) with optimal outcomes after transplantation.

Concerning the inhabitants of islands in New Zealand, as well as those of Rapa Nui, the genetic evidence confirms the link between these populations (15). It is recognized that geographically and culturally isolated regions often exhibit higher rates of consanguinity. This contributes to the occurrence of rare autosomal recessive phenotypes related to alleles carried by historic settlers and subsequent migrants. To our knowledge, the patient we describe here is the first reported case outside New Zealand with this unique genotype as a homozygous carrier of the Maori founder variant. This is more likely to be explained by the inheritance of the variant over many generations, supported by the historical relationship between Rapa Nui and the Maoris. Herein, we describe her clinical course for at least 4 years, evidencing a less severe phenotype similar to the one reported in Maori CNS patients.

In summary, a comprehensive evaluation of CNS is necessary to enhance our understanding of its pathogenesis, involving genetic, viral studies and biopsy. Molecular testing is crucial for determining both short-term and long-term prognosis, as well as formulating an effective treatment plan.

Data availability statement

The datasets for this article are not publicly available due to concerns regarding participant/patient anonymity. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Comité Ético Científico Servicio de Salud Valdivia. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

PK: Conceptualization, Formal Analysis, Funding acquisition, Methodology, Supervision, Writing – original draft, Writing – review & editing, Data curation, Project administration, Resources, Validation. AR: Data curation, Writing – review & editing. AP: Data curation, Methodology, Writing – review & editing. SC: Data curation, Writing – review & editing. MC: Data curation, Writing – review & editing. FC: Data curation, Writing – review & editing. JG: Conceptualization, Data curation, Formal Analysis, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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*CORRESPONDENCE
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paola.krall@uchile.cl

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Corrigendum: Case report: Unveiling a less severe congenital nephrotic syndrome in a Rapa Nui patient with a *NPHS1* Maori founder variant

Paola Krall[1,2]*, Angélica Rojo[3], Anita Plaza[1], Sofia Canals[4], María Luisa Ceballos[2,3], Francisco Cano[2,3] and José Luis Guerrero[2,3,5]

[1]Instituto de Medicina, Facultad de Medicina, Universidad Austral de Chile, Valdivia, Chile, [2]Departamento de Pediatría y Cirugía Infantil Oriente, Facultad de Medicina, Universidad de Chile, Santiago de Chile, Chile, [3]Unidad de Nefrología, Diálisis y Trasplante Renal, Hospital Luis Calvo Mackenna, Santiago de Chile, Chile, [4]Unidad de Lactantes, Hospital Luis Calvo Mackenna, Santiago de Chile, Chile, [5]Programa de Telesalud, Hospital Luis Calvo Mackenna, Santiago de Chile, Chile

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Clay Block,
Dartmouth College, United States

REVIEWED BY
Ana Carina Ferreira,
Lisbon Central Hospital Center, Portugal
Buyun Wu,
Nanjing Medical University, China

*CORRESPONDENCE
Praveen Errabelli
errabelli.praveen@mayo.edu

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Case report: A case of pseudo-acute kidney injury due to cyclin-dependent kinase inhibitor

Praveen Errabelli[1]*, Maulik Lathiya[2] and Devender Singh[1]

[1]Department of Nephrology and Hypertension, Mayo Clinic Health System, Eau Claire, WI, United States, [2]University of Minnesota Health Sciences, University of Minnesota Medical Center, Minneapolis, MN, United States

Various classes of targeted therapies have emerged in the last few years, which have revolutionized cancer treatment, and improved the prognosis and survival of cancer patients. Unfortunately, these agents have serious toxic effects on the kidneys. Some of the toxic effects are hypertension, acute kidney injury (AKI), and proteinuria. One interesting phenomenon that has emerged recently is pseudo-acute kidney injury due to the interference with the tubular secretion of creatinine by some of the targeted therapeutic agents. Understanding this physiology is needed to avoid unnecessary investigation and withholding of lifesaving chemo regimen. Alternative methods to assess renal function such as cystatin C-based estimated glomerular filtration rate (eGFR) can differentiate true AKI from pseudo-AKI. Here, we describe one such case of pseudo-AKI from cyclin-dependent kinase (CDK) 4/6 inhibitor, abemaciclib, which inhibits tubular secretion of creatinine. Using cystatin-C-based eGFR revealed pseudo-AKI in this case.

KEYWORDS

acute kidney injury, pseudo acute kidney injury, CDK (cyclin-dependent kinase), cystatin C (Cys C), EGFR, creatinine clearance, abemaciclib

Introduction

Significant progress has been made when it comes to targeted cancer therapies in recent years. These newer agents pose new challenges to nephrologists due to their various adverse effects on the kidneys. Knowledge about various adverse effects associated with each agent is essential as the lack of in-depth understanding of the underlying pathophysiology of these effects can lead to untimely discontinuation of much-needed cancer therapy. Here, we present a case of suspected nephrotoxicity associated with abemaciclib (CDK4/6 inhibitor), which turned out to be a pseudo-acute kidney injury due to its interference with the tubular secretion of creatinine. The purpose of reporting this case is to increase awareness among

clinicians about this entity, which would help avoid unnecessary investigations, delays in treatment, and inadvertent discontinuation of chemotherapeutic agents.

Case description

A 55-year-old postmenopausal female patient was referred by an oncologist for declining renal function. She was diagnosed with invasive ductal carcinoma of the left breast, stage II A, ERPR positive, HER2/neu negative, cT1c N1 M0. She underwent neoadjuvant chemotherapy with four cycles of docetaxel/cyclophosphamide, left lumpectomy, and axillary node dissection. Despite a seemingly positive response to neoadjuvant treatment, posttreatment MRI showed a significant residual disease and the final pathology report revealed pT1c N1 disease with 2/12 lymph nodes positive for carcinoma, one lymph node showing extranodal extension. The treatment plan included adjuvant radiation therapy and Arimidex 1 mg daily for 10 years, and adjuvant abemaciclib 150 mg twice a day for 2 years. Prior to starting abemaciclib, the patient had a baseline plasma creatinine of 0.8–0.9 mg/dL with a creatinine-based eGFR of 80 mL/min. However, a month after initiation of abemaciclib, creatinine rose to 1.13 mg/dL and creatinine-based eGFR dropped to 45 mL/min. A month later, plasma creatinine remained elevated at approximately 1.2–1.4 mg/dl (Figure 1), prompting nephrology referral.

During the visit to a nephrology clinic, the patient denied any shortness of breath, chest pain, palpitation, vomiting, pain abdomen, dysuria, hematuria, foamy urine, increased frequency of urination, lower extremity swelling, and skin rash. She had no prior history of kidney disease but she had fatigue, night sweats, stiffness in the joints, numbness in hands and feet, and headaches. She did report taking ibuprofen 600 mg intermittently for at least 1–2 years to manage headaches, which she had stopped taking 2 months prior to nephrology visit. Her blood pressure was 121/83 mm/hg, pulse rate 68 beats/min, and the rest of the physical examination was normal.

Laboratory tests including urinalysis, 24-h urine protein, cystatin C-based eGFR, basic metabolic panel, and 24-h creatinine clearance were done. Urine sediment did not show any hematuria, pyuria, or proteinuria. Cystatin C-based eGFR was 95 mL/min/BSA and 97 mL/min/BSA (checked twice 1 month apart). The 24-h urine creatinine clearance was 67 mL/min/BSA and the 24-h urine protein was only 115 mg (Table 1).

Since cystatin C-based eGFR was much higher than creatinine-based eGFR and renal function was stable, it was determined that we were dealing with pseudo-AKI due to reduced creatinine secretion with the use of abemaciclib. This is also confirmed by low 24-h creatinine clearance when compared to cystatin C-based eGFR.

After this determination, we recommended that abemaciclib be continued and cystatin C-based eGFR with regular Basic Metabolic panel (BMP) be checked. The patient continues to have stable renal function despite being on abemaciclib for more than a year (Figure 1).

Discussion

The advent of targeted therapies has revolutionized cancer care and enhanced outcomes. Nonetheless, their nephrotoxic properties have introduced new challenges to nephrology. These therapies have the potential to induce renal damage by targeting molecules like vascular endothelial growth factor and platelet-derived growth factor, which are expressed in normal nephrons (1). The predominant adverse event is acute kidney injury, which may manifest as acute tubular necrosis, acute interstitial nephritis, or glomerular injury leading to hematuria and proteinuria. This condition is diagnosed by monitoring the patient's serum creatinine levels, creatinine-based eGFR, urine sediment for hematuria and proteinuria, and, in certain cases, performing a kidney biopsy. Additionally, a new entity termed pseudo-AKI has recently emerged. This is attributed to the disruption of the tubular secretion of serum creatinine by certain targeted therapies. Some of these targeted therapies interfere with the tubular secretion of serum creatinine by affecting the activity of organic cation transporter (OCT) and multidrug and toxic compound extrusion (MATE) transporters. Specifically, the facilitation of creatinine secretion from proximal tubules is

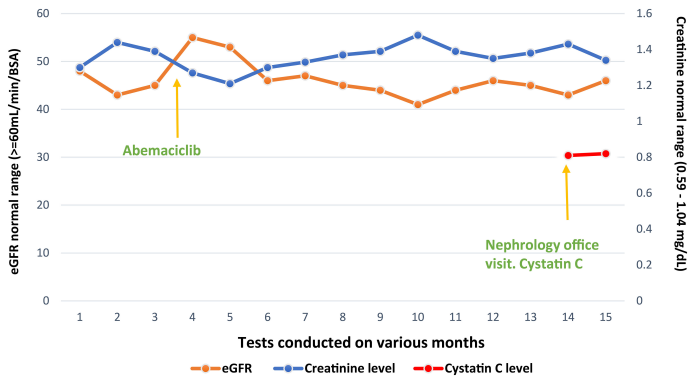

FIGURE 1
Serum creatinine-based eGFR and serum cystatin C.

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TABLE 1 Laboratory results.

Parameter	Value		Unit
24-h urine protein	115		mg
Creatinine clearance	67		mL/min
24-h urine volume	2,300		mL
Creatinine	59		mg/dL
Plasma creatinine	1.37		mg/dL
Test	**17/07/2023**	**14/08/2023**	**18/08/2023**
Cystatin C	0.82	0.81	
Cystatin C eGFR	95	97	
Sodium, P	140	139	140
Potassium, P	4.5	4.2	4.4
Chloride, P	105	102	102
Bicarbonate, P	26	27	26
Anion gap, P	9	10	12
Blood urea nitrogen (BUN), P	16	15	16
Creatinine	1.38 (H)	1.43 (H)	1.34 (H)
Estimated GFR (eGFR)	45 (L)	43 (L)	46 (L)
Calcium, total, P	9.5	9.1	9.6
Glucose, P	91	65 (L)	91
Phosphorus (inorganic), P	3.2		3.5
Albumin, P	4.5	4.0	4.4
Bilirubin, total, P		0.3	
Bilirubin, direct, P		<0.2	
Alanine aminotransferase (ALT), P		16	
Aspartate aminotransferase (AST), P		22	
Alkaline phosphatase, P		33 (L)	
Protein, total, P		6.3	
Parameter		**17/07/2023**	
Color, U		Yellow	
Clarity		Clear	
Source		Urine, midstream	
Nitrite, U		Negative	
Leukocyte esterase		Negative	
pH		7.5	
Specific gravity		1.005	
Glucose		Negative	
Protein urine random		Negative	
Ketone		Negative	
Bilirubin		Negative	
Blood		Negative	
Urobilinogen		0.2	
White blood cells		None seen	
Red blood cells in urine		None seen	

(H, high; L, low).

mediated by organic cation transporter 2 (OCT2) and multidrug and toxin compound extrusion protein 1 (MATE1) (2).

The way to differentiate pseudo-AKI from true AKI is by measuring serum cystatin C-based eGFR along with serum creatinine-based eGFR and using alternative clearance estimation methods like iothalamate clearance. Various targeted therapies, including anaplastic lymphoma kinase (ALK) inhibitors, mesenchymal epithelial transition (MET) inhibitors, cyclin-dependent kinase (CDK4/6) inhibitors, poly ADP-ribose polymerase inhibitors (PARP), v-raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitors, Breakpoint Cluster Region–v-Abl Abelson murine leukemia viral oncogene homolog (BCR-ABL) inhibitors, HER-2 inhibitors, and tyrosine kinase inhibitors, have been associated with pseudo-AKI. If the patient has true AKI, treatment should be withheld or modified to avoid further complications. However, if pseudo-AKI is identified, discontinuing chemotherapy can be avoided, potentially benefiting the patient (1).

Cyclin-dependent kinases 2/4/6 (CDK 2/4/6) control the progression of cell cycle checkpoints from G1 to S phase (3). CDK4/6 inhibitors promote G0/G1 arrest in renal epithelial cells (3). The combination of a cyclin-dependent kinase (CDK) 4/6 inhibitor with an aromatase inhibitor represents the primary therapy for hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (1). CDK 4/6 inhibitors block renal transporters such as organic cation transporter 2 (OCT 2), MATE1, and MATE-2K, resulting in decreased creatinine secretion into the renal tubule. This mechanism results in elevated creatinine levels and should not be interpreted as indicative of acute kidney injury (2).

Abemaciclib, an oral chemotherapeutic medication, is indicated for the treatment of metastatic breast cancer. Abemaciclib was approved as adjuvant therapy for the treatment of high-risk hormone receptor-positive, HER2 negative breast cancer based on MONARCH 1, 2, and 3 trials. The trials demonstrated that the addition of abemaciclib led to a significant and clinically meaningful improvement in invasive disease-free survival in the intention-to-treat population compared with endocrine therapy alone (4–6).

It acts as a potent and selective inhibitor of cyclin-dependent kinases 4 and 6 (7). Abemaciclib is known to inhibit OCT2, MATE1, and MATE2-K. Clinically assessed parameters such as glomerular filtration rate, serum cystatin-C levels, serum neutrophil gelatinase-associated lipocalin (NGAL), and urine markers of kidney tubular injury, such as kidney injury molecule-1, are minimally affected by abemaciclib (7). These findings suggest that the observed elevations in serum creatinine, commonly utilized to estimate glomerular filtration rate (creatinine-based eGFR), are likely attributable to the suppression of proximal tubule secretory

transporters (7). Abemaciclib treatment may lead to a slight (approximately 10%–40%) reversible increase in serum creatinine in patients. However, for accurate assessment of renal function in abemaciclib-treated patients, alternative methods for evaluating renal function should be employed as needed (7). The active transport of creatinine within renal tubules involves various transport proteins, such as OCT2, MATE1, and MATE2-K. OCT2 facilitates creatinine uptake from the blood into proximal tubule cells via facilitated diffusion at the basolateral membrane, while MATE1 and MATE2-K, located at the apical membrane, promote creatinine and other compound efflux from cells into urine through proton-coupled transport. The inhibition of OCT2 and MATEs reduces creatinine clearance, leading to elevated serum creatinine levels due to impaired tubular secretion. These alterations may occur without significant changes in renal function or measured glomerular filtration rate (GFR) (7). Alternative markers like cystatin C offer a dependable approach for assessing GFR and renal function, as they are not influenced by active secretion and remain unaffected by dietary variations or changes in muscle mass (7). Cystatin C, a non-glycosylated protein weighing 13.3 kDa, is part of the cystatin superfamily of cysteine protease inhibitors. It acts as a pro-survival protein in cells under stress conditions. Being entirely catabolized in the proximal renal tubule without reabsorption into circulation following glomerular filtration, cystatin C serves as an ideal indicator for estimating GFR. Its measurement is less influenced by factors like age, gender, muscle mass, and ethnicity under normal conditions, making it particularly valuable for early therapeutic interventions. Consequently, cystatin C emerges as an excellent marker for estimating GFR, especially in the initial therapeutic stages and during patient monitoring (8).

Clearance rates of exogenous compounds like iohexol, which are freely filtered and not metabolized, provide a reliable method for accurately determining absolute glomerular filtration rate (GFR) and offering a more precise assessment of glomerular filtration activity. Several biomarkers, including kidney injury molecule 1 (KIM-1) and NGAL, show potential in identifying acute kidney injury compared to serum creatinine (7). Notably, although the creatinine-based GFR [via Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)] decreased following abemaciclib administration, this decline was not reflected in the measured GFR determined by iohexol clearance or GFR calculated from serum cystatin-C concentrations. Furthermore, significant changes were not observed in the levels of NGAL and KIM-1 in urine normalized to creatinine, both indicative of renal injury. These findings suggest that the observed increases in serum creatinine post-abemaciclib administration stem from reversible inhibition of renal tubular creatinine secretion rather than acute kidney injury (7). Therefore, the impact of abemaciclib on renal function, as assessed by measured GFR and urinary biomarkers of renal injury, appears minimal. Patients receiving abemaciclib may experience a mild and reversible (~10%–40%) elevation in serum creatinine due to inhibition of renal transport, highlighting the need for alternative renal function assessment methods when clinically indicated (7). Similar observations were made during MONARCH 1, 2, and 3 trials (4–6). In practical terms, the measurement of cystatin C-based estimated GFR, which remains unaffected by medications inhibiting creatinine secretion, may assist in distinguishing nephrotoxicity from pseudo-acute kidney injury (9). It is important to note that factors such as inflammation, thyroid dysfunction, and smoking influence cystatin C levels (10, 11).

The primary adverse effects linked with CDK4/6 inhibitors include neutropenia, leukopenia, and fatigue, although acute kidney injury is rarely observed (12). Distinguishing between pseudo-acute kidney injury (AKI) and true AKI presents a challenge. Simultaneous evaluation of serum creatinine, kidney iothalamate clearance, and estimated glomerular filtration rate (eGFR) based on cystatin C levels assists in distinguishing between these conditions. Recent eGFR equations that incorporate both creatinine and cystatin C levels, without considering race, provide more accurate estimations of measured GFR compared to formulas utilizing either marker independently. This results in reduced differences in measured GFR across various racial demographics (13, 14).

Various drugs known to inhibit the tubular secretion of creatinine are summarized in Table 2 (15–17).

TABLE 2 Summary of medications known to inhibit tubular secretion of creatinine leading to a rise in plasma creatinine.

Drugs	Mechanism of action	Uses
Cimetidine, famotidine, and ranitidine	Histamine 2 receptor blocker	Antacid
Trimethoprim	Folate synthesis inhibitor	Antibiotic
Pyrimethamine	Dihydrofolate inhibitor	Malaria and toxoplasma
Salicylates	Cyclooxygenase inhibitors	Anti-inflammatory and antiplatelet
Cobicistat	Cytochrome P450 (CYP) 3A inhibitor	HIV infection
Calcitriol	Synthetic vitamin D analog	Osteoporosis and hypocalcemia
Abemaciclib, ribociclib, and palbociclib	CDK 4/ 6 inhibitors	Metastatic HR-positive and HER2-negative breast cancer
Olaparib, niraparib, and rucaparib	PARP Inhibitors	Ovarian cancer (BRCA1/2 +), metastatic breast cancer (BRCA1/ 2 +), and endometrial cancer
Imatinib, crizotinib, alectinib, ceritinib, gefitinib, pazopanib, sunitinib, sorafenib, and tucatinib	Tyrosine kinase inhibitors	NSCLC, CML, ALL, GIST, RCC, soft tissue sarcomas, GIST, HCC, thyroid cancer, and advanced or metastatic HER2-positive breast cancer
Capmatinib	MET inhibitors	NSCLC

CDK, cyclin-dependent kinase; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; PARP, poly(adenosine diphosphate-ribose) polymerase; NSCLC, non-small cell lung cancer; CML, chronic myelogenous leukemia; ALL, acute lymphocytic leukemia; GIST, gastrointestinal stromal tumor; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; and MET, mesenchymal-epithelial transition.

Conclusion

In our patient's case, serum creatinine was elevated, and the creatinine-based eGFR has declined after starting on abemaciclib. However, after checking cystatin C levels and cystatin C-based eGFR, it was confirmed that the patient was having pseudo-AKI due to inhibition of creatinine secretion. This in turn has helped us reassure the patient and our oncology colleagues that the patient does not have any true kidney injury from abemaciclib and that chemotherapy can be continued. Our goal in presenting this article is to create awareness among clinicians about pseudo-AKI in patients receiving CDK inhibitors and the importance of checking alternate markers of estimating renal function like cystatin C.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the patient for writing up and publishing this case report.

Author contributions

PE: Conceptualization, Investigation, Supervision, Writing – original draft, Writing – review & editing. ML: Data curation, Writing – review & editing. DS: Investigation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Xuefei Tian,
Yale University, United States

REVIEWED BY
Jad A. Degheili,
Ibn Sina Hospital, Kuwait
Devajit Chowlek Shyam,
Aster DM Healthcare, United Arab Emirates

*CORRESPONDENCE
Haixing Lin
✉ linhaixing12@126.com

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Report on the diagnosis and treatment of 3 cases of emphysematous pyelonephritis with two different outcomes

Minna Zhang[1], Hongxing Luo[2], Su Tan[2], Tao Fei[2], Zhimin Tang[2], Qiang Li[2] and Haixing Lin[2]*

[1]Department of Nephrology, Tongren Municipal People's Hospital, Tongren, China, [2]Department of Urology, Tongren Municipal People's Hospital, Tongren, China

Background: Emphysematous pyelonephritis (EPN) is a rare acute severe necrotising infection of the kidneys in clinical practice. It is characterized by the presence of gas in the renal parenchyma, collecting system, or perirenal tissue. The prognosis is poor, with a high nephrectomy rate and a mortality rate of up to 20–40%.

Methods: Retrospective analysis of 3 cases of emphysematous pyelonephritis with two different outcomes.

Results: Three patients who we described were all female with diabetes mellitus, and their blood sugar was poorly controlled. One patient with the advanced age and poor general health died due to the patient's family choosing to terminate therapy. Two patients underwent surgical procedures achieved an excellent clinical recovery. Both of them underwent percutaneous nephrostomy and perinephric abscess puncture drainage before nephrectomy. *Escherichia coli* were the microorganisms implicated.

Conclusion: EPN is a rare and severe urinary system infection. Computed tomography (CT) and microbiological culture confirmed the diagnosis. Control of diabetes, sensitive antibiotic therapy, fluid resuscitation and prompt surgical intervention are crucial.

KEYWORDS

emphysematous pyelonephritis, urinary system infection, microbiological culture, nephrectomy, case series

1 Introduction

Emphysematous pyelonephritis (EPN) is a rare acute severe renal necrotising infection, characterized by extensive necrosis and gas accumulation of renal parenchyma, renal collecting system and surrounding tissues (1). EPN was first reported by Kelly and McCullum in 1898 (2), it involves various bacteria, particularly Gram-negative facultative anaerobic bacteria like *Escherichia coli* (*E. coli*), Klebsiella and Aerobacter (3). Fungi are pathogens also (4). EPN is more common in female patients than male patients and usually associated with poorly controlled diabetes, urolithiasis, urinary tract obstruction or chronic kidney disease (5). The frequency of involvement in the left kidney is higher than that in the right kidney (6).

There is no universal consensus on the diagnosis and treatment of EPN currently. Computer tomography (CT) scan and laboratory evaluations are the main diagnostic procedures. A meta-analysis reported that the mortality rate of EPN is up to 20–40% (7), which is primarily attributable to septic complications. Currently, the main treatment methods include conservative medication and surgical intervention, such as surgical drainage or nephrectomy (8, 9). However, the ideal treatment method and timing of surgical intervention are still controversial. In this study, we reported 3 cases of EPN with two different outcomes, aiming to help guide treatment and improve patient prognosis (see Figures 1, 2).

2 Case presentation

Case 1: A 77-year-old female presented to a local hospital with fever and left loin pain for 3 days. Then she was referred to our department for diagnosis of septic shock and emphysematous pyelonephritis. CT indicated the possibility of left EPN, while the CT films were lost. The patient has a 5-year history of diabetes mellitus and poor glycemic control. Her vital signs were as follows: body temperature, 38.2°C; pulse rate, 126 beats/min; respiratory rate, 28 breaths/min; blood pressure, 64/46 mmHg; and pulse oxygen saturation, 98% with high flow oxygen therapy. We immediately performed resuscitation, including fluid resuscitation, intravenous norepinephrine, broad-spectrum antibiotics, glucose control and proceeded blood routine tests. Unfortunately, because of advanced age and poor general health, the patient's family chose to terminate treatment and she died subsequently.

Case 2: A 39-year-old female was referred to intensive care unit (ICU) for septic shock caused by EPN. She was admitted with complaints of frequent micturition, urgency, pain in urination over 10 days, and fever over 7 days. She received medical treatment for acute pyelonephritis, characterized by fever, acute urinary retention, and significant thrombocytopenia (5×10^9/L). At that time, laboratory tests revealed the following: white blood cell count of 8.69×10^9/L, creatinine of 141 μmol/L, C-reactive protein of 316 mg/L, glycosylated hemoglobin (Hgb) of 12.3% and blood glucose of 39.14 mmol/L. *E. coli* was identified by blood culture. CT scan showed loss of normal morphology of the right kidney, with a significant decreased density and a large amount of gas density shadows, indicating the possibility of EPN. After active resuscitation, adequate hydration, glycemic control, and antibiotic therapy with meropenem, the patient's condition was stabilized and transferred to the Department of Urology. We used subcutaneous insulin and glycemic insulin to control the patient's blood glucose under the supervision of an endocrinologist. Percutaneous drainage (PCD) was performed promptly after the patient's shock was corrected and platelet levels reached 207×10^9/L. Afterwards, the patient's condition stabilized. While considering the severe damage to the renal parenchyma, nephrectomy was finally performed.

Case 3: A 61-year-old female was referred to the Department of Urology with left loin pain over 10 days and fever lasting for 2 days. She received internal medicine treatment at a local

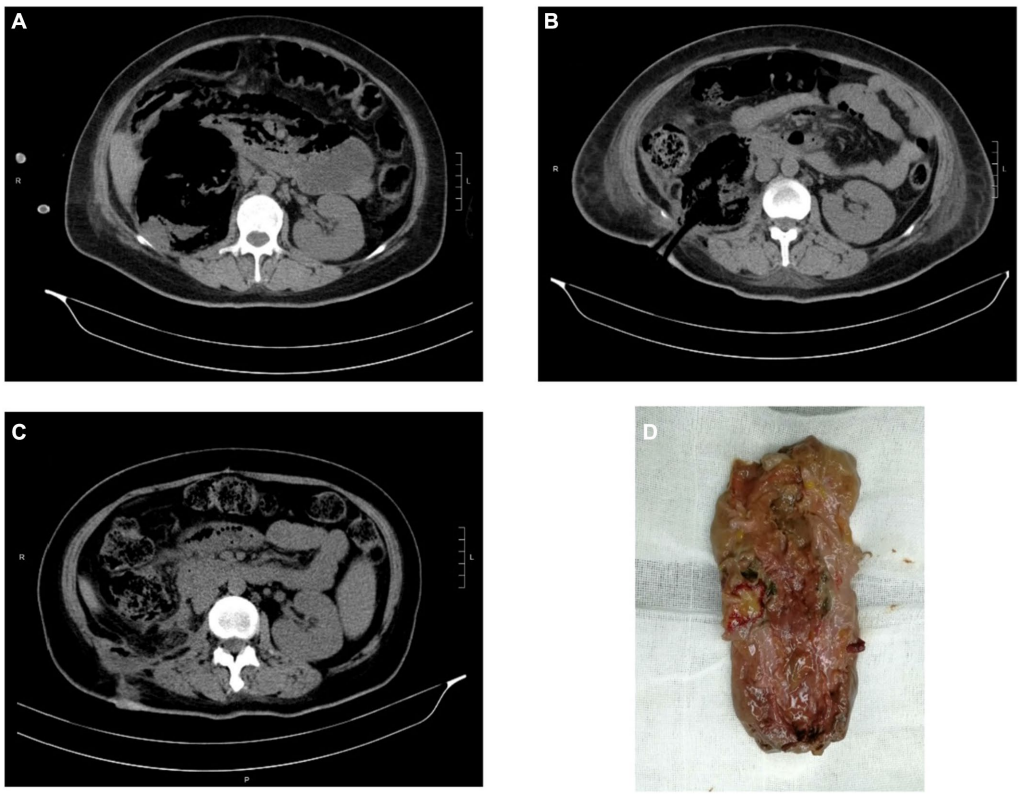

FIGURE 1
CT images and kidney specimen of Case 2. **(A)** The extension of gas beyond Gerota's fascia of right kidney. **(B)** CT imaging after PCD. **(C)** CT imaging after open nephrectomy. **(D)** The removed right kidney tissue.

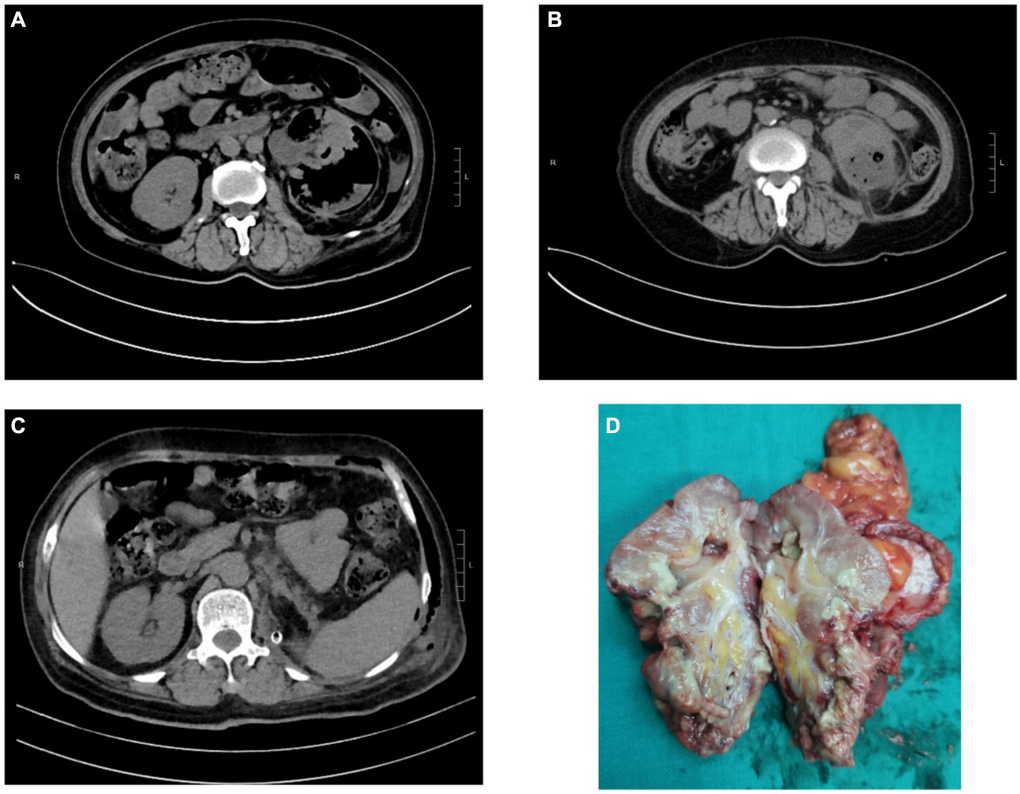

FIGURE 2
CT images and kidney specimen of Case 3. **(A)** Gas and abscess in the left kidney and perirenal tissue. **(B)** CT imaging after PCN. **(C)** CT imaging after laparoscopic nephrectomy. **(D)** The excised left kidney tissue.

hospital, considering EPN by CT examination. However, the treatment effect was not satisfactory, and she was transferred to our hospital due to fever and weakness. She denied the medical history of diabetes mellitus, while her blood glucose was up to 16.7 mmol/L at admission. Laboratory tests revealed the following: glycosylated Hgb12.2%, white blood cell count 14.5×10^9/L, hemoglobin 96 g/L, creatinine 120.4 μmol/L, procalcitonin 79.34 ng/L, C-reactive protein 116.78 mg/L, and interleukin-6 (IL-6) 100.2 pg/mL. Also, *E. coli* was identified by blood culture which was sensitive to cefoperazone/sulbactam sodium. After 8 days of internal medicine treatment, the patient's acute signs and symptoms were relieved, she underwent percutaneous nephrostomy (PCN) after stabilization. However, due to severe damage to the renal parenchyma and loss of function, she ultimately underwent nephrectomy.

3 Discussion

EPN is a life-endangering suppurative infection of the renal parenchyma and perirenal tissue (7), Its mortality rate up to 78% in 1970s (10). Recently, many reports indicated a decrease in mortality rates, ranging from 11 to 42% (11, 12). Its mortality rate is related to many factors, including thrombocytopenia, altered sensorium and/or shock at initial presentation, as well as polymicrobial infections (13). In this study, an elderly patient with poor general health died due to the patient's family choosing to terminate therapy.

Lack of specific clinical manifestations makes early diagnosis of EPN difficult. Its physical symptoms and signs are those of pyelonephritis such as dysuria, fever/rigours, nausea, vomiting, and flank pain (2). However, it progresses rapidly, and patients can manifest as severe sepsis, thrombocytopenia, renal failure, respiration failure, consciousness disorders and even shock on admission, which is life-threatening (8, 14, 15). Therefore, prompt diagnosis and treatment are crucial. Imaging modality, including CT and ultrasonography, plays a major role in the diagnosis and management of EPN (16). CT is preferred as it is more sensitive and also defines the extent by identifying features of renal parenchymal damage (2). Based on CT examination, Huang He classified EPN and offered subsequent treatments (17). The classification as follow: Class 1 indicates gas confined to the collecting system; Class 2 indicates gas confined to the renal parenchyma without extension to the extrarenal space; Class 3A indicates extension of gas or abscess to the perinephric space; Class 3B pertains to extension of the gas or abscess to the pararenal space; and Class 4 refers to bilateral EPN or a solitary kidney with EPN. For our patients, Case 1 cannot be classified due to the loss of CT films. Case 2 can be classified as 3B with extension of gas beyond Gerota's fascia. Case 3 can be classified as 3A with perinephric extension of gas and abscess.

In addition, laboratory tests provide guidance for treatment. Leukocyte and platelets play an active role in the systemic inflammatory response to infection and antimicrobial host defense. Platelets support leucocytes in pathogen arrest and transmigration (18). Elbaset et al. (19) found that lower platelet to leucocytic count ratio (PLR) is an independent simple predictor for sepsis and mortality

in EPN patients. Lower PLR was found to be correlated with the lower albumin level and higher blood glucose levels. And the most frequent comorbidity of EPN was diabetes mellitus, reported in 69–85% of the patients (20). The high glucose content in tissues provides a favorable environment for the gas-producing fermentation of bacteria, thus promoting the growth of bacteria, leading to renal parenchyma destruction and higher morbidity (1, 8). Also, the high glucose content in tissues impairs leukocytic function and leads to higher incidence of sepsis (18). In our study, all cases were comorbid with diabetes mellitus, and had poor glycemic control at admission.

IL-6 is a soluble protein synthesized by T cells, which induces the synthesis and secretion of acute phase proteins by multiple cells and is involved in regulating inflammation and immune responses (21–23). IL-6 serves as an important mediator during the acute phase of response to inflammation in sepsis (21, 24), which is considered a biomarker with high diagnostic and prognostic value in sepsis (25). IL-6 levels can increase hundreds of times and reach their peak within 2 h after an inflammatory response occurs, earlier than other cytokines, as well as C-reactive protein (CRP) and procalcitonin (PCT) (22, 23). Song et al. (21) reported that IL-6 is an independent risk factor for 28 day mortality in patients with sepsis and septic shock. While another report showed that IL-6 was not significantly associated with 28-day mortality in patients with sepsis, suggesting that IL-6 cannot predict mortality in patients with sepsis (26). This requires further research. In our study, the IL-6 level reached 100.2 pg/mL within 2 h of admission in Case 3. However, this was not the level within 2 h of the initial of the inflammatory response.

Bacterial culture and drug sensitivity testing help in the selection of sensitive antibiotics. The most common pathogen was *E. coli*, followed by *Klebsiella pneumoniae* and *Proteus* spp. (7, 27). Of course, there are also poly-microbial infections. Some literature suggests that the increased EPN mortality is not related to the strains of infection, but rather to poly-microbial infections and failure of conservative treatment (7, 28). Hence, early diagnosis and intensive care with focus on broad-spectrum antibiotics, fluid resuscitation, and insulin infusion for glycemic control improves prognosis and reduces mortality (29). A study from Mexico reported that the rate of ESBL-producing microorganisms in EPN was 31.7% (20). Another study from a large, multicenter series shown that 52.3% of urine cultures were positive for ESBL agents in EPN (30). It pointed out that the most common antibiotics associated with ESBL agents are prior use of third-generation cephalosporins and quinolones. When it comes to antibiotic selection, appropriate empirical antibiotic is essential before bacterial culture and drug sensitivity testing. Gram-negative bacteria remain the most common causative organisms, so the empirical antibiotic should target them (2). Lu et al. (31) recommend third-generation cephalosporins as initial treatment of EPN. While in patients with risk factors for antibiotic resistance, carbapenem is the empiric antibiotic of choice. In this study, we selected meropenem as empirical antibiotic. Subsequent bacterial cultures indicate that both Case 2 and Case 3 were infected with *E. coli* and which sensitive to meropenem.

Compared to conservative treatment with antibiotics alone, additional interventions of PCD of the abscess or nephrectomy is associated with lower mortality (27). Class 1 and 2 can be treated conservatively whilst Class 3 and 4 warranted further procedures such as drain placement, including JJ ureteral stenting, PCD, PCN, and nephrectomy (13). In our study, there was a case that the patient's family chose to terminate therapy after conservative treatment was ineffective and ultimately died. The other two patients, after conservative treatment, showed stable condition. Their condition was controlled by timely surgical drainage. However, due to severe structural damage and loss of physiological function, the affected kidney was ultimately removed, with one case undergoing open nephrectomy and the other one undergoing laparoscopic nephrectomy.

4 Conclusion

Clinicians should be aware of the seriousness of EPN, which requires prompt diagnosis and therapy. Early diagnosis and intensive care with focus on broad-spectrum antibiotics, fluid resuscitation, and insulin infusion for glycemic control can improve prognosis and reduce mortality. For severe patients, further procedures are required, including JJ ureteral stenting, PCD, PCN, and nephrectomy.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MZ: Data curation, Methodology, Writing – original draft. HoL: Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. ST: Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing. TF: Data curation, Investigation, Writing – review & editing. ZT: Methodology, Writing – review & editing. QL: Data curation, Methodology, Writing – review & editing. HaL: Conceptualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Leopoldo Ardiles,
Universidad Austral de Chile, Chile

REVIEWED BY
Maria Amicone,
Federico II University Hospital, Italy
Patricia Herrera,
Salvador Hospital, Chile

*CORRESPONDENCE
Xiang-Yang Li
lixy@hku-shz.org

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Case report: Roxadustat overdose in an anemia patient of chronic kidney disease: insight beyond insignificant consequence

Long-Guang Zhang, Xue-Juan Ma and Xiang-Yang Li*

Department of Nephrology, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

A 71-year-old man with a 20-year history of grade 3 hypertension experienced kidney dysfunction 2 years earlier. His serum creatinine (SCr) at the time was 140 μmol/L [with estimated glomerular filtration rate (eGFR) of 43.9 ml/min per 1.73m^2], for which he received irbesartan since. At initial presentation, the spot urine dipstick protein was 1+, with an albumin-to-creatinine ratio of 230 mg/g (0–30) and normal urine sediments. The SCr was 176 μmol/L (eGFR = 32.8 ml/min per 1.73m^2). The hemoglobulin (Hb) level decreased from 102 to 96 g/L despite oral ferrous succinate 100 mg twice daily starting 2 months ago. Roxadustat (ROXA) 50 mg (body weight, 70 kg) three times weekly was then prescribed. Unfortunately, the patient mistakenly took the drug at 50 mg three times a day (i.e., 1,050 mg instead of the intended 150 mg per week), which was 3.5 times the recommended starting dose for non-dialysis-dependent chronic kidney disease (CKD) patients (100 mg three times weekly for body weight >60 kg) and two times the highest drug manual-recommended weekly dose (2.5 mg/kg three times weekly) approved in the country. When the attending nephrologist discovered the misuse 1 month later, the patient reported no apparent discomfort, and his home blood pressure was in the range 110–130/60–80 mmHg. Repeat blood tests showed that the Hb increased from 96 to 163 g/L and the SCr from 199 to 201 μmol/L in a month. The serum alanine transaminase (ALT) remained within the normal range (from 12 U/L at baseline to 20 U/L), while the serum total and indirect bilirubin levels were slightly elevated. ROXA was withheld immediately. In 30 days, the serum bilirubin returned to baseline, but the Hb decreased from 163 to 140 g/L, and then to 108 g/L after 3 months. On the other hand, the SCr increased from 179 to 203 μmol/L. At 9 months after the initial dosing, when the SCr increased to 256 μmol/L and the Hb decreased to 94 g/L again, ROXA 50 mg three times weekly was reinitiated uneventfully. Herein, by introducing a case who erroneously consumed twice the highest recommended dose of ROXA for a month, but had apparently no obvious discomfort or unfavorable consequence, we attempt to provide a brief overview of the mechanism of action, characteristics, drug metabolism, and side effect profile associated with this agent.

KEYWORDS

roxadustat, anemia, chronic kidney disease, hypoxia-inducible factor, prolyl hydroxylase inhibitor

Introduction

Anemia is a common complication of chronic kidney disease (CKD) that occurs more frequently with declining renal function. Erythropoietin (EPO) inadequacy, abnormal iron metabolism, systemic inflammation, blunted bone marrow response, and nutritional deficiency, along with a reduced erythrocyte lifetime, are the major causes of anemia of CKD (ACKD) (1, 2). Successful cloning of the *EPO* gene in the early 1980s and the ensuing development of recombinant *EPO* and its analogs enabled erythropoiesis-stimulating agents (ESAs), along with iron supplementation, to become the mainstay of treatment for renal anemia (3). Roxadustat (ROXA) is a first-in-class orally administered hypoxia-inducible factor–prolyl hydroxylase inhibitor (HIF-PHI) that primarily works by promoting the EPO production and iron availability in the treatment of ACKD. It has an established efficacy in an array of phase 3 clinical trials over placebo or ESAs. Notwithstanding, whether ROXA and generics could play a predominant role in ACKD depends on their safety profile, such as the risks of thrombosis and cardiovascular events and the likelihood of oncogenicity (4), which warrant due post-market clinical observation and quality investigations. In this paper, by introducing the case of a patient who erroneously took twofold the highest recommended dose of ROXA for a month, we attempt to provide a brief overview of the mechanism of action, the characteristics, the drug metabolism, and the common side effect profile of this agent.

Case presentation

A 71-year-old man with a 20-year history of grade 3 hypertension presented for renal dysfunction. He was a retired farmer and non-smoker with otherwise insignificant past medical or family history. His hypertension was sub-optimally controlled at 130–150/90–100 mmHg with 5 mg amlodipine daily. He discovered kidney functional impairment 2 years earlier. His serum creatinine (SCr) at the time was 140 μmol/L [estimated glomerular filtration rate (eGFR) of 43.9 ml/min per 1.73m^2], for which he received irbesartan, metoprolol extended-release tablet, and atorvastatin. At presentation, the spot urine dipstick protein was 1+, with an albumin-to-creatinine ratio of 230 mg/g (0–30) and normal urine sediments. His SCr decreased from 193 to 176 μmol/L (eGFR = 32.8 ml/min per 1.73 m^2) after 150 mg irbesartan was switched to sacubitril/valsartan 50 mg plus amlodipine 5 mg daily. The serological examinations for infections, autoimmunity, monoclonal gammopathy, and other potential secondary causes of renal dysfunction were negative. Ultrasonography revealed patent bilateral renal arteries and basically normal kidney sizes. He was diagnosed with hypertensive nephropathy and CKD A2G3b. When low-dose furosemide and spironolactone (20 mg of each agent daily) were taken due to emerging distal leg edema, the home blood pressure was in the range 100–130/54–70 mmHg and his SCr was again elevated from 177 to 199 μmol/L. The diuretics were discontinued. However, the hemoglobulin (Hb) level decreased from 102 to 96 g/L despite oral ferrous succinate 100 mg twice daily starting 2 months prior. Given his old age and the elevated risks of cardiovascular disease, mild anemia, and stage 3 CKD in the absence of chronic comorbidities, as well as in an attempt to avoid a potential quick Hb rise in the short term, ROXA 50 mg three times weekly was prescribed (instead of 100 mg three times a week for a patient with a bodyweight of 70 kg) as a trial treatment. Unfortunately, the patient mistakenly took the drug at 50 mg three times a day (i.e., 1,050 mg instead of the intended 150 mg per week), which was 3.5 times the recommended starting dose for non-dialysis-dependent CKD patients (100 mg three times weekly for body weight >60 kg) and two times the highest drug manual-recommended weekly dose (2.5 mg/kg three times weekly) approved in the country. When the attending nephrologist found the misuse 1 month later, the patient reported no apparent discomfort, and his home blood pressure was in the range 110–130/60–80 mmHg. Repeat blood tests showed that the Hb level increased from 96 to 163 g/L and the SCr from 199 to 201 μmol/L in a month. The serum alanine transaminase (ALT) remained within the normal range (from 12 U/L at baseline to 20 U/L), while the serum total and indirect bilirubin levels increased from 9.6 to 21.7 μmol/L (0–21) and from 4.5 to 12.4 μmol/L (0–5), respectively. The serum creatine kinase was not determined due to the absence of muscular discomfort. ROXA was withheld immediately. After 30 days, the serum bilirubin returned to baseline; however, the Hb decreased from 163 to 140 g/L and subsequently to 108 g/L after 3 months. On the other hand, the SCr increased from 179 to 203 μmol/L. At 9 months after the initial dosing, when the SCr increased to 256 μmol/L and the Hb decreased to 94 g/L again, ROXA 50 mg three times weekly was reinitiated uneventfully. The baseline values and fluctuations of Scr and Hb within 9 months are shown in detail in Figure 1.

Discussion

The essential function of red blood cells (RBCs) is oxygen delivery. ACKD impairs the patient's health-related quality of life and is associated with increased morbidity and mortality, particularly when Hb falls below 100 g/L. The introduction of epoetin four decades ago revolutionized the treatment for anemia. However, evidence revealed that full anemia correction for a Hb target of above 130 g/L with ESAs is related to the increased incidence of cardiovascular events, hypertension, thrombosis, or stroke. Although the underlying pathophysiology remains so far inadequately elucidated, the proposed mechanisms include, but are not limited to, a supra-physiological concentration of EPO during treatment, extensive presence of the EPO receptor (EPOR) in organ tissues, endothelial activation, and enhanced platelet reactivity (5). In 2012, the KDIGO guideline recommended that oral iron therapy for 1–3 months be applied before the start of ESA treatment until the Hb falls to below 100 g/L, a near-normal correction of anemia to a Hb target of ≤115 g/L, that ESAs not be used to intentionally maintain the Hb concentration above 130 g/L, and that individualization of treatment be applied (3).

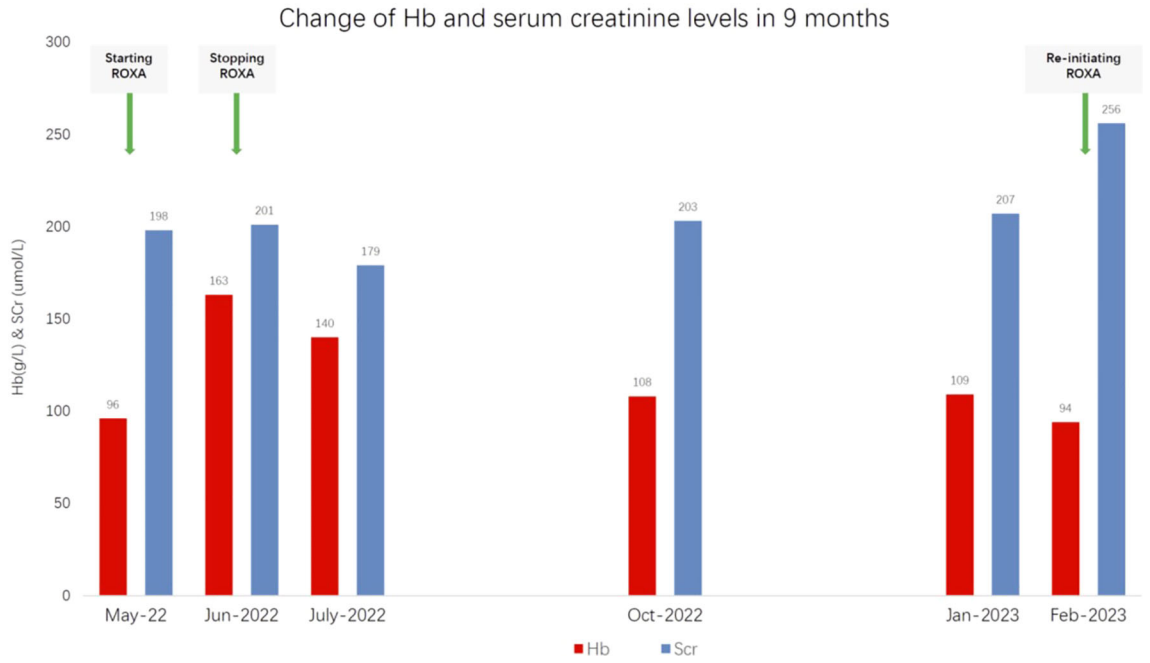

FIGURE 1
Changes in the hemoglobulin (Hb) and serum creatinine levels 9 months after the initiation of roxadustat (*ROXA*).

HIF is a heterodimeric transcription factor discovered during the search for transcriptional regulators of EPO. It plays a central role in the adaptive response of cells to changes in oxygen availability. HIF consists of an oxygen-labile α-subunit and a constitutive β-subunit. HIF-α has three isoforms. HIF-1α is widely expressed across cell types and is induced more strongly by severe hypoxemia. The expression of HIF-2α is organ-specific (e.g., endothelial cell, kidney, liver, and gut) and is sensitive to moderate hypoxemia. HIF-3α, which possesses multiple variants, supplements or acts as a negative regulator of HIF-1α/HIF-2α. The activity of HIF relies on HIF-α, whose level is tightly regulated by the prolyl hydroxylase domain (PHD). In normoxia, co-factored by Fe^{2+} and using molecular oxygen and 2-oxoglutarate (2-OG) as substrates, PHD hydroxylates two prolyl residues of HIF-α, leading to its ubiquitylation and subsequent proteasomal degradation by the von Hippel–Lindau protein–E3 ligase complex. HIF-α has a mean half-life of only a few minutes. The transcription of EPO is fine-tuned by the HIF-2α/PHD2 axis (6). In hypoxemia, the activity of PHD is suppressed, and an increased level of HIF mediates the upregulation of hundreds of target genes that are implicated in erythropoiesis, iron and energy metabolism, angiogenesis, and cell growth and survival, among others, to defend oxygen homeostasis.

ROXA is the first oral HIF-PHI developed to treat anemia in a more "physiological manner" by simulating moderate hypoxemia. As of 2023, there have been six HIF-PHIs that obtained approval globally, each possessing a similar core structure working as an Fe^{2+} chelator by reversibly binding to the active site of PHD (7). HIF-PHIs act through multiple effects encompassing the induction of the EPO/EPO receptor, promoting iron absorption and transport and heme production, and can effect serum hepcidin reduction (4). They dose-dependently increase endogenous EPO synthesis, but expose patients to lower supra-physiological EPO concentrations. ROXA is a small-molecule carboxylic acid compound, is easily absorbable, and is eliminated via the urine and feces after metabolism, with a mean half-life of 10–12 h among the CKD population. Moderate hepatic impairment, a reduced eGFR, or dialysis does not impact its pharmacodynamics with clinical relevance. The EPO levels in the general population range from 5 to 20 IU/L. Approximately 1–2 mg/kg of ROXA can induce a median peak endogenous EPO level of 110–350 IU/L, which returns to baseline at 48 h. Therefore, a ROXA dose range above 3–4 mg/kg, corresponding to an EPO concentration of higher than 700–1,000 IU/L, is not otherwise recommended (8). Data have shown that ROXA decreases the serum total and low-density lipoprotein (LDL) cholesterol levels (9). Through the inhibition of CYP2C8 and OATP1B1, 100–200 mg of ROXA can increase the drug exposure (area under the curve, AUC) of gemfibrozil and statins by two- to threefold (10), which could predispose rhabdomyolysis in susceptible patients (11). Sevelamer carbonate, calcium acetate, and ferrous sulfate reduce the AUC of ROXA, and a separate dosing of at least 1 h is recommended. Owing to the promotion of EPO production and the pleiotropic effects of HIF, issues on the drug safety of HIF-PHIs include cardiovascular morbidities and risks of thrombosis and tumorigenicity, among others, particularly at higher doses. ROXA is non-inferior to ESAs concerning MACE (major adverse cardiovascular event) among patients on dialysis; however, it did not meet the non-inferior margin agreed upon with the U.S. Food and Drug Administration (FDA) on non-dialysis patients (4, 12). The relative risk of thrombosis is higher in ROXA than in ESA by 1.35 (7.27 *vs.* 5.37 per 100 patient-year) among dialysis-dependent patients (12), which is thought to be related to the interference of HIF with the coagulation system and the induction of plasminogen activator inhibitor expression.

Healthy adults can generate as much as 2×10^{11} of erythrocytes daily, with an average life span of approximately 120 days. The lifetime of RBCs in CKD is reduced with deteriorating kidney function, even by half in stage 5 disease (13). The rapid decline of Hb (−14.1%) within the first 30 days in our case was thought to be associated with neocytolysis. Neocytolysis refers to selective hemolysis or the destruction of newly formed RBCs after sudden EPO withdrawal or rapid reduction (such as in the setting of descent from high altitude to sea level, with a 10%–18% fall of Hb detectable after 8–10 days), forming a tier of erythrocyte regulation during environmental change from hypoxia to normoxia (9), a phenomenon preventable with the administration of low-dose EPO (14). The subsequent Hb decline in this case, aside from EPO insufficiency, could also be related to eryptosis, a programmed cell death of erythrocyte analogous to apoptosis in nucleated cells, which is now considered an important contributor to ACKD. The pathomechanism of eryptosis, although has not been completely elucidated, is linked with the overload of cytosolic Ca^{2+} and the breakdown of cell membrane phospholipid asymmetry and phosphatidylserine externalization resulting from stressful insults (e.g., CKD, malignancies, sepsis, diabetes, heart and hepatic failure, among others) (15). Eryptotic RBCs undergo degradation in the reticulo-endothelial system. In our case, the elevated serum indirect bilirubin level after 1 month of ROXA use was an indicator of hemoglobin breakdown and a heightened RBC turnover rate, which is thought to be associated with the enhanced phagocytosis of erythrocytes due to the decreased anti-deoxidant ability of the newly generated RBCs (16) and eryptosis in the context of CKD. The Scr levels almost did not change after 1 month of ROXA overdose. HIF-PHIs have no proven effect on kidney protection yet; hence, it was difficult to associate the decreased Scr (201–179 μmol/L) in the second month in this connection. Given no additional insult, the subsequent gradual deterioration of renal dysfunction in this case was possibly related to the progression of CKD hypertensive nephropathy.

Hypoxemia represents a feature of tumoral tissue, and the adaptive hypoxemic response of malignant cells influences the cellular growth, metastasis, and therapeutic response. EPOR has been identified in a number of cancer cells, and therapy with ESAs has a known effect of negatively impacting the survival of patients with malignancy. For patients with malignancy, ESAs are now recommended specifically for subjects with chemotherapy-induced anemia whose cancer treatment is not curative in intent (17). However, there is a lack of global guidelines or consensus to inform the management of ACKD in patients with cancer. Intravenous iron therapy offers an alternative to ESAs in this setting, although the relevant protocol and the long-term safety of which are yet to be established. Although current phase 3 trials have not shown an increased tumorigenicity by ROXA, clinicians await the results of a dedicated clinical study in this respect. Moreover, as the HIF-PHIs now in use indiscriminately inhibit PHD1–3 and can increase the levels of HIF-α isoforms, which potentially offer advantages in the hypoxemic adaptation of cancer, we argue for caution in this area. Except for specific malignancies, such as von Hippel-Lindau disease and renal clear cell carcinoma, in which cases the overactivation of HIF is directly related to tumorigenesis, HIF-PHIs should be avoided. The prospects of HIF-PHIs in the therapeutics for ACKD lie in the optimization of treatment precision and individualized drug application for a balanced benefit and risk.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was performed in accordance with Helsinki Declaration revised in 2013 and has been approved by the Ethics Committee of the University of Hong Kong-Shenzhen Hospital (approval number: [2023]126). Written informed consent was obtained from the participants or from their relatives for the use of their social and medical data for publication of this case report. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

L-GZ: Writing – original draft. X-JM: Writing – original draft. X-YL: Writing – review & editing, Conceptualization, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Xuefei Tian,
Yale University, United States

REVIEWED BY
Jad A. Degheili,
Ibn Sina Hospital, Kuwait
Stefania Tamburrini,
Ospedale del Mare, Italy

*CORRESPONDENCE
Dong Jun Park
✉ drpdj@naver.com

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Xanthogranulomatous pyelonephritis in a patient with polycystic kidney disease without underlying risk factors: a case report

Yoomee Kang[1], Tae Won Lee[1], Eunjin Bae[1,2,3], Ha Nee Jang[4], Sehyun Jung[4], Seunghye Lee[4], Se-Ho Chang[2,3,4] and Dong Jun Park[1,2,3]*

[1]Department of Internal Medicine, Gyeongsang National University Changwon Hospital, Changwon, Republic of Korea, [2]Department of Internal Medicine, Gyeongsang National University College of Medicine, Jinju, Republic of Korea, [3]Institute of Health Science, Gyeongsang National University, Jinju, Republic of Korea, [4]Department of Internal Medicine, Gyeongsang National University Hospital, Jinju, Republic of Korea

Xanthogranulomatous pyelonephritis (XGP) is an extremely rare, chronic granulomatous inflammatory condition thought to arise secondary to a combination of obstruction, recurrent bacterial infection and an incomplete immune response although the etiology of XGP is more complex. We would like to report a case of XGP occurring in a patient with polycystic kidney disease (PCKD), which has not been previously documented in etiology. A 29-year-old woman presented to our hospital with right upper quadrant pain for 5 days. She had experienced a low-grade fever, generalized weakness, and myalgia throughout her body for 2 weeks. She had no history of renal stones or recurrent UTIs. Contrast-enhanced CT revealed a well-enhancing large septated cystic mass in the right kidney and numerous cysts in the liver and both kidneys. Open right radical nephrectomy was performed due to the suspicion of renal cell carcinoma, as there was no response to antibiotics over 7 days. Gross specimen demonstrated architectural distortion due to xanthomatous nodules and a dilated pelvico-calyceal system filled with pus and blood. Microscopic examination revealed infiltration of neutrophils and lipid-laden macrophages. The patient is currently being followed up in the outpatient clinic without recurrence of XGP. This is the first reported case of XGP in a patient with underlying PCKD. Physicians should consider PCKD as a potential underlying cause of XGP.

KEYWORDS

xanthogranulomatous pyelonephritis, polycystic kidney disease, fever, abdominal pain, renal mass

Introduction

Xanthogranulomatous pyelonephritis (XGP) is a rare form of chronic granulomatous inflammation, characterized by the destruction of renal parenchyma and its replacement by solid sheets of lipid-laden macrophages, resulting in a non-functioning kidney (1). The prevalence of XGP varies from 0.6 to 1% of all cases of renal infections, with an incidence of

1.4 cases per 100,000 population per year. While the disease can occur in all age groups, it is more common in women than in men, typically affecting individuals in their fifth and sixth decades of life. There is no racial predilection (2–5). XGP is frequently referred to as a pseudotumor because the enlarged kidney resembles a tumor and leads to local invasion and destruction (1–5).

The term "xantho" originates from the infiltration of lipid-laden macrophages, which appear yellow in pathological sections. XGP typically arises in the setting of obstructive uropathy, nephrolithiasis, or urinary tract infections (UTIs) (1). The current concept of XGP was established by Osterlind (6) in 1944, although it was initially described by Schlagenhaufer (7) in 1916. While the disease typically manifests diffusely, it can sometimes be focal. The diagnosis of XGP is challenging due to its nonspecific findings, often progressing insidiously until the development of late-stage extrarenal sequelae (1). Preoperative diagnosis is also difficult because radiological imaging features can overlap with various other conditions, including abscess, lymphomas, angiolipomas, leiomyosarcomas, Wilms tumor, renal cell carcinoma (RCC), transitional cell carcinoma, renal tuberculosis, and malakoplakia (1, 2, 8). If left untreated, the disease can progress to complications necessitating nephrectomy. We present the first reported case of XGP occurring in a patient with polycystic kidney disease (PCKD) without major risk factors such as obstructive uropathy or recurrent UTIs.

Case report

A 29-year-old Korean woman presented to our hospital with worsening pain in her right upper quadrant (RUQ) for 5 days. She had experienced a mild fever, generalized weakness, and myalgia throughout her body for 2 weeks, without any urinary symptoms such as frequency, dysuria, or urgency. Initially, she attributed her symptoms to a cold and took acetaminophen. However, the pain worsened and the fever persisted. She had no significant medical history, such as renal stones or recurrent UTIs, and denied any genetic diseases, including PCKD. She also denied any recent travel or use of drugs or herbal medications except for acetaminophen. Upon physical examination, she appeared acutely ill.

Her vital signs were as follows: blood pressure (BP), 130/80 mmHg; body temperature (BT), 38.5°C; heart rate (HR), 68 beats per min; and respiratory rate (RR), 20 breaths per min. She was alert and oriented with no abnormalities noted on neurological examination. Conjunctival pallor was present, but sclerae were not icteric. No palpable cervical lymphadenopathy or skin color changes were observed. Lung auscultation revealed no wheeze or murmurs. A soft, tender mass was palpable in the RUQ, and there was tenderness on percussion over the right costovertebral angle. There was no pitting edema noted in her lower extremities.

Her initial laboratory findings were as follows: leukocyte count, 12.09 (range: 4.0–10.0) × 10^9/L; neutrophils, 80%; lymphocytes, 10.9%; monocytes, 5.9%; hemoglobin, 8.3 (range: 12–16) g/dL; platelet count, 167 (range: 130–400) × 10^9/L; blood urea nitrogen, 6 (range: 8.0–20.0) mg/dL; creatinine, 0.5 (range: 0.51–0.95) mg/dL; total protein, 6.9 (range: 6.6–8.7) g/dL; albumin, 3.3 (range: 3.5–5.2) g/dL; total cholesterol, 105 (range: 120–200) mg/dL; aspartate transaminase, 18 (range: 1–37) U/L; alanine transaminase, 14 (1–37) U/L; glucose, 103 (range: 70–110) mg/dL; sodium, 133 (range: 135–145) mmol/L; potassium, 3.4 (range: 3.4–5.1) mmol/L; chloride, 97 (range: 98–110) mmol/L; prothrombin time, 13.2 (range: 11.9–14.3) s; aPTT, 35.2 (range: 29.1–43.5) s; and C-reactive protein, 131 (range: 0–3) mg/L. Her serum iron profile was as follows: iron, 13 (normal range: 60–180) μg/dL; total iron-binding capacity, 294 (range: 230–430) μg/dL; transferrin saturation, 4% (range: 20–55%); and ferritin, 81.97 (range: 13–150) ng/mL. Urinalysis revealed specific gravity of 1.010, no proteins or blood, and 3+ white blood cells. Microscopy revealed numerous white blood cells, whereas urine smear did not detect any bacteria. Furthermore, urine and blood cultures were negative.

The initial kidney ultrasonography (USG) performed on admission day revealed variable sized renal cysts on both kidneys and an 8.8 cm multiseptate cystic mass on the mid-lower pole of the right kidney (Figure 1). Empirical treatment with intravenous ciprofloxacin was initiated under the suspicion of renal abscess, but the patient's RUQ pain and fever persisted despite 3 days of antibiotic therapy. Her vital sings and significant laboratory tests measured on the third day of her hospitalization were as follows: BP, 120/70 mmHg; BT, 38.9°C; HR, 80 beats per min; and RR, 20 breaths per min and leukocyte count, 15.12 (range: 4.0–10.0) × 10^9/L; neutrophils, 82%; lymphocytes, 11%; monocytes, 4.2%; hemoglobin, 8.1 (range: 12–16) g/dL; platelet count, 123 (range: 130–400) × 10^9/L; blood urea nitrogen, 12 (range: 8.0–20.0) mg/dL; creatinine, 0.5 (range: 0.51–0.95) mg/dL; total protein, 6.9 (range: 6.6–8.7) g/dL; albumin, 3.1 (range: 3.5–5.2) g/dL; and C-reactive protein, 101 (range: 0–3) mg/L. Contrast-enhanced CT performed on the third day of hospitalization revealed multiple cysts in the liver and both kidneys, as well as a well-enhancing septate cystic mass measuring approximately 10 cm in length on the right kidney. Mass was limited to the kidney and there was no lymph node enlargement, invasion into major veins or perinephric tissues, and distant metastasis (T2a, N0, M0, stage II) (Figure 2). Open radical nephrectomy was performed on the seventh day after admission based on the presumed diagnosis of cystic RCC due to persistent clinical symptoms and signs. Upon sectioning the kidney, distortion of the normal architecture by xanthomatous nodules and dilated pelvicocalyces filled with pus and blood were observed (Figure 2). Microscopic examination revealed numerous lipid-laden CD68-positive macrophages (Figure 3). *Escherichia coli* was cultured from

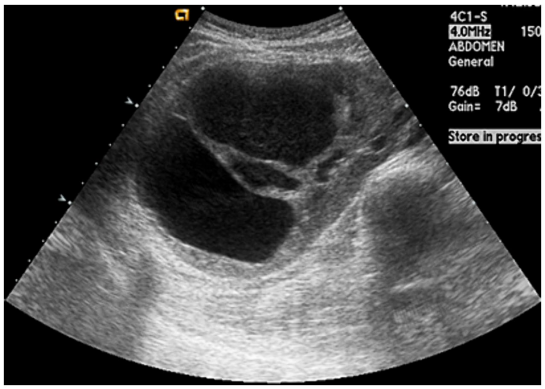

FIGURE 1
Ultrasonogaphy showing variable-sized numerous cysts and 8.8 cm multi-septated cystic mass on mid-lower pole of the right kidney.

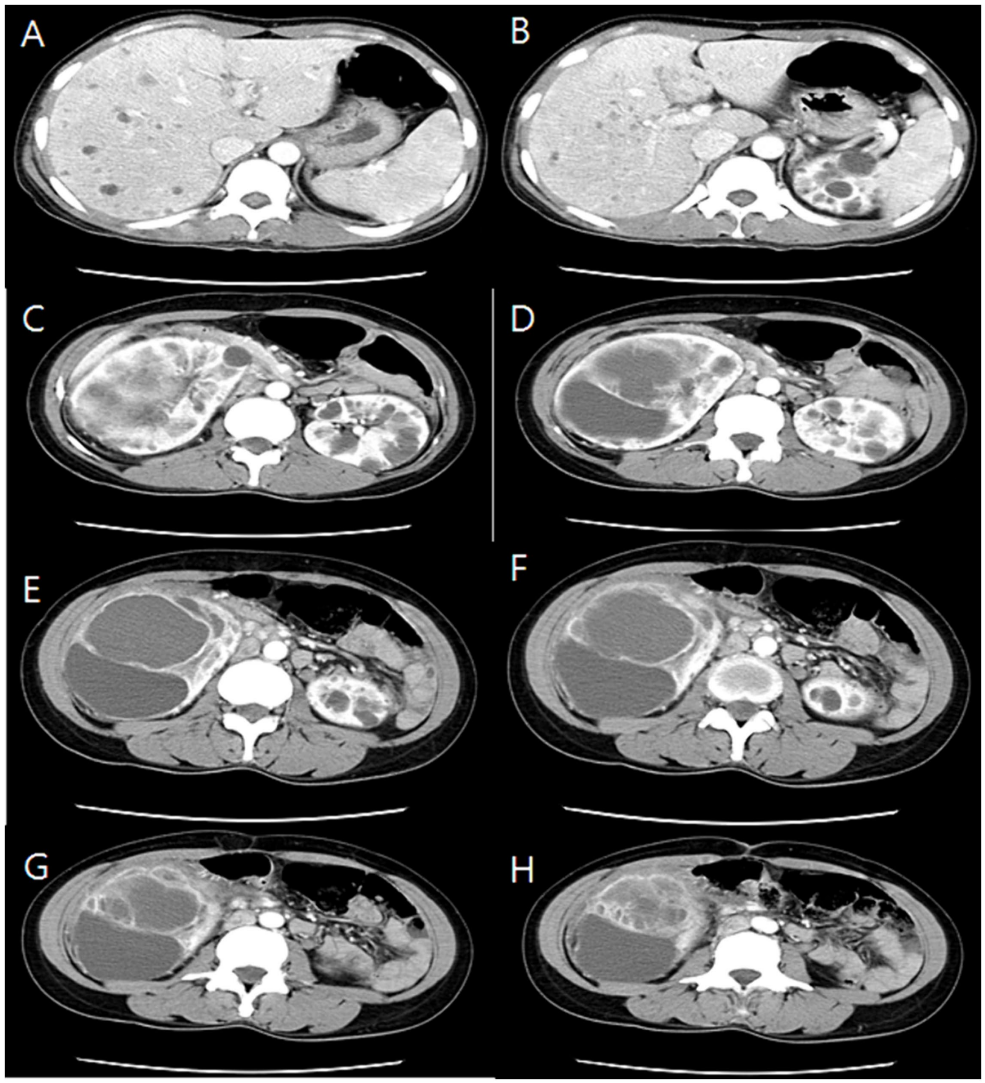

FIGURE 2
Serial section of computed tomography (CT) showing numeral cysts on liver **(A,B)** and upper pole of both kidneys **(C,D)** and 10 cm sized huge cystic mass with well-enhancing wall from mid-lower pole of right kidney **(E–H)**.

tissue samples obtained during the operation. Additional intravenous ciprofloxacin was administered starting 7 days postoperatively. The patient's clinical symptoms and signs improved on the third day after nephrectomy. She was discharged on the seventh day postoperatively and has been followed up in our outpatient clinic without XGP recurrence. Her last recorded creatinine level was 1.3 mg/dL, and her estimated glomerular filtration rate was 52 mL/min/1.73 m^2. Her father's USG which was done at outpatient clinic revealed numerous cysts on both kidneys and liver. Genetic test for ADPKD could not be performed because her family did not consent.

Discussion

This report presents the first documented case of XGP in a patient with PCKD, without known predisposing factors such as obstructive uropathy, recurrent UTIs, or a significant medical history. The diagnosis of PCKD was established for the first time during this hospitalization. CT played a crucial role in the diagnosis, as XGP presented a preoperative diagnostic challenge resembling cystic RCC, necessitating nephrectomy.

The etiology of XGP in adults remains largely unknown. However, most cases are associated with chronic urinary obstruction and infection. Urinary obstruction often occurs due to calculi, particularly staghorn stones, which are found in approximately 80% of patients. These calculi serve as a nidus for infection (1, 9). In addition, conditions leading to urinary obstruction, such as pyelo-ureteric junction obstruction, ureteropelvic duplication, ureteral schistosomiasis, and obstructing tumors (renal and transitional cell carcinomas), have been implicated (9). However, in our case, there was no radiologic evidence of urinary obstruction, and our patient denied experiencing recurrent UTIs. It is possible that the numerous cysts observed in our patient may have contributed to urinary flow obstruction, leading to asymptomatic recurrent bacterial superinfection and ultimately inducing XGP, although the exact mechanism remains unclear.

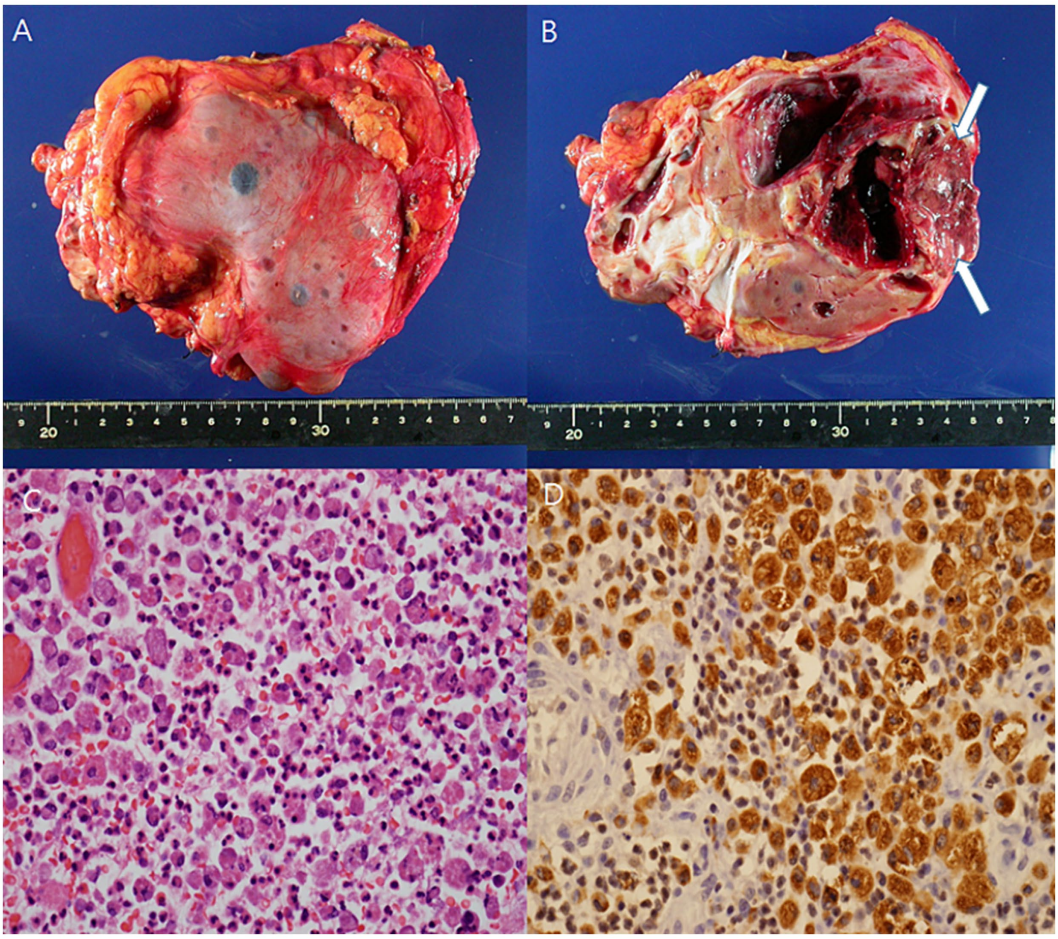

FIGURE 3
The gross specimen showed distortion of the architecture by xanthomatous nodule (arrow), and dilated pelvi-calyceal system filled with pus and blood **(A,B)**. Microscopic finding revealed infiltration of neutrophils and lipid-laden macrophages **(C)** (H/E, x400). Lipid-laden macrophage was diffusely stained for CD68 **(D)** (x400).

The exact pathophysiology of XGP remains unclear. It is presumed to involve a combination of obstruction and infection, leading to a chronic granulomatous immune response that fails to completely eradicate the inciting agent (10). This chronic inflammatory response, triggered by persistent infected debris, results in granuloma formation and destruction of renal parenchyma. The inability to clear bacterial products is associated with a limited or incomplete host immune response (11, 12). The pathogenesis of XGP involves various mechanisms, including alterations in immunologic response, changes in lipid metabolism, increased lymphatic blockage, and local vascular occlusion (13, 14). A recent study demonstrated that XGP specimens contain both classically activated macrophages (M1) and alternatively activated macrophages (M2), suggesting that the disease pathogenesis is related to repeated cycles of infection, inflammation, and attempted healing (15). Persistent obstructive uropathy perpetuates these cycles, leading to further inflammation and worsening of XGP until the renal parenchyma is extensively destroyed.

Symptoms of XGP depend on the disease severity and stage. Patients typically present with flank or abdominal pain, fever, dysuria, hematuria, a palpable mass, and weight loss. However, symptoms are often nonspecific, such as fatigue and general malaise, and may persist for more than 6 months in 42% of patients (9). Interestingly, urinary tract symptoms may be minimal or absent, leading to initial misdiagnosis. In some instances, the only symptoms may arise from extrarenal complications affecting organs such as the liver, spleen, chest wall, pleural space, abdominal wall, gluteus, and skin (1, 9). Patients with XGP often present in poor general condition due to the chronic nature of the disease, which can mimic malignancy or debilitating infections such as tuberculosis. Our patient initially experienced nonspecific symptoms of fatigue and general malaise without symptoms of UTIs.

Diagnosing XGP can be challenging due to its variable clinical presentation, ranging from asymptomatic radiological findings to more severe complications. It should be suspected in cases of recurrent UTIs occurring in the setting of chronic obstructive uropathy (1). CT is the primary imaging modality for its diagnosis, despite the possibility of overlapping imaging features with other conditions such as RCC, TCC, renal tuberculosis, and malakoplakia. The "bear-paw" sign on contrast-enhanced CT is a characteristic but not pathognomonic feature of XGP. However, a previous study demonstrated significant variation in imaging features in confirmed XGP cases (16), with a preoperative diagnosis accuracy of 28.2%. Another study reported that only 27.3% of patients are correctly diagnosed with XGP preoperatively (17). In one study, the preoperative

suspected diagnosis rate of XGP using multidetector CT was 66.67% (18). Definitive diagnosis is typically established through histological examination of tissue specimens. In our patient, the preoperative suspicion was cystic RCC, leading to open nephrectomy due to lack of history of recurrent UTIs and the absence of urinary calculi on radiological imaging, despite XGP being suspected in CT exams. Notably, surgical intervention is often necessary in cases where there is no response to antibiotics.

XGP is staged according to the classification system proposed by Malek and Elder (19), which categorizes the disease into three stages based on the extent of surrounding tissue involvement. Stage I (nephric) typically involves only the nephric tissue, with some studies using the term focal disease to describe early-stage XGP where kidneys are partially affected and renal function remains partially preserved (1, 14, 16, 17). Stage II (perinephric) involves both the nephric and perinephric fatty tissues, often termed diffuse disease (1, 20, 21). Stage III (paranephric) involves the additional infiltration of paranephric tissues and organs, leading to complications with extrarenal involvement in surrounding organs (1, 22, 23). The classification of focal and diffuse diseases helps distinguish between different forms of XGP and facilitates potential management strategies. In addition, Goyal et al. (1) proposed a new category of extrarenal disease to highlight the unique clinical presentations and management challenges. Advancements in radiological imaging techniques have significantly helped delineate the extent of XGP and have helped guide treatment decisions. In our patient, the XGP was categorized as diffuse disease.

In the management of XGP, two primary therapeutic approaches are commonly employed, depending on the extent of disease: nephrectomy and antibiotics. Nephrectomy serves as the mainstay of XGP treatment due to the significant inflammation associated with the condition, which can obscure surgical planes and compromise renal function. Previously, nephrectomy was performed for nearly all cases (1–5, 24). The choice between partial and total nephrectomy, as well as between robotic/laparoscopic and open surgical approaches, remains controversial. Antibiotics and drainage alone are typically inadequate for focal XGP. Partial nephrectomy has shown limited success, with only 5% of cases reportedly being effectively treated using this approach (14). Salvaging viable renal tissue is challenging due to the extensive destruction typically observed in XGP, often resulting in obliteration of surgical planes. Nuclear medicine renal scans have revealed minimal renal function in the affected kidney in up to 80% of cases, rendering partial nephrectomy unnecessary (9). As a result, open total nephrectomy has been the preferred approach. While the use of laparoscopic nephrectomy for XGP is controversial, it may be considered in cases where an experienced surgeon is available and the inflammation is contained within Gerota's fascia in focal and diffuse disease. However, Guzzo et al. (25) suggested that this is often challenging for XGP as it requires advanced surgical skills, and it should be offered only to highly selected patients.

Antibiotics should be utilized as adjunctive therapy in all XGP cases, as medical management alone is rarely sufficient to eradicate the infection (1). The selection of antibiotics depends on the organism cultured and antimicrobial susceptibility testing results. *E. coli* and *Proteus mirabilis* are the most commonly isolated pathogens, accounting for approximately 90% of positive urinary cultures in XGP patients, although sterile urine cultures are common (26). Studies have reported varying rates of positive urine cultures in XGP patients, ranging from 48.1 to 62.06% (26, 27). Empirical broad-spectrum antibiotics, such as extended-spectrum penicillin, third-generation cephalosporin, fluoroquinolone, and carbapenem, should be initiated until organism identification and antimicrobial susceptibility results are available. In our case, urine culture was sterile but tissue culture revealed *E. coli* susceptible to third-generation cephalosporin and fluoroquinolone.

In summary, XGP is a rare complication of pyelonephritis often associated with recurrent UTIs in the setting of chronic urologic obstruction. Its diagnosis is challenging as it can remain asymptomatic and its clinical and imaging findings may mimic other pathologies. Integrated analysis of clinical, laboratory, and imaging findings is crucial for accurate diagnosis. Physicians should be aware that the presence of numerous cysts in patients with PCKD may serve as a potential etiology for XGP, even in the absence of renal calculi and symptomatic UTIs. Early diagnosis and intervention are crucial for preserving kidney function and preventing life-threatening complications.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study protocol was approved by the Institutional Review Board of Gyeongsang National University Changwon Hospital (IRB no. 2024-02-004). Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

YK: Conceptualization, Writing – original draft, Validation. TL: Investigation, Resources, Writing – original draft. EB: Conceptualization, Methodology, Resources, Writing – review & editing. HJ: Conceptualization, Investigation, Resources, Writing – review & editing. SJ: Conceptualization, Resources, Validation, Writing – review & editing. SL: Conceptualization, Methodology, Resources, Writing – review & editing. S-HC: Investigation, Supervision, Validation, Writing – review & editing. DP: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Leopoldo Ardiles,
Universidad Austral de Chile, Chile

REVIEWED BY
Jorge Vega,
Universidad de Valparaiso, Chile
Felipe Oyanedel,
Austral University of Chile, Chile

*CORRESPONDENCE
Juan S. Izquierdo-Condoy
✉ juan1izquierdo11@gmail.com

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Fatal nephrobronchial fistula arising from xanthogranulomatous pyelonephritis: a case report

María Alejandra Burbano[1], H. A. Nati-Castillo[1], Natalia Castaño-Giraldo[2], Gildardo López[1], Romina Placencia-André[3], Camila Salazar-Santoliva[3], Melissa Villavicencio-Gomezjurado[3] and Juan S. Izquierdo-Condoy[3]*

[1]Interinstitutional Internal Medicine Group (GIMI 1), Department of Internal Medicine, Universidad Libre, Cali, Colombia, [2]Urology Department, School of Medicine, Universidad de Cartagena, Cartagena, Colombia, [3]One Health Research Group, Universidad de las Americas, Quito, Ecuador

Introduction: Nephrobronchial fistula is an exceptionally rare complication of renal infections, including the uncommon xanthogranulomatous pyelonephritis. Existing literature is limited to a few case reports, with antibiotic therapy and nephrectomy being the preferred treatments.

Case: We present the case of a 63-year-old woman with a history of recurrent xanthogranulomatous pyelonephritis in her right kidney, requiring drainage through lumbotomy. She presented with a chronic dry cough and weight loss, without other noticeable symptoms. Imaging suggested a pulmonary abscess and nephrobronchial fistula. Despite antibiotic treatment and surgical intervention, her condition progressed fatally.

Conclusion: Nephrobronchial fistulas are extremely complications of renal infections, often presenting with nonspecific symptoms. This case highlights their significant impact on morbidity and mortality, especially in resource-limited settings, and underscoring the urgent need for prompt diagnosis and treatment.

KEYWORDS

nephrobronchial fistula, lung abscess, chronic infection, xanthogranulomatous pyelonephritis, fatal outcome

1 Introduction

Fistulas between the kidney and the thoracic cavity are rare events that can arise from multiple causes, including abdominal trauma, complicated lithiasis, and, in very rare cases, renal infections such as tuberculosis, renal abscesses, and xanthogranulomatous pyelonephritis (1–3). Xanthogranulomatous pyelonephritis is a rare, aggressive variant of pyelonephritis, typically related to chronic infection and nephrolithiasis, resulting in a nonfunctioning kidney characterized by the destruction and replacement of renal or perirenal tissue with granulomatous tissue containing lipid-laden macrophages (4, 5).

The first documented case of a nephropulmonary fistula dates back to the 19th century, with approximately 70 cases reported in the first half of the 20th century (6). Since then, the incidence of nephropulmonary fistulas of infectious origin has drastically decreased, primarily

due to the availability of antibiotics that control renal infections (7, 8). Currently, nephrobronchial fistulas of infectious origin are exceedingly rare, and the association of xanthogranulomatous pyelonephritis with pulmonary abscess and nephrobronchial fistula is particularly uncommon (2, 9–11).

The standard treatment protocol involves initial antibiotic therapy followed by nephrectomy, which remains the preferred management strategy. Establishing an early diagnosis has proven to reduce further complications (11–13).

In this report, we present a case of xanthogranulomatous pyelonephritis with pulmonary abscess formation and nephrobronchial fistula, diagnosed via computed tomography in a patient with a long-standing cough and ongoing weight loss, which ultimately resulted in a fatal outcome after surgical intervention.

2 Case presentation

We present the case of a 63-year-old female patient with a history of biomass exposure, xanthogranulomatous pyelonephritis, and perirenal collection managed with drainage by lumbotomy 3 years ago. She presented to a primary care outpatient clinic with long-standing, nonspecific respiratory symptoms, including a persistent dry cough lasting for 2 years and associated weight loss. Approximately 2 weeks later, an ultrasound revealed a right lung abscess, bronchiectasis in the upper lobe of the left lung, and an abnormal lung-kidney communication, which led to hospital admission.

Seven days later, upon admission, the physical examination revealed an acceptable general condition, with a heart rate and respiratory rate at the upper limit of normal and positive percussion pain in the right flank. Laboratory tests, including a complete blood count and C-reactive protein levels, showed no evidence of a systemic inflammatory response, while urinalysis indicated pyuria without bacteriuria. Additionally, urine and blood cultures showed no microbial growth after 48 h of evaluation. However, contrast-enhanced computed tomography (CT) scan of the thorax and abdomen showed extensive heterogeneous alveolar occupation with a collection and a hydroaerial level (Figure 1). The largest abscessed communicated with the upper collecting system of the ipsilateral kidney, featuring an active fistula approximately 17 mm in transverse diameter and 32 mm in length, containing fluid, air bubbles, and calcifications of about 10 mm. In addition, a coralliform calculus measuring 85 × 34 × 40 mm within the collecting system was noted, thinning the wall and altering the architecture of the genitourinary system (Figure 2). Given the imaging findings, the patient was diagnosed with necrotizing pneumonia in the right lower lobe (RLL), in contact with the renal lesion on the same side. Initial management included empirical antibiotic therapy with ampicillin/sulbactam, which was later switched to piperacillin/tazobactam. Right renal exclusion was confirmed by scintigraphy after 13 days of antibiotic therapy.

During antibiotic management, a staged surgical resolution was planned, starting with a laparoscopic nephrectomy 13 days after admission, followed by a lower lobe lobectomy. During the first surgical stage, lax peritoneal adhesions and a retroperitoneal plastron were encountered, leading to an open right nephrectomy. Extensive inflammatory involvement compromised the base of the right hemidiaphragm, sub-hepatic bed, and vena cava, necessitating repair of the right hemidiaphragm.

In the immediate postoperative period, the patient developed hypovolemic shock, requiring double vasopressor support with norepinephrine and vasopressin at maximum doses, as well as the initiation of inotropic support. She had limited tolerance to the withdrawal of these medications. Hours later, emergency second-stage surgery revealed a 1,500 cc retroperitoneal bleed and bleeding in the adrenal bed with no identifiable vascular injury. Despite aggressive treatment, which included triple vasopressor support and transfusion of 10 units of red blood cells in 24 h, the patient remained hemodynamically unstable.

During this period, the patient developed multiorgan failure, initially presenting with rapidly evolving acute kidney injury requiring

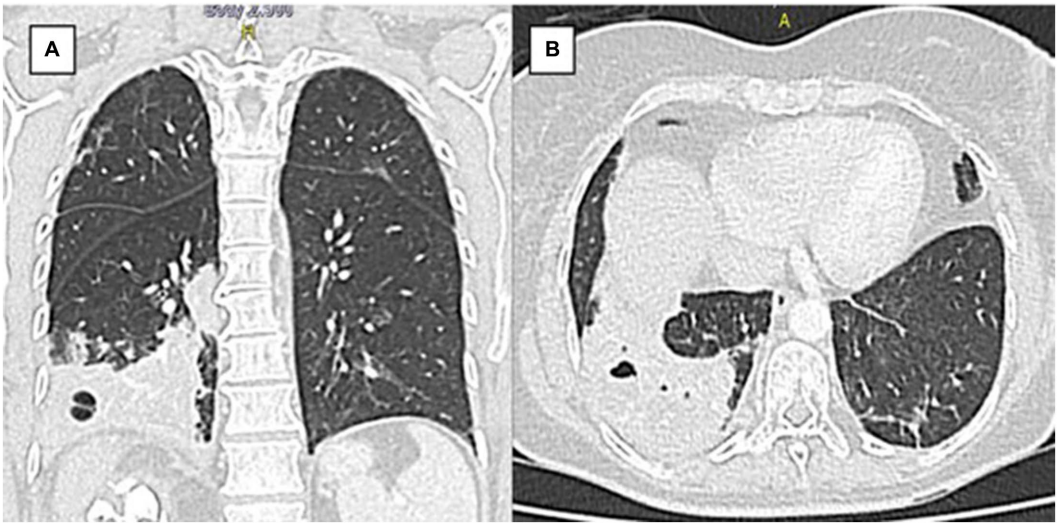

FIGURE 1
Chest tomography pulmonary **(A)** Coronal section. **(B)** Axial section. Axial view. There is extensive heterogeneous alveolar occupation involving basal segments of the right lower lobe, with intraparenchymal collection with hydroaerial level of 24 mm in diameter.

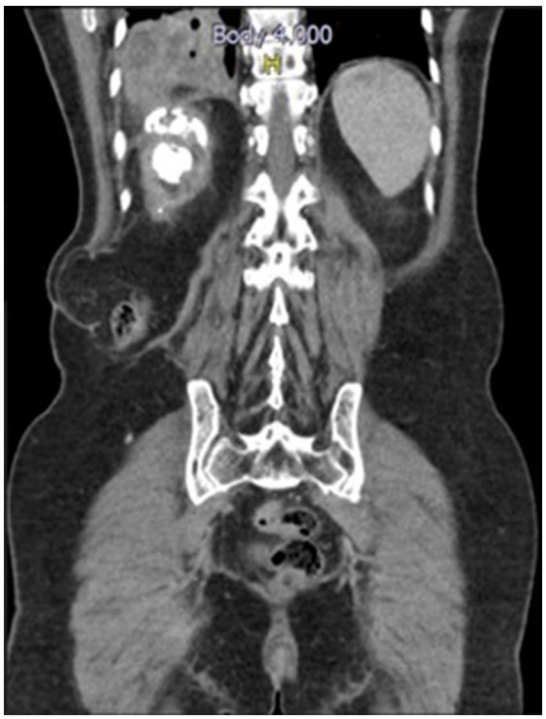

FIGURE 2
CT scan of the abdomen and pelvis with soft tissue contrast window sagittal view shows a coralliform calculus occupying all the right renal collectors with active fistula between the upper collector and the right basal lung parenchyma.

hemodialysis. Elevated bilirubin levels, progressive respiratory compromise, and severe metabolic acidosis were identified and treated with insulin and bicarbonate infusion. In addition, the patient developed bleeding from the surgical wound, as well as at the nasogastric and vaginal sites, leading to a decrease in hemoglobin levels to 4 g/dL. In this state, the patient showed a slight prolongation in laboratory coagulation times and international normalized ratio (INR). The platelet count was at the lower limit of normal, and there was no evidence of fibrinogen consumption, thus not meeting the criteria for disseminated intravascular coagulation.

A third surgical intervention revealed a new collection of serohematic fluid and patchy ischemia in the small and large bowel, leading to concerns about generalized intestinal ischemia. The renal fossa was repacked, and the abdomen was left open with VAC therapy. Despite these efforts, persistent hemodynamic instability led to the patient's demise. Figure 3 shows the chronology of patient events.

The final pathological report of the right kidney showed severe acute and chronic pyelonephritis with intrarenal abscess and terminal changes due to hydronephrosis caused by nephrolithiasis. Dystrophic calcifications with bone metaplasia were also present in the ureter, indicating slight chronic involvement, with no perirenal or vascular compromise.

3 Discussion

In this case, chronic xanthogranulomatous pyelonephritis was a risk factor that precipitated the subsequent chain of events. This

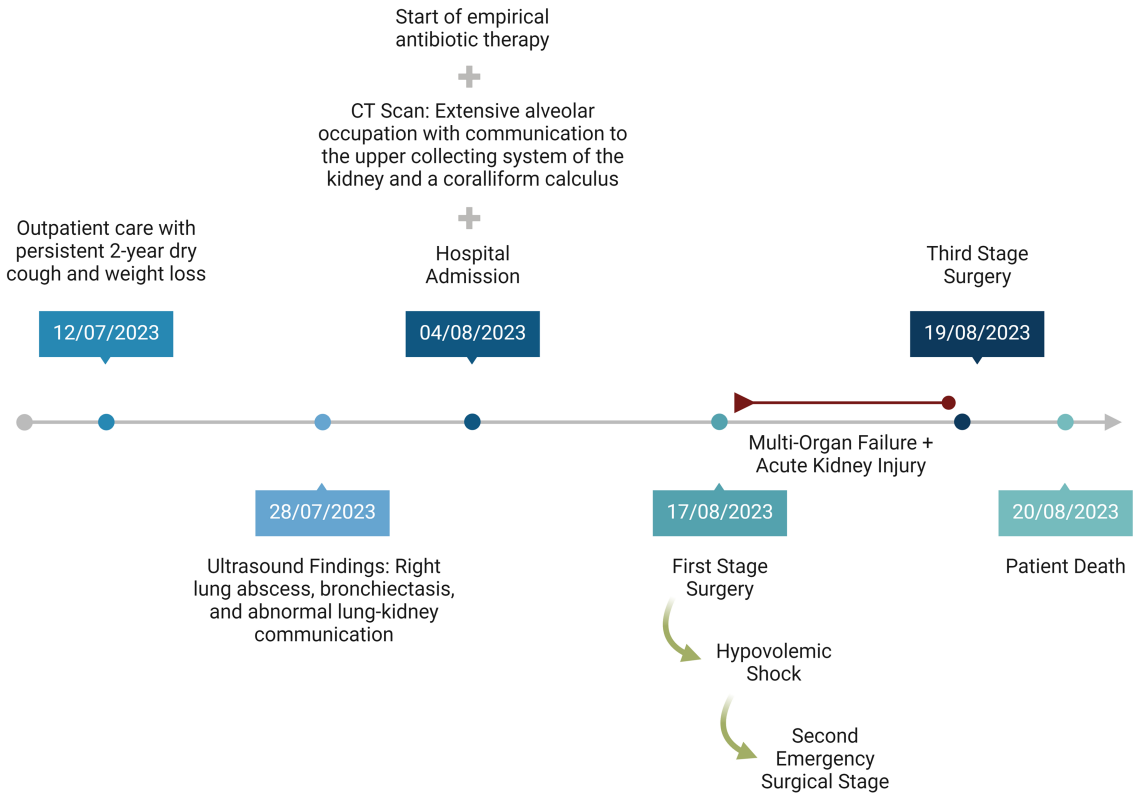

FIGURE 3
Timeline of patient management.

condition, being exceedingly rare and aggressive, accounts for merely 1% of all renal infections. It is associated with nephrolithiasis and persistent infection, leading to the replacement of renal and perirenal tissues with extensive granulomatous tissue and infiltration by fatty macrophages. This process distorts the renal architecture and ultimately results in a non-functional kidney, as observed in this case (14).

The etiology of this condition typically involves microorganisms like those causing urinary tract infections in the general population, often facilitated by obstructive processes such as lithiasis. In 80% of these cases, coraliform calculi are observed, as in this patient (7). The presence of abscesses and fistulas as complications, including those with different outlets, is not unusual, presenting diagnostic challenges due to the largely nonspecific symptomatology dependent on the affected tissues. Symptoms may range from general malaise, fever, and weight loss to more specific symptoms like flank or abdominal pain, dry or productive cough, foul-smelling sputum, hemoptysis, uroptisis, and a taste of urine in the mouth (15, 16). According to the findings of the review by Tamburrini et al. (7), from 21 nephrobronchial fistula cases, respiratory symptoms were the most common (47.6%), with productive cough present in half of the cases, and urinary symptoms in 42.9%, differing from this case which presented with only a dry cough and weight loss.

Despite the low incidence of nephrobronchial fistulas since the latter half of the 20th century—with only 31 cases reported since 1949 (7). Nephrobronchial fistulas are the most common type of reno-visceral fistulas, followed by nephrocolonic fistulas, and can pose serious risks to patient survival (13). This case exhibits several characteristics consistent with previous reports, such as a higher frequency in female patients (80.9%), ages ranging from 12 to 68 years (median 45.7 years), with xanthogranulomatous pyelonephritis frequently identified as the primary cause (47.6%), followed by pyonephrosis (38.1%) and renal infections (14.3%) (7). However, contrary to most cases which typically affect the left side (66.7%), our patient exhibited involvement on the right side (7).

Although there is evidence of success in conservative management, characterized by a positive response to antibiotic therapy and perfunctory drainage of the abscess, surgical resolution based on nephrectomy remains the mainstay even today (3, 9, 17–19). In the case of our patient, the treatment approach was in line with the literature and consisted of antibiotic therapy followed by nephrectomy. We consider that the long duration of the condition could have affected the results of antibiotic therapy (7, 19, 20).

Previous reports indicate that fatal outcomes in nephrobronchial fistulas are relatively uncommon and have been rare over the last two decades. However, the fatal outcome of nephrobronchial fistula is typically associated with acute respiratory failure due to purulent secretions through the endotracheal tube during surgery (21). In our patient's case, the multiorgan failure observed postoperatively broadens the clinical perspective and highlights the serious complications that must be considered in the management of nephrobronchial fistulas, especially in cases with chronic progression.

The delay in the treatment of our patient, a frequent situation in developing countries, must be considered a crucial factor contributing to the patient's fatal outcome, which underlines the critical importance of early treatment (17). In our patient, diagnosis was made secondary to the investigation of nonspecific symptoms, as described in previously reported cases (7). However, it should be noted that the onset of the patient's respiratory symptoms was prolonged, leading to an unfavorable delay in accessing healthcare services, making the diagnosis an incidental finding, and contributing to delays in outpatient care. These characteristics, while determining the clinical course, also expose significant limitations in access to healthcare. Although the patient's condition led to immediate in-hospital management with antibiotics and subsequent surgery, these actions ultimately proved insufficient.

This case underscores the necessity of considering a diagnosis of nephrobronchial fistula and pulmonary abscess, particularly when there is a history indicative of such conditions, as commonly seen in patients with this disease. Despite an imprecise clinical presentation, the presence of an ipsilateral thoracic lesion in a patient with renal disease (xanthogranulomatous pyelonephritis) should alert physicians to the potential for pulmonary extension of the renal process (7). A particularly timely, comprehensive approach, accompanied by a search for complications in unusual locations, is essential, because although this is a very rare complication, it can lead to high morbidity and mortality, as observed in our patient (7).

4 Conclusion

Nephrobronchial fistulas represent a very rare complication of renal infections, often presenting with nonspecific clinical symptoms. This case exemplifies the serious potential effects on morbidity and even mortality, especially in resource-limited settings where interventions may be delayed. It underscores the crucial importance of maintaining a high level of clinical suspicion and ensuring timely treatment.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Comite de Universidad Libre Cali. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

MB: Conceptualization, Data curation, Investigation, Methodology, Resources, Visualization, Writing – original draft. HN-C: Investigation, Methodology, Supervision, Validation, Conceptualization, Data curation, Resources, Writing – original draft. NC-G: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Visualization, Writing – original draft. GL:

Conceptualization, Data curation, Investigation, Resources, Visualization, Writing – original draft. RP-A: Investigation, Methodology, Resources, Validation, Visualization, Writing – review & editing. CS-S: Data curation, Investigation, Resources, Validation, Writing – review & editing. MV-G: Data curation, Investigation, Methodology, Supervision, Writing – review & editing. JI-C: Data curation, Funding acquisition, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing.

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EDITED BY
Leopoldo Ardiles,
Universidad Austral de Chile, Chile

REVIEWED BY
Maria Amicone,
Federico II University Hospital, Italy
Paola Krall,
University of Chile, Chile
Ignacia Pezantes,
Hospital Dipreca, Chile

*CORRESPONDENCE
Muralinath Vukkadala
dr.muralinath@gmail.com

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Renal hypouricemia type 2 with SLC2A9 compound heterozygous variants: a case report of recurrent acute kidney injury triggered by low-intensity exercise

Niranjana Rekha Paladugu and Muralinath Vukkadala*

Department of Nephrology, AIG (Mayo Clinic Care Network) Hospitals, Hyderabad, Telangana, India

Renal hypouricemia (RHUC) is a rare genetic disorder characterized by impaired uric acid reabsorption which leads to persistently low serum uric acid levels. This condition predisposes individuals to complications such as uric acid kidney stones and exercise-induced acute kidney injury (EIAKI). Although mutations in SLC22A12 and SLC2A9 are commonly implicated in RHUC, the precise pathophysiological mechanisms, particularly those contributing to AKI, remain incompletely understood. We report the case of a 30-year-old male who experienced recurrent episodes of EIAKI despite the absence of high-intensity exercise, suggesting the involvement of factors beyond the traditional risk. Genetic analysis confirmed the diagnosis of RHUC type 2 (RHUC2) and identified compound heterozygous variants of SLC2A9. Although these variants are not novel, this case contributes to the limited literature on RHUC2, particularly in male patients with recurrent EIAKI. These findings highlight the importance of maintaining a high index of suspicion for RHUC in cases of unexplained AKI, especially when recurrent episodes follow physical activity, and the need for targeted genetic testing for an accurate diagnosis. The genomic data related to this case are available in Mendeley Data: Vukkadala, Muralinath; Paladugu, Niranjana Rekha (2024), "Renal hypouricemia," Mendeley Data, V2, doi: 10.17632/7z84mkdgn9.2.

KEYWORDS

renal hypouricemia, exercise-induced acute kidney injury, SLC2A9 gene variants, fractional excretion of uric acid, compound heterozygous

Introduction

Renal hypouricemia (RHUC) is a rare genetic disorder marked by defective uric acid reabsorption in the kidneys, resulting in persistently low serum uric acid levels. This condition increases the risk of uric acid kidney stones and exercise-induced acute kidney injury (EIAKI), especially post-exertion. RHUC is categorized into RHUC type 1 (RHUC1) and RHUC type 2 (RHUC2) based on genetic mutations. RHUC1 is linked to mutations in SLC22A12, which encodes the URAT1 transporter essential for uric acid reabsorption. RHUC2 is associated with mutations in SLC2A9, encoding the GLUT9 transporter, also critical for uric acid reabsorption. Both types lead to hypouricemia and related complications (1).

Recent studies have pinpointed specific genetic mutations causing RHUC, such as those in SLC22A12 and SLC2A9, but the exact mechanisms by which these mutations contribute to RHUC-related AKI, including oxidative stress and renal vasoconstriction, remain unclear. Aomura et al. (2020) indicated that although some RHUC patients develop EIAKI at varying levels of physical exertion, additional risk factors likely play a role in the condition's onset beyond exercise alone (2). This underscores the necessity for a thorough investigation into the interplay between genetic predispositions and other potential risk factors for EIAKI development.

We present a case of a 30-year-old Indian male experiencing recurrent post-exercise AKI without prior high-intensity exercise. Whole-genome sequencing confirmed RHUC2 diagnosis by identifying compound heterozygous variants in SLC2A9. These findings emphasize SLC2A9 variants' role in EIAKI pathogenesis and raise considerations about sex-based susceptibility. Although these variants are not novel, this case enhances the understanding of RHUC2, especially regarding variants of uncertain significance (VUS), and adds to the syndrome's genetic diversity. The genomic data have been published in Mendeley Data to support further research and validation (Vukkadala, Muralinath; Paladugu, Niranjana Rekha (2024), "Renal hypouricemia," Mendeley Data, V2, doi: 10.17632/7z84mkdgn9.2).

Case report

In June 2023, a 30-year-old male presented with a three-year history of recurrent, self-resolving acute kidney injury (AKI), exhibiting symptoms of nausea, generalized weakness, and occasional hematuria. His medical history revealed no chronic conditions, family history of kidney disease, smoking, alcohol use, NSAIDs, or other medications. The patient had previously visited multiple hospitals and consulted various physicians.

Clinical history

The patient's health was stable until November 2020, when he sought medical attention for nausea and weakness, with a serum creatinine level of 2 mg/dL. He was treated with intravenous hydration (1000 ml/day) for three days, reducing serum creatinine from 2.0 mg/dL to 1.1 mg/dL without additional pharmacological intervention. In April 2021, he contracted COVID-19, with a creatinine level of 1.4 mg/dL, recovering within five days of conservative management. In September 2021, he experienced similar symptoms of nausea and weakness, with a creatinine level of 1.5 mg/dL. A complete urine examination yielded negative results, with a urine protein-to-creatinine ratio of 0.04. Laboratory tests, including complete blood counts, liver function tests, and iron levels, were normal. During this period, the patient had been using Ayurvedic medicine for one month.

In November 2021, the patient experienced nausea and generalized weakness with a creatinine level of 1.6 mg/dL. Urine examination showed 14-16 RBCs/HPF, but no albumin or WBCs. The 24-hour urine protein was 72 mg, and the ANA profile was negative. A renal biopsy was suggested but postponed. A month later, the creatinine level normalized to 1.1 mg/dL, and the urine examination was negative.

In May 2022, the patient had gross hematuria, and creatinine was 2.57 mg/dL. Urine analysis showed RBCs and WBCs (5-6 cells/HPF). The ASO titer was negative, and C3 and C4 levels were normal. Suspected acute interstitial nephritis was treated with intravenous solumedrol 500 mg for three days, reducing creatinine to 1.7 mg/dL, and stabilizing at 1.2 mg/dL within a week. Subsequent urine examination revealed no abnormalities. A one-month tapering course of oral steroids was prescribed.

In June 2022, the patient had similar symptoms with a creatinine level of 2.7 mg/dL. Urine examination was negative. A renal biopsy showed unremarkable glomeruli, tubulointerstitial compartments, and vessels. Electron microscopy showed normal glomerular basement membrane thickness and well-preserved visceral epithelial cell foot processes. Within a week, creatinine decreased to 1.4 mg/dL. Blood examination, including hemoglobin, hematocrit, and RBC indices, was normal, ruling out anemia. Liver function tests and iron levels were also normal, excluding iron deficiency.

The patient maintained a daily exercise regimen of 60 minutes, including aerobic activities and moderate strength training with both isotonic and isometric movements, without using protein supplements. The diet included a moderate amount of meat. Family history was unremarkable for kidney diseases or genetic conditions. Psychosocial history, including lifestyle and stress levels, did not reveal significant contributing factors.

Clinical evaluation and genetic diagnosis

The patient was well until June 2023 when he experienced prodromal symptoms and significant hematuria. Serum creatinine was 2.3 mg/dL. Urine examination showed numerous RBCs and a negative WBC count. Total bilirubin was 1.64 mg/dL, direct bilirubin 0.25 mg/dL, and indirect bilirubin 1.39 mg/dL. Imaging studies, including ultrasound and CT, showed no kidney stones or structural abnormalities.

Despite no significant glomerular or tubular damage on kidney biopsy and a normal glomerular basement membrane, recurrent AKI episodes with hematuria suggested exercise-induced acute kidney injury. Laboratory tests indicated elevated creatine

phosphokinase (CPK) levels at 460 U/L, three times the normal level, while lactate dehydrogenase (LDH) remained normal. Calcium, phosphate, bicarbonate, and intact parathyroid hormone (iPTH) levels were normal. Uric acid was low at 0.3 mg/dL, with a fractional excretion of uric acid at 120% (normal, <10%). Creatinine normalized to 1.1 mg/dL within a week.

Throughout the follow-up period, the patient did not exhibit any signs of hypertension, with blood pressure consistently within the normal range, and no hypertensive episodes were observed during the treatment (Figure 1).

On the basis of the clinical presentation, renal hypouricemia was suspected. Whole-genome sequencing (WGS) confirmed the diagnosis of RHUC type 2 by identifying compound heterozygous mutations in SLC2A9: c.646G>A in exon 5 and c.1004T>A in exon 8 (Figures 2 and 3, respectively; Figure 4). These findings were consistent with the diagnosis of RHUC2. The family members were screened for uric acid levels, which were normal at the time, and genetic testing was recommended but they denied.

Management and follow-up

The patient was provided with comprehensive information regarding RHUC2 and prognosis. The patient received supportive care, which included strict monitoring of fluid intake to maintain adequate hydration, correction of electrolyte imbalances with oral supplements, and close observation for any signs of worsening kidney function, adhere to a low-purine diet, and modify his exercise routine to include non-aggressive activities, such as walking, light jogging, swimming, or moderate cycling. Allopurinol has been discussed as a potential treatment option for acute episodes; however, given the lack of robust evidence, it has not yet been prescribed. During the two-month follow-up, the patient's creatinine levels remained stable at 1.1 mg/dL, with no further episodes of AKI.

Discussion

Overview of renal hypouricemia

Renal Hypouricemia (RHUC) is a rare genetic disorder marked by impaired uric acid reabsorption in the kidneys, leading to persistently low serum uric acid levels. While many individuals with RHUC are asymptomatic, the condition can cause significant complications, including uric acid kidney stones and exercise-induced acute kidney injury (EIAKI). The rare and often silent nature of RHUC presents diagnostic challenges, necessitating a comprehensive understanding of its mechanisms and clinical implications for effective management (3).

Genetic basis and the role of SLC2A9 and GLUT9 transporters

RHUC pathogenesis centers on the dysfunction of the GLUT9 transporter, encoded by the SLC2A9 gene. This transporter is crucial for uric acid reabsorption in the renal proximal tubules. Mutations in the SLC2A9 gene disrupt GLUT9 function, decreasing reabsorption and increasing urinary excretion of uric acid (4). This dysfunction leads to hypouricemia and a higher risk of kidney stones and EIAKI. Understanding the GLUT9 transporter and the impact of SLC2A9 mutations is essential for recognizing and managing RHUC's clinical manifestations.

Pathophysiological mechanisms in RHUC

The pathophysiology of RHUC involves genetic mutations, oxidative stress, and renal hemodynamic changes, which are essential for understanding related complications.

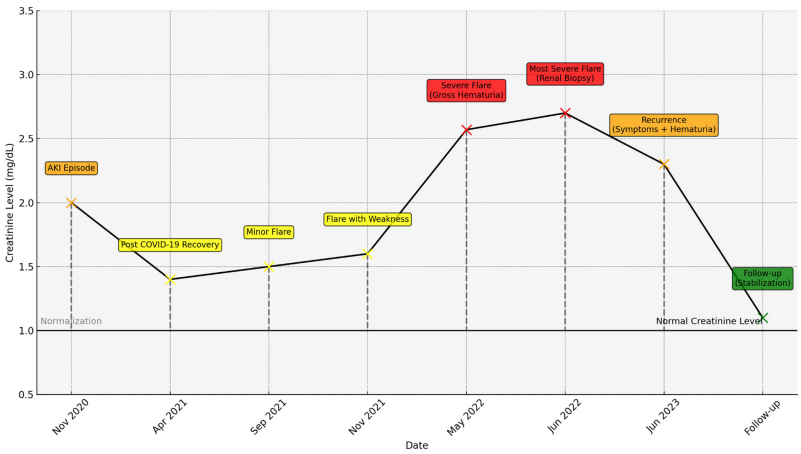

FIGURE 1
Creatinine levels over time with key clinical events, color-coded (yellow for mild, orange for moderate, red for severe), and dashed lines indicating normalization periods.

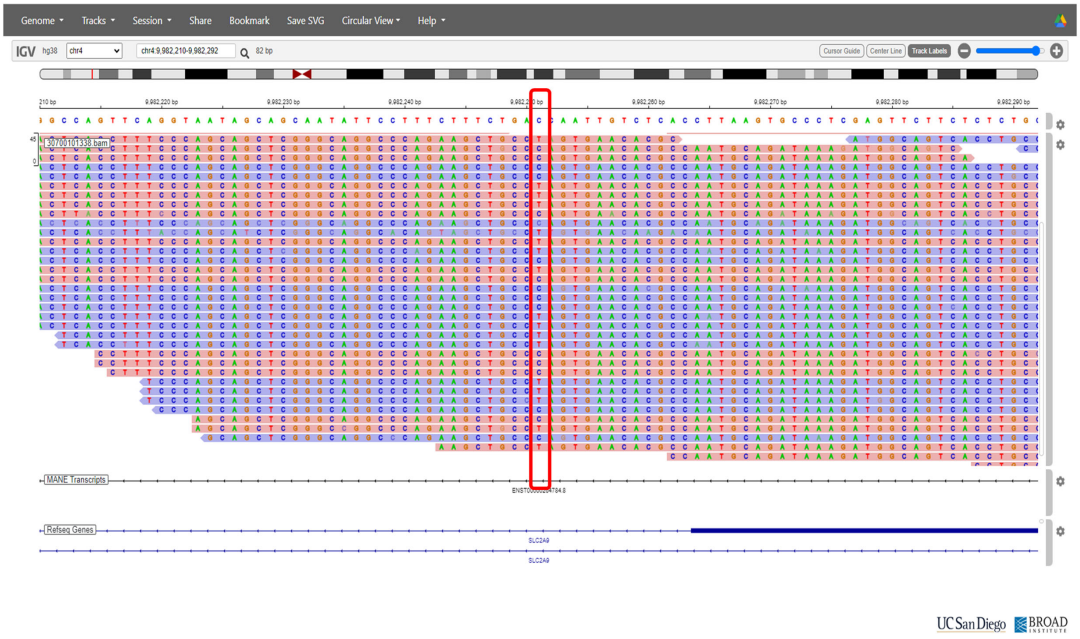

FIGURE 2
Chromosomal position of significant variant c.646G>A in the SLC2A9 gene.

Impaired Uric Acid Reabsorption: Mutations in the SLC2A9 gene result in defective GLUT9 transporters, reducing uric acid reabsorption from renal tubules. This leads to low serum uric acid levels and increased urinary excretion, contributing to uric acid crystals and kidney stones.

Exercise-Induced Acute Kidney Injury (EIAKI): Physical exertion raises the demand for uric acid clearance. In RHUC individuals, defective GLUT9 transporters fail to manage this increased load, causing uric acid accumulation in renal tubules. This triggers oxidative stress, inflammation, and renal vasoconstriction, key factors in AKI development (5).

Oxidative Stress and Inflammation: Uric acid accumulation in renal tubular cells generates reactive oxygen species (ROS), leading to oxidative stress. This, along with inflammation, damages renal tissues and increases AKI risk (6).

FIGURE 3
Chromosomal position of significant variant c.1004T>A in the SLC2A9 g.

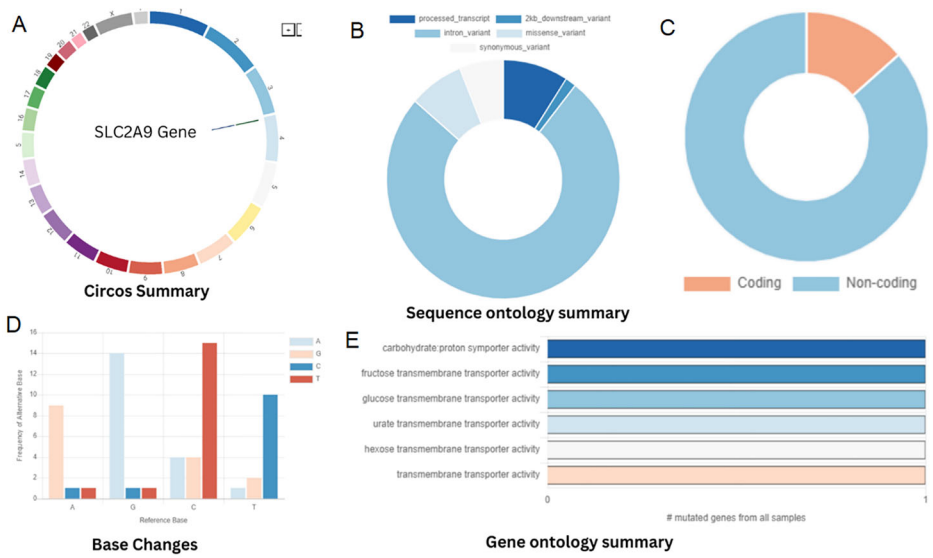

FIGURE 4
(A) Chromosomal location of SLC2A9 gene. **(B)** Classification of SNPs. **(C)** Percentage of genes distributed among the protein-coding and non-coding genes. **(D)** Base alteration frequency. **(E)** Gene ontology.

Renal Vasoconstriction: Physical activity can cause transient renal vasoconstriction and reduced renal blood flow. In RHUC, where uric acid reabsorption is already impaired, this further reduction in renal perfusion heightens the risk of ischemic injury (7).

Genetic testing in RHUC

Genetic testing is vital for confirming RHUC diagnosis and distinguishing between RHUC types 1 and 2. RHUC1 involves mutations in SLC22A12, responsible for the URAT1 transporter, while RHUC2 involves mutations in SLC2A9, which encodes the GLUT9 transporter. Identifying these mutations confirms the diagnosis and provides insights into inheritance patterns and potential risks for family members. Advanced methods like whole-genome sequencing (WGS) and whole-exome sequencing (WES) are effective in identifying these mutations, especially when clinical presentation is unclear or rare variants are suspected (8). However, due to their complexity and cost, targeted genetic panels focusing on commonly implicated RHUC genes are often preferred for efficient and accurate diagnosis.

Clinical presentation, diagnosis, and management of RHUC

Diagnosing RHUC, especially when leading to EIAKI, requires a high index of suspicion due to the silent nature of the condition and non-specific AKI symptoms like fatigue, nausea, and weakness. A thorough clinical history is essential, particularly in patients with AKI following physical exertion. Important history aspects include previous AKI episodes, kidney stones, and the intensity and duration of physical activity preceding symptoms.

Diagnostic evaluation

- Hypouricemia, defined as serum uric acid < 2 mg/dL, is a key indicator but not diagnostic alone, as low uric acid can occur in various conditions.
- Evaluating urine uric acid levels and fractional excretion of uric acid (FEUA) is crucial for diagnosis. High urinary uric acid with low serum levels indicates a renal reabsorption defect characteristic of RHUC (9).

Management of RHUC-AKI

- Supportive Care: Prioritize hydration, correct electrolyte imbalances, and monitor for early AKI signs.
- Pharmacological Intervention: Xanthine oxidase inhibitors like allopurinol might reduce uric acid production, though evidence for this in RHUC is limited.
- Patient Education: Advise on lifestyle changes, such as avoiding high-purine foods and nephrotoxic medications, to prevent RHUC-AKI recurrence (8).

Insights from this case and comparison with other studies

This case of a 30-year-old Indian male with RHUC and EIAKI reveals the genetic and clinical complexities of RHUC, particularly with compound heterozygous mutations in the SLC2A9 gene. It

enhances understanding of genetic variations and their clinical manifestations, and how these variations compare with similar cases reported in the literature.

Genetic insights and variability

The compound heterozygous mutations in the SLC2A9 gene, c.646G>A (p.Gly212Arg) and c.1004T>A (p.Ile335Asn), demonstrate the genetic diversity linked to RHUC. The I335N variant, classified as a Variant of Uncertain Significance (VUS), is especially significant. Its relatively higher frequency in South Asian populations (0.036% in gnomAD) and its intron-exon boundary location suggest potential splicing impact, although its clinical significance remains unclear (2). This highlights the need for further research to fully understand these variants' implications.

The variability in clinical presentation among individuals with similar genetic mutations complicates predicting disease severity and outcomes. While our patient experienced multiple EIAKI episodes without high-intensity exercise, others with the same or similar mutations may have been asymptomatic or exhibited mild symptoms. This variability emphasizes the importance of considering the full genetic context, including potential interactions between different variants and other genetic or environmental factors (5).

Comparison with Other Studies: Common themes emerged when comparing cases of compound heterozygous SLC2A9 mutations. Literature shows patients with similar mutations exhibiting a spectrum of symptoms, from asymptomatic hypouricemia to recurrent EIAKI (2). This supports the idea that RHUC is genetically heterogeneous with diverse phenotypes. Previous research identified individuals with the I335N variant of SLC2A9, classified either as pathogenic or VUS based on genetic context and clinical presentation (10, 11). The variability in clinical expression suggests that additional factors—genetic, environmental, or lifestyle-related—significantly influence RHUC manifestation. Comparing our case emphasizes the challenge in establishing clear genotype-phenotype correlations in conditions like RHUC, influenced by multiple factors.

Clinical implications

The presentation of a 30-year-old Indian male with RHUC illustrates the variability and diagnostic challenges of the condition. Consistent with literature, our patient experienced AKI without an identifiable trigger, a common RHUC pattern often linked to strenuous exercise. However, AKI episodes in this case occurred without high-intensity physical activity, underscoring RHUC's unpredictable nature and the necessity for heightened clinical vigilance (12).

Clinical Course and Presentation: The patient experienced recurrent AKI episodes that resolved spontaneously, consistent with the natural recovery seen in RHUC-related AKI. This spontaneous recovery highlights the need to recognize this pattern in patients with unexplained kidney injury. Elevated creatine phosphokinase (CPK) without a corresponding increase in lactate dehydrogenase (LDH) suggests muscle stress or mild rhabdomyolysis, indicating muscle damage without significant cell lysis. The elevated indirect bilirubin level may suggest mild hemolysis or Gilbert's syndrome, characterized by intermittent jaundice. These findings require further investigation to understand their implications for RHUC.

Diagnosis: RHUC was confirmed through clinical history, laboratory tests, and genetic analysis. Low serum uric acid levels, combined with high urinary uric acid excretion, suggested RHUC, confirmed by identifying compound heterozygous mutations in the SLC2A9 gene. Whole-genome sequencing (WGS) was crucial for detecting these mutations, especially in atypical presentations. The identification of the c.646G>A (p.Gly212Arg) and c.1004T>A (p.Ile335Asn) mutations provided significant diagnostic context, with the I335N variant classified as a Variant of Uncertain Significance (VUS) due to its potential impact on splicing and its prevalence in South Asian populations.

Management: The management of RHUC-AKI in this patient centered on supportive care, including ensuring adequate hydration, correcting electrolyte imbalances, and monitoring early signs of kidney injury. Although xanthine oxidase inhibitors like allopurinol were considered to reduce uric acid production, they were not used due to insufficient evidence supporting their effectiveness in RHUC. Instead, the focus shifted to patient education, emphasizing lifestyle modifications such as avoiding high-purine foods, staying well-hydrated, and avoiding strenuous physical activity that could trigger AKI episodes.

A major strength of this case is the comprehensive genetic analysis, which identified compound heterozygous mutations in the SLC2A9 gene. This, combined with thorough clinical evaluations, provided a definitive diagnosis of RHUC2 and offered valuable insights into the pathophysiology of EIAKI in this context. However, limitations include the absence of genetic testing in the patient's family, restricting the understanding of inheritance patterns. Additionally, as a single case study, these findings may not be generalizable to all patients with RHUC, indicating the need for further research in a larger cohort.

This case adds to the growing literature on RHUC2, particularly regarding EIAKI. While similar cases have been documented, the identification of specific SLC2A9 mutations in this patient provides new insights that align with and expand upon existing research, highlighting the importance of early genetic testing in at-risk individuals.

Patient perspective

The patient experienced significant relief with a definitive diagnosis of Renal Hypouricemia Type 2 after years of unexplained symptoms and acute kidney injury episodes. The previous uncertainty had caused considerable stress, affecting his physical and psychological well-being. He appreciated the thorough investigation leading to a clear diagnosis and targeted treatment. However, he expressed concerns about lifelong management, especially the necessary exercise routine modifications, given his active lifestyle. Despite these challenges, he reported improved quality of life after adjusting his diet and exercise as recommended by healthcare providers. He remains vigilant about symptom recurrence, stressing the importance of ongoing monitoring and lifestyle adjustments.

Conclusion

This case report highlights the complexity of Renal Hypouricemia Type 2 (RHUC2) associated with compound heterozygous mutations in the SLC2A9 gene in a 30-year-old Indian male with recurrent exercise-induced acute kidney injury (EIAKI). Significantly, EIAKI episodes occurred even without intense exercise, indicating that factors beyond traditional risk factors can trigger AKI in RHUC2 patients. Although the identified genetic variants were not novel, this case adds valuable insights to the limited RHUC2 literature and underscores the importance of considering this condition in unexplained AKI cases. These findings highlight the need for personalized diagnostic and management strategies in RHUC2 patients.

Data availability statement

The original contributions presented in the study are included in the article/supplementary materials. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

NP: Investigation, Supervision, Writing – review & editing. MV: Conceptualization, Investigation, Resources, Visualization, Writing – original draft, Writing – review & editing.

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EDITED BY
Clay Block,
Dartmouth College, United States

REVIEWED BY
William Morello,
Policlinico di Milano, Italy
Dipak Maskey,
Henry Ford Health System, United States

*CORRESPONDENCE
Paola Krall
paola.krall@uchile.cl

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Case report: Novel *ACTN4* variant of uncertain significance in a pediatric case of steroid-resistant nephrotic syndrome requesting kidney transplantation

Ignacio Alarcón[1], Carolina Peralta[2], Francisco Cammarata-Scalisi[2], Maykol Araya Castillo[3], Francisco Cano[4,5], Angélica Rojo[5], María Luisa Ceballos[4,5] and Paola Krall[4,6]*

[1]Escuela de Medicina, Facultad de Medicina, Universidad de Chile, Santiago, Chile, [2]Servicio de Pediatría, Hospital de Antofagasta, Antofagasta, Chile, [3]Laboratorio Clínico, Hospital de Antofagasta, Antofagasta, Chile, [4]Departamento de Pediatría y Cirugía Infantil Oriente, Facultad de Medicina, Universidad de Chile, Santiago, Chile, [5]Unidad de Nefrología, Hospital Luis Calvo Mackenna, Santiago, Chile, [6]Instituto de Medicina, Facultad de Medicina, Universidad Austral de Chile, Valdivia, Chile

Background: Steroid-resistant nephrotic syndrome (SRNS) is a rare kidney disease commonly characterized histopathologically by focal and segmental glomerulosclerosis (FSGS) or minimal change disease. One-third of SRNS-FSGS cases are attributed to a genetic cause ultimately leading to end-stage kidney disease (ESKD) during childhood or adulthood. *ACTN4* variants, although rare, typically manifest in early adulthood as SRNS-FSGS with autosomal dominant inheritance pattern and are associated with variable progression toward ESKD.

Case–diagnosis/treatment: A 10-year-old Chilean male patient, born to a complicated pregnancy without any history of prenatal care, was incidentally found to have mild proteinuria during pre-surgery analysis. He was diagnosed with nephrotic syndrome and treatment with prednisone was started, but 12 months later, he persisted with hyperlipidemia, hypoalbuminemia, and proteinuria. Within a few weeks, proteinuria rapidly increased, and a kidney biopsy exhibited FSGS features. At the age of 12, he reached ESKD and initiated peritoneal dialysis, experiencing an episode of posterior reversible encephalopathy syndrome. Exome sequencing identified a novel variant of uncertain significance (VUS), *ACTN4* c.625_633del that predicted the in-frame deletion p.L209_E211del in a highly conserved functional domain. He requested to be considered for kidney transplantation and the VUS in *ACTN4* was re-analyzed to assess potential risks, resulting in a reclassification as likely pathogenic (PM1+PM2+PM4 criteria). At 14 years old, he received a deceased donor kidney allograft without recurrence during the subsequent 5 months.

Conclusions: Identifying VUS is a recurring challenge in routine clinical genetics, particularly for patients with rare diseases or atypical phenotypes in underrepresented populations. This case underscores the benefit of timely genetic diagnosis taking into account the patient's request. VUS reassessment becomes more relevant when considering a kidney transplant not only as an appropriate procedure, but as the therapy of choice, especially considering the patient's history of complications with variable long-term consequences.

KEYWORDS

steroid-resistant nephrotic syndrome, variant of uncertain significance, ACTN4, pediatric kidney transplantation, focal and segmental glomerulosclerosis, recurrence risk

Introduction

Steroid-resistant nephrotic syndrome (SRNS) is a kidney disease with annual incidence estimated at 1/390,000 that is characterized by a failed response to steroid treatment in patients, evident after a 4–6-week course of daily prednisone (1). Clinically, SRNS presents with proteinuria, hypoalbuminemia, edema, and hyperlipidemia. Histopathologically, the biopsy reveals the presence of focal and segmental glomerulosclerosis (FSGS) or minimal change disease (MCD). A subgroup of SRNS patients might achieve remission, but up to 50% that start in childhood reach end-stage kidney disease (ESKD) within 10-15 years (2). Once the SRNS diagnosis is established, it is essential to elucidate the underlying mechanism to propose clinical management. However, this condition exhibits different etiologies, attributing one-third of all cases to genes related to the podocytes and the glomerular basement membrane. To date, more than 60 genes have been linked to SRNS-FSGS, with variants most frequently identified in key genes such as nephrin (*NPHS1*) and podocin (*NPHS2*), integral membrane proteins of the slit diaphragm; Wilms tumor protein (*WT1*), a transcription tumor suppressor protein; phospholipase C epsilon (*PLCE1*), involved in podocyte proliferation and differentiation; and alpha-actinin-4 (*ACTN4*), which regulates the podocyte cytoskeleton; among other genes (3, 4).

ACTN4 gene is located on chromosome 19q13.2 and comprises 21 exons, which encode a protein consisting of 911 amino acids (5). ACTN4 is an actin crosslinking protein that structurally consists of a long rod domain that connects the amino terminal functional actin-binding domain (ABD) and the carboxyl calcium binding motif and presents in antiparallel homodimers (6). Of note, the ABD contains two calponin-homology (CH1 and CH2) domains that harbor the majority of *ACTN4* variants described in association with SRNS-FSGS (7).

To date, at least 20 pathogenic or likely pathogenic *ACTN4* variants have been identified. Patients carrying these allele variations are unique and typically manifest the adult-onset form of SRNS (8). On the other hand, Varsome (https://varsome.com/) reports over 100 variants of unknown significance (VUS) in *ACTN4*, which, according to the Standards and Guidelines for the interpretation of Sequence Variants by the American College of Medical Genetics (ACMG), should not be used solely for clinical decision-making. In these cases, and in the absence of proactive updates, the recommendation is to perform segregation analysis within the patient family, whenever possible, or to perform periodic consultations to determine whether there have been modifications or reclassification of any VUS that would allow for therapeutic decision-making (9).

In this study, we present a Chilean male patient who was carrier of a novel variant in *ACTN4*, initially classified as VUS, that was re-evaluated given the rapid progression to ESKD in order to guide decisions regarding kidney transplantation.

Case report

A 10-year-old Chilean male patient, born to a cocaine-abuse complicated pregnancy without any history of prenatal care, was found to have mild proteinuria (spot dipstick +1) on a urine analysis. This finding occurred in the context of planning a relapsed bilateral cryptorchidism surgery. The grandmother was mentioned to be his legal tutor since he was 12 months old and she could not provide information about his gestational age and birth weight. He did not receive breastfeeding and his parents were non-consanguineous. He had a history of hypothyroidism and asthma, both under treatment, during early childhood. No significant familial background of kidney disease was documented, and the patient had three healthy paternal siblings (Figure 1).

At the time of the first nephrological evaluation, he did not present psychomotor retardation, hypertension, edema, dysuria, pollakiuria, previous urinary tract infections or enuresis. A renal ultrasound was requested, which reported inadequate cortico-medullary differentiation and renal sinus displaying a duplicated

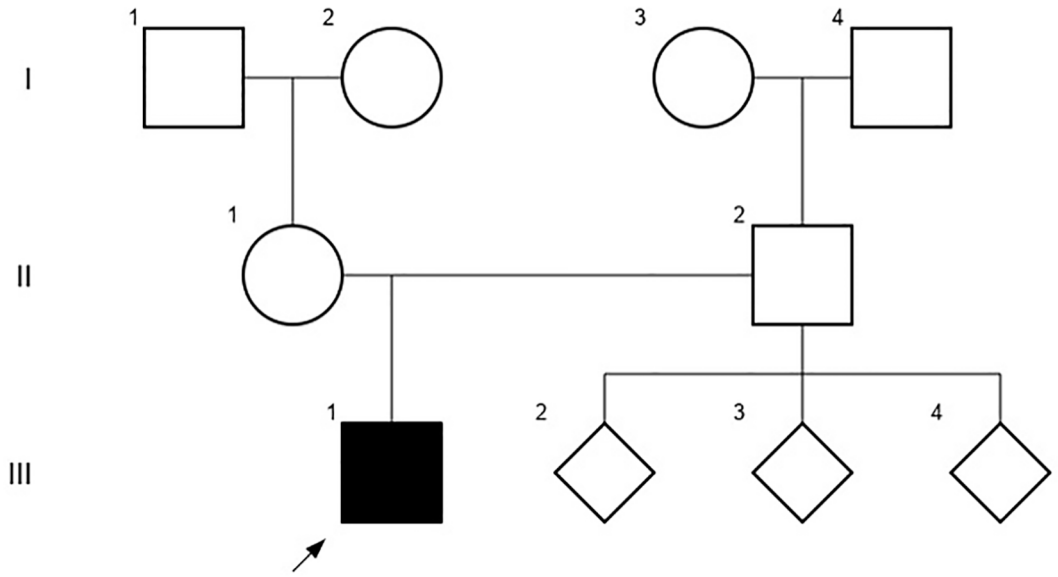

FIGURE 1
The patient´s pedigree chart, including third-degree relatives that did not document history of kidney disease at the time of the study.

pyelocalyceal system in the right kidney with no other significant findings. Blood tests revealed normal serum creatinine (0.8 mg/dL), hypoalbuminemia (2.47 g/dL) and increased total cholesterol (499 mg/dL). Uric acid, calcium, phosphorus and magnesium serum levels were in normal range. A urine analysis showed increased isolated proteinuria (300 mg/dL).

The patient was reevaluated 7 months later, where the presence of edema became evident, with the following laboratory findings: hemoglobin 13 g/dL, hematocrit 34%, albuminemia 2.3 g/dL, serum creatinine 0.7 mg/dL, total cholesterol 579 mg/dL, urea nitrogen 34 mg/dL and a urine albumin to creatinine ratio of 4.0 mg/g. Oral prednisone treatment was initiated, but 4 weeks later no remission was observed. Bolus albumin was administered with no improvement of symptoms, leading to his hospitalization. Upon admission, the patient presented with urinary sodium <10 mEq/L, severe hypoalbuminemia (1.7 g/dL) and dry cough with clinical evidence of ascites and pleural effusion. Thoracentesis was performed to obtain pleural fluid for cytological analysis, which resulted negative for infections. Three boluses of albumin were administered with persistence of ascites and pleural effusion. Additionally, three intravenous boluses of methylprednisolone were given, with no changes in proteinuria. Due to the steroid-resistant behavior, a renal biopsy was performed, obtaining samples for light microscopy (LM), electron microscopy (EM), and immunofluorescence (IF). The biopsy specimen in LM comprised 18 glomeruli, with 8 of them globally and 2 segmentally sclerosed (Figures 2A, B). Additionally, there was moderate interstitial fibrosis and tubular atrophy. The examination performed by IF resulted negative after incubation with specific antibodies against heavy chains of IgA, IgG, and IgM, light chains Kappa and Lambda, complement factors C3c, C4, and C1q, as well as Albumin and Fibrinogen (Supplementary Figure 1). The sample submitted for EM did not contain glomeruli, limiting our ability to assess ultrastructural features in this specific case. Nevertheless, the combination of histopathological LM and IF features were considered compatible with FSGS and provided valuable insights into the structural alterations.

At this point, considering that remission remained elusive despite conventional therapeutic intervention, genetic analysis emerged as a critical diagnostic priority. The first genetic analysis was performed for *NPHS2*, considering that the p.R229Q and p.A284V variants in *NPHS2* are highly prevalent among Chilean patients with SRNS-FSGS (10). This genetic test was easily available but did not identify variants. Meanwhile, a protocol with cyclophosphamide was initiated, and oral prednisone dosage was reduced to 50 mg due to the high suspicion of SRNS. Whole Exome Sequencing (WES) identified a novel heterozygous variant of uncertain significance (VUS), *ACTN4* c.625_633del. This 9-bp deletion identified in exon 6 predicted an in-frame deletion of 3 amino acids, L209, I210 and E211, located within the ABD. Segregation analysis within the family was not possible and the *ACTN4* p.L209_E211del variant identified in our patient was assumed *de novo*.

Given a rapid progression to ESKD in less than 2 years, peritoneal dialysis was initiated. During this period, the patient presented an episode of reversible encephalopathy syndrome that evolved with a successful recovery. When the patient reached 14 years, he requested to be considered for kidney transplantation. Within this period a re-analysis of the VUS in *ACTN4* was performed. No registries of individuals carrying this variant were found in population databases (gnomAD, ESP and 1000 G). The analysis by a multiple sequence alignment program (Clustal Omega (https://www.ebi.ac.uk/Tools/msa/clustalo/) showed that the ACTN4 p.L209_E211del variant was located within the CH2

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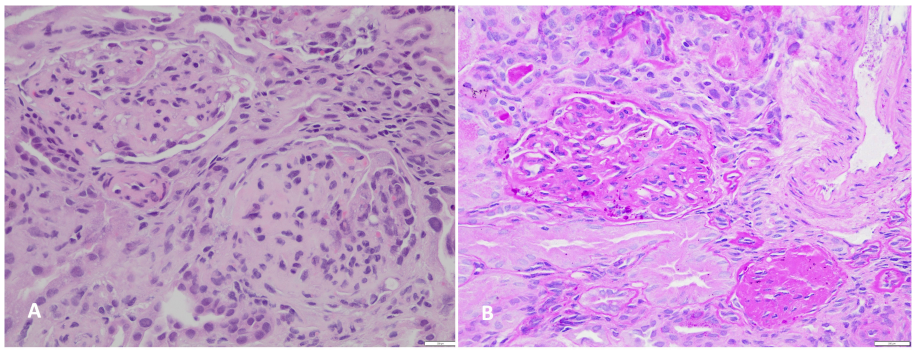

FIGURE 2
Histological findings in kidney biopsy revealed focal and segmental glomerulosclerosis. **(A)** Hematoxylin and eosin stain, 200x magnification. **(B)** Periodic acid-Schiff stain, 200x magnification.

domain in a highly conserved sequence across vertebrate species (Figure 3). This suggests the critical importance of these amino acids and underscores their intolerance to substitution or elimination, thereby highlighting the functional significance and evolutionary conservation of this region. Until date, only one male patient with sporadic SRNS-FSGS had been identified carrying ACTN4 in-frame deletion of 3 amino acids (11). The variant involved Y260, V261 and S262 at the ending of the CH2 domain and was classified as likely pathogenic (PM1+PM2+PM4+PP3+PP4 criteria). Regarding our patient, the analysis by the metapredictor Varsome classified the ACTN4 p.L209_E211del variant as likely pathogenic (PM1+PM2+PM4 criteria). In addition, the heterozygous condition of the *ACTN4* variant resulted compatible with the autosomal dominant inheritance pattern described for SRNS-FSGS. Taking all this information into account, recurrence after transplant was considered to have a very low risk of recurrence. After a multidisciplinary evaluation, it was decided to enlist the patient in the national deceased donor waiting list.

Three months after enlistment, our patient received an allogeneic kidney allograft from a deceased donor, with a significant and progressive reduction of proteinuria within the first weeks. At his nephrological visit 5 months after transplantation, he presented serum creatinine 0.57 mg/dL, albumin 4.1 g/dL, and cholesterol 143 mg/dL. His creatinine clearance resulted in 101 mL/min, indicative of an optimal kidney function and a favorable prognosis.

Discussion

In this case, incidental proteinuria was discovered in the context of a non-related pre-surgery analysis. This illustrates the importance of exhaustively studying and not ignoring these findings, especially in pediatric patients that start steroids in the context of proteinuric disease, since complications can be avoided with early diagnosis and prompt treatment (12).

Regarding the patient's history, given the family circumstances, there is no perinatal information available, such as gestational age and birth weight, which would have been valuable during the case analysis. In addition, the presence of drug abuse during pregnancy is a known risk factor that cannot be ruled out as a phenotype modifier in our patient (13). Despite several atypical features during the initial nephrological evaluation, such as reduced kidney function, the absence of edema, and cryptorchidism, all highly suggestive of a genetic disease, genetic testing was not pursued at this time. Biopsy indication was made since the guidelines recommend that patients with SRNS undergo biopsy, except children with known or strongly suspected monogenic forms (14, 15) and the procedure is still considered the "gold standard" for the diagnostic evaluation of glomerular diseases (16). The biopsy results in our patient reported classical FSGS findings and the combination of LM and IF analysis provided valuable insights, prompting further genetic analysis to elucidate the specific molecular mechanisms underlying the clinical phenotype.

FIGURE 3
The sequence surrounding the position of the ACTN4 variant identified in the patient, was aligned with Homo sapiens (human), Macaco mulatta (monkey), Mus musculus (mouse), Sus scrofa (pig), Bos taurus (cow), Gallus gallus (chicken), Xenopus tropicalis (frog) and Danio rerio. The predicted deletion in *ACTN4* of the 3 amino acids, L209, I210 and E211, is highlighted in the black box.

Considering resistance to first-line treatment, genetic analysis was initially conducted for NPHS2, as it is the most common genetic cause of SRNS in patients who present symptoms in late childhood. However, since the result was negative, a WES approach had to be performed. It identified a variant, *ACTN4* p.L209_E211del, located in the ABD, where most FSGS-associated variants are found. The variant was classified as VUS which could be explained mainly by the absence of registries of this specific variant in databases. Approximately two years later, in a report case published by He et al. (7), a novel heterozygous missense variant was found in the ABD in a 17-year-old Chinese girl, which motivated a literature review that reported 17 VUS and 22 pathogenic or likely pathogenic variants in the *ACTN4* gene. Notably, the majorities of the pathogenic or likely pathogenic variants were confirmed to be *de novo* and were located in the ABD between amino acids 50-269. This was a significant finding considering that the variant in our patient was a deletion of amino acids 209-211 in *ACTN4*, playing a fundamental role in the decision making process, because it motivated the re-analysis of the VUS, and consequently led to the consideration of kidney transplantation. After the surgery, the patient did not present recurrence during the subsequent 5 months, suggesting that the *ACTN4* p.L209_E211del variant, classified initially as VUS, was most likely the cause of the SRNS-FSGS.

The identification of VUS is a recurrent problem in routine clinical genetics, especially in patients with rare diseases or atypical phenotypes, who carry novel variants either through *de novo* occurrences or founder effects in populations with limited genomic resources. Recently, it has been noted that VUS variants make up the largest proportion of human genomic variations, comprising approximately 2 million entries in the ClinVar database (17). Rather than representing a dead end without further solutions, VUS should be re-analyzed as a standard of care in benefit of patients' outcomes, considering the patient's clinical evolution.

Within the last decade, an exponential growth in clinical genetics has been observed contributing to the ongoing development of bioinformatic tools for variant analysis, such as dynamic protein conformation, flexibility and stability predictors (19). Genetic testing is increasingly becoming accessible, even in countries with limited genomic resources. It has been suggested that the cost-effectiveness is notable when conducted during the early stages of specific kidney diseases, potentially resulting in significant cost savings, especially in pediatric cases (20). However, potential risks should always be assessed by a multidisciplinary team to balance risks and benefits that need to be communicated to the patients and their families. Our concern in the patient was the probability that he had an idiopathic non-genetic SRNS that in over 60% of cases showed a complicated clinical course after transplantation according to a recent systematic review and meta-analysis (18).

The use of exome sequencing to identify variants has demonstrated clinical utility, particularly in the context of rare diseases. Establishing a program for these conditions appears indispensable and feasible in countries with limited genomic resources (21). Its global adoption is foreseen to increase over time, provided that costs continue to decrease, and researchers and physicians enhance their training. Undoubtedly, more efforts are needed to foster research and to promote reaching a genetic diagnosis in patients, aligning with the goal to 'leave no one behind' as advocated by the World Health Organization and the United Nations, ideally through collaborative data-sharing initiatives.

Data availability statement

The dataset presented in the study are deposited in the FigShare repository, accession DOI number is https://doi.org/10.6084/m9.figshare.28212140.v1.

Ethics statement

The studies involving humans were approved by Comite Ético Científico-Servicio de Salud Valdivia. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

IA: Writing – original draft, Writing – review & editing, Data curation. CP: Data curation, Writing – review & editing, Resources. FC: Data curation, Resources, Writing – review & editing. MA: Data curation, Resources, Writing – review & editing. FC: Writing – review & editing. AR: Data curation, Writing – review & editing. ML: Data curation, Writing – review & editing. PK: Conceptualization, Formal analysis, Funding acquisition, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneph.2024.1375538/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Immunofluorescence analysis resulted negative for IgG, Kappa, and Lambda. IgA, IgM, and C3c were also negative (not shown).

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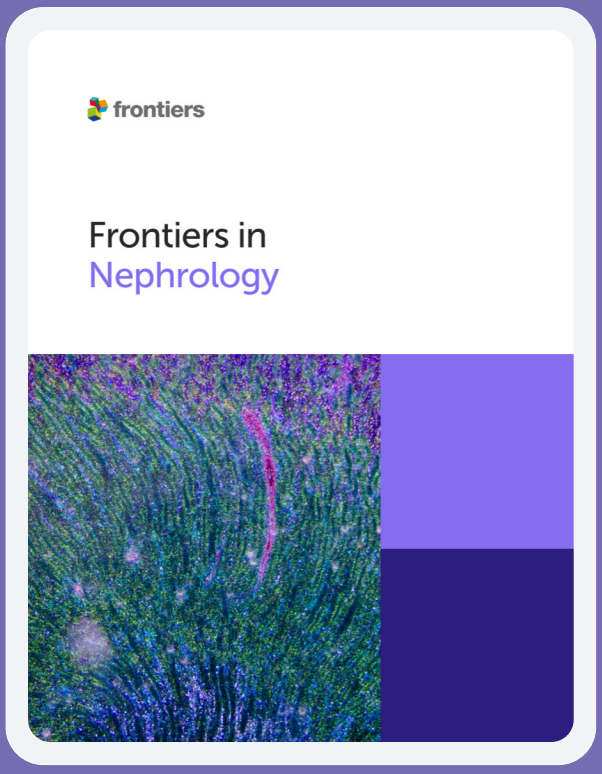

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